Electronic Structure and Hydrolytic Reactivity of N-Sulfinyl Species

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Abstract

Electronic Structure and Hydrolytic Reactivity of N-Sulfinyl Species

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The mechanism of the uncatalyzed hydrolysis of various classes of N-sulfinyl compounds (N=S=O) has been studied with the B3LYP/6-31+G(2d,2p) model chemistry, which was validated to provide reliable results in terms of the reproduction of experimental geometries and determination of energies of the reaction. N-sulfinylamines (R–N=S=O), -hydrazines (R–NH–N=S=O), -hydrazides (R–CO–NH–N=S=O) and -amides (R–CO–N=S=O), known to possess a widely varying hydrolytic behaviour, were studied in comparison, and the electronic structures of many were determined for the first time. The effect of the substituent was investigated through R = H, CH_3 and Ph for each class of N-sulfinyl species; the series was expanded by eight more substituents for N-sulfinylamines. The hydrolysis of selected N-sulfinylamines was compared to that of the related isocyanates (R–N=C=O).

Hydrolysis of all N-sulfinyl species involves the electrostatic interaction of water towards sulfur, with either close-to-perpendicular or in-plane alignment of a water molecule, with respect to the NSO plane, in a pre-reaction complex. A two-water-molecule model in gas phase calculations was determined to be sufficient for an adequate description of the hydrolysis. The rate-determining step of the reaction consists of the concerted hydroxylation of sulfur with protonation of either nitrogen (attack across the N=S bond) or oxygen (attack across the S=O bond) atoms of the NSO group. Electron-withdrawing substituents were found to decrease, electron-donating substituents to increase the reaction barrier. A fundamental difference in the resonance description of the various classes of N-sulfinyl species was found to be responsible for their distinctively varying sensitivity towards moisture.

Activation barriers for hydrolysis correlate well with the strength of the S…O interaction, governed by the charge on the electrophilic sulfur atom, which can be accurately determined by both the Quantum Theory of Atoms in Molecules and the Natural Bond Orbital Analysis. The computationally determined order of reactivity of the various classes of NSO compounds, quantitatively defined through the charge on sulfur, agrees well with the available qualitative experimental data. Thus, N-sulfinylamides and aliphatic N-sulfinylamines are most reactive, N-sulfinylhydrazides are much less reactive, and N-sulfinylhydrazines are completely inert to water.

The clear dependence of the hydrolytic reactivity of N-sulfinyl species on the charge of the reactive center suggests the possibility of using such dependences in the prediction of the general reactivity of N-sulfinyl compounds, as most of their reactions involve the sulfur atom or the N=S bond.

Dedicated to my husband Qadir K. Timerghazin

and my parents Tatyana N. Ivanova and Valerii A. Ivanov

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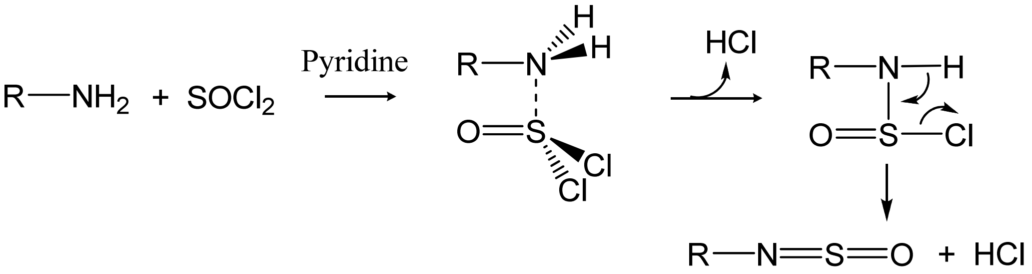
AIM	Atoms in molecules
B3LYP	Becke's three-parameter hybrid exchange/Lee-Yang-Parr correlation functional
BCP	Bond critical point
BSSE	Basis set superposition error
CP	Counterpoise
CPCM	Conductor-like polarizable continuum model
CT	Charge transfer
DFT	Density functional theory
HB	Hydrogen bonding
HF	Hartree-Fock
IAS	Interatomic surface
IR	Infrared
MP2	Second-order Møller-Plesset theory
NBO	Natural Bond Orbital
NPA	Natural Population Analysis
NRT	Natural Resonance Theory
PES	Potential energy surface
PA	Proton affinity
QTAIM	Quantum Theory of Atoms In Molecules
TS	Transition state
UV-Vis	Ultraviolet-visible
ZPVE	Zero-point vibrational energy
QCISD(T)	Quadratic configuration interaction with single and double excitations and perturbative triple excitations

Chapter 1.

Literature review

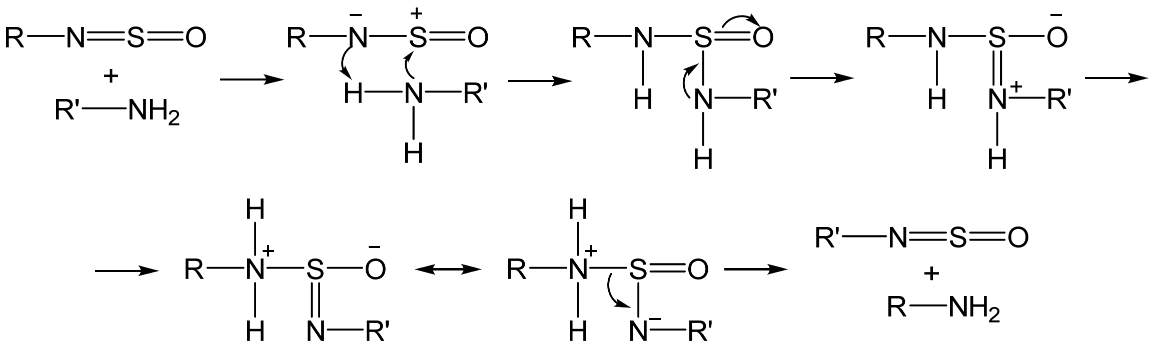
1.1. N-sulfinyl compounds: synthesis and historical background

The first referral to N-sulfinyl species (R–N=S=O) can be traced back to as far as 1878, when they were first mentioned by Böttinger, however, without specifics on their structure.[1] Subsequently, many more N-sulfinyl species were synthesized by Michaelis and co-workers in the 1890s[2-7] as the products of the reaction of a primary amine with thionyl chloride ($SOCl_2$), and the name N-thionylamine was coined for this class of compounds.[8-11] The mechanism of this reaction, which was not described in detail in the literature, should involve the interaction of the electrophilic sulfur of thionylchloride with the nitrogen atom of the amine, according to Scheme 1-1. The thionylation is known to be catalyzed by bases which also take up the HCl evolving in the course of the reaction. Since the beginning, this technique has become one of the most widely used for the synthesis of RNSO compounds, which are now also called N-sulphinyl-,[12-16] -amines,[17-19] -imines,[20-22] -imides[9,16] or iminooxosulfuranes.[23]



Scheme 1-1. Synthesis of N-sulfinyl species by reaction of thionylchloride with amines.

Michaelis and coworkers also were the first to study the general reactivity of N-sulfinyl species, mostly their reactions with water, acids and bases, with particular attention to the aromatic species.[2-7] In the reaction of N-sulfinylaniline (PhNSO) with phenylhydrazine, Michaelis was first to determine the transfer of the sulfinyl moiety from the amine to the hydrazine.[4] Since then this technique, called transsulfinylation (Scheme 1-2), has become second in importance for the generation of N-sulfinyl species, and can be advantageously applied for the preparation of even sensitive N-sulfinylamines, such as 4-hydroxy-, mercapto-, carboxy-, and more.[24] Similar to thionylation, transsulfinylation involves the nucleophilic attack of the nitrogen atom on the electrophilic sulfur of the N-sulfinylamine. In the latter case, this interaction happens presumably simultaneously with protonation of the N-sulfinyl nitrogen atom (four-center reaction). The higher basicity of the interacting amine facilitates the transfer of the SO moiety, rendering N-sulfinylsulfonamides (R–SO_2–NSO) with their low basicity the best sulfinylating agents.[19,24,25]



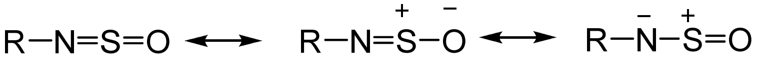
Scheme 1-2. Transsulfinylation reaction.

After a period of inactivity, the interest in this class of compounds was reopened in the late 1960s and early 1970s because of their growing importance for various cycloadditions with formation of heterocycles, “quasi-Wittig” (reactions with dipoles) and reactions with proton-active compounds,[19,24,26] which will be addressed in Chapter 1.3 in more detail.

1.2. Electronic structure of N-sulfinyl species

With a few exceptions,[27,28] most of the known reactions of N-sulfinyl species occur across the NS bond, with cleavage of either only the π- or of both bonds, which in the latter case is accompanied by the evolution of sulfur dioxide.[19,24] Consequently, the “four electron (double) bond” nature[24] of the NS bond, able to enter in conjugation with an available π-system, was not doubted from the beginning of the studies of N-sulfinyl species. The nature of the SO bond, on the other hand, provoked much discussion in the past, which explains the absence of any closer specification, such as dative ($S \rightarrow O$)[10,29] or charge-separated ($S^+{-}O^-$).[30-34] In spite of attempts to apply a resonance structure description to the N-sulfinyl moiety,[35-38] the first referral to the N=S=O group as a "cumulated π-system" can be traced back to 1973 in the work of Kroner *et al.*[39] In several following NMR studies of various sulfur compounds, the double bond nature of the S=O bond in the NSO group was confirmed.[18,40] ^{17}O NMR chemical shifts of various N-sulfinyl compounds are found significantly further downfield ($\delta > 400$ppm) compared to more typical SO compounds. For example, ^{17}O nuclei of sulfoxides or sulfinic acid derivatives resonate at higher field, and their chemical shifts vary in the wide range from −10 to about 225 ppm.[16,18,40] Furthermore, the close resemblance of the oxygen chemical shift of sulfur dioxide (~513 ppm)[41] to those of N-sulfinylamines suggests a similarity of their electronic structures. The difference in chemical shift of about 100 ppm is attributed to the smaller electronegativity of the RNSO nitrogen compared to the second SO_2 oxygen, which leads to an increased charge density for the RNSO oxygen.[40]

The nature of bonding in SO_2, best described as the combination of one true double and one semipolar bond in resonance, also resembles that in N-sulfinyl species as presented in Scheme 1-3,[35,36,42,43] where the sulfur atom is considered to be the positive end of the dipole, while either oxygen or nitrogen are the negative ends, obliterating the "hypervalency" term for their proper description. The larger weight of the mesomeric form **I** compared to **II** was again attributed to the larger electronegativity of the oxygen atom.[42]



$$R{-}N{=}S{=}O \longleftrightarrow R{-}N{=}\overset{+}{S}{-}\overset{-}{O} \longleftrightarrow R{-}\overset{-}{N}{-}\overset{+}{S}{=}O$$

I **II**

Scheme 1-3. Resonance structures of N-sulfinyl compounds.

The similarity of the N-sulfinyl species and sulfur dioxide can further be seen in the comparison of their corresponding NSO and OSO angles, determined to be approximately 120°,[15,20,36,44-50] and through the analysis of their electron densities[49] in the framework of the Quantum Theory of Atoms in Molecules.[51] In the case of N-sufinylamines, the bent NSO angle gives rise to the existence of two configurational isomers due to isomerization around the N=S bond. Intense IR and Raman spectroscopic studies by Della Védova's group, combined with computational chemistry investigations, reveal that the syn configuration is the general structural motif demonstrated by all representatives of this class of compounds structurally characterized.[20,45,48,52,53] This statement is also correct for sterically demanding di-*ortho*-substituted N-sulfinylamines, where repulsive interactions of the substituents with the NSO group causes NSO rotation out of the plane of the aromatic ring, for phenyl- (Ph–NH–NSO) and for disubstituted N-sulfinylhydrazines (NR_2–NSO), and for other N-sulfinylamines, characterized by X-ray and neutron diffraction.[15,54-56]

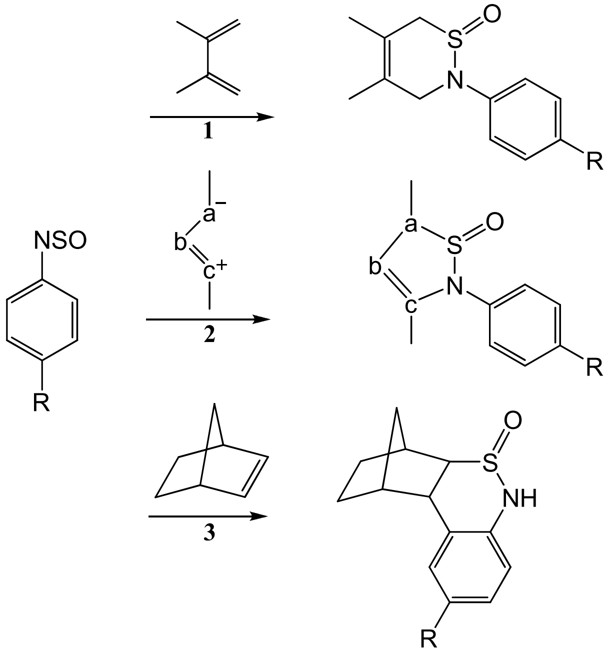
The cumulated, conjugated NSO group is a good chromophore, responsible for the colour of the N-sulfinyl species, which varies from colourless to yellow, orange and red in liquids, well crystallized solids and oily compounds.[24] Both aromatic and aliphatic N-sulfinylamines possess two distinctive absorption bands in the UV-Vis region (near 230-240 and 310-330 nm).[42,43,57,58] In earlier studies, both bands for aliphatic N-sulfinyl amines were assigned to the excitation of the NSO group, while in aromatic compounds the longer-wavelength band was attributed to the interaction of the N-sulfinyl moiety with the π-system, expanding the chromophore to the entire Ph−N=S=O molecule.[42,43,57]

This fact, full conjugation, was further supported through the analysis of aromatic substituent effects. Electron-donating substituents in para position were found to shift the first primary (longer-wavelength) band of increased intensity to even longer wavelengths. For example, the strongest electron donor $(Me)_2N$ leads to a band with extinction coefficient log $\varepsilon = 4.5$ at 408 nm.[42,43] In contrast, electron acceptors in para position and substituents of various nature in other ring positions cause a hypsochromic (blue) shift in the UV-Vis spectra of aromatic N-sulfinylamines.[42,43,57] The loss of co-planarity of NSO moiety and aromatic ring, induced by bulky substituents, reduces the π-conjugation and also causes a lower-wavelength absorption band.[57]

Based on these findings, bands at around 240 nm were assigned to $n \rightarrow \pi^*$ excitations of one electron from the sulfur lone pair (n_S) into the π^* orbital for sulfur and nitrogen ($\pi^*_{N=S}$), and bands around 310-330 nm to $\pi \rightarrow \pi^*$ transitions of non-bonded, π-type electrons of nitrogen and oxygen into the same $\pi^*_{N=S}$.[42,43] In newer studies that incorporated results from quantum chemical calculations and experiment, both transition are ascribed to delocalized $\pi \rightarrow \pi^*$ interactions; $n \rightarrow \pi^*$ transitions were not observed as discrete bands.[47,48]

1.3. Complexation ability and reactivity of N-sulfinyl compounds

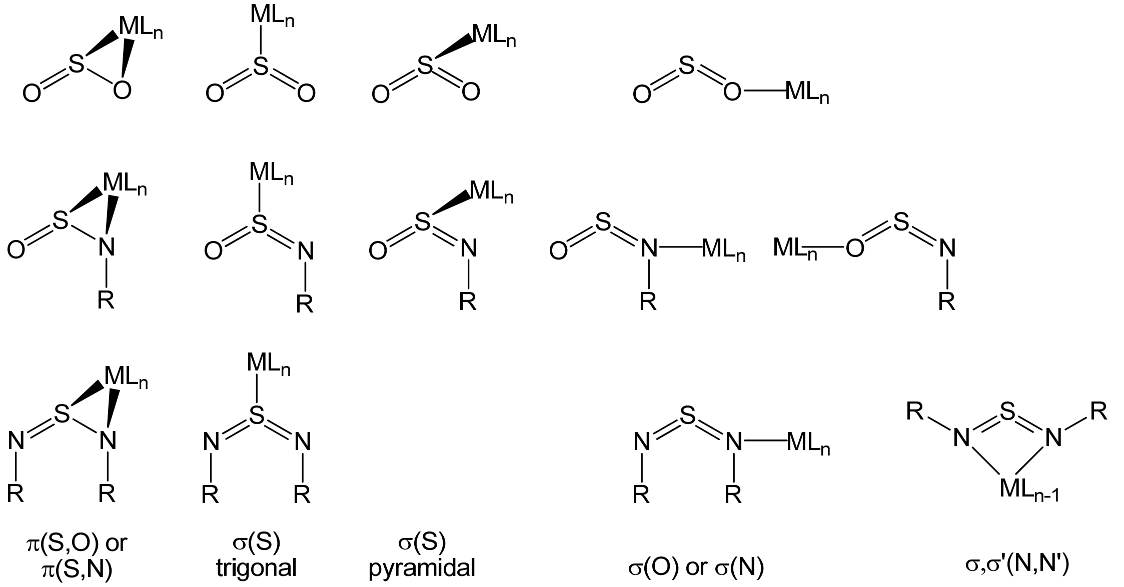
Cycloaddition reactions are probably one of the most important reactions of N-sulfinylamines of synthetic utility, resulting in the formation of heterocycles; reactivity increases with increasing electron-withdrawing ability of the substituent on the N-sulfinyl group.[19] In reactions with 1,3-dipolar systems and with 1,3-dienes, aromatic N-sulfinylamines act as the ene-component, as presented in Scheme 1-4 (reactions **1** and **2**), while the aliphatic species do not react.[19,25,29] Interestingly, in reactions with norbornene derivatives, aromatic N-sulfinylamines act as dienes (reaction **3**, Scheme 1-4).[29] These reactions were found to be stereospecific, and product analyses suggests the necessity of the existence of the less populated RNSO anti configuration at least in the transient state. In fact, the conclusion of a possible participation of the anti configuration was also reached in a computational study of Diels-Alder reactions involving N-sulfinyl dienophiles.[59] In that work, the cycloaddition from the anti (or E) configuration was found to be energetically considerably more favourable (by about 5-9 kcal mol^{-1}, determined as gas phase Gibbs free energies) compared to that from the Z configuration. Electron-withdrawing substituents significantly reduce the reaction barriers.[59]



Scheme 1-4. Typical cycloaddition reactions of N-sulfinylamines.

The reactivity of N-sulfinylamines, as seen in their cycloaddition reactions, is similar to those of the isoelectronic species sulfur dioxide and sulfurdiimide (R–NSN–R), which also have been thoroughly studied.[23,30,31,60-64] The binding modes of complexation with transition metals for all three classes of compounds are depicted in Scheme 1-5.[23] This comparison seems to be essential for a better understanding of the nature of bonding and reactivity of N-sulfinyl compounds, because of their intermediate position in this series. RNSOs are less reactive than sulfur diimides because of the presence of only one reactive N=S bond, giving rise to a lower probability for fragmentation, which might prevent the formation of the complexes. At the same time, the higher basicity of the nitrogen compared to the oxygen atom increases their propensity for N-coordination as well as for coordination in the side-on fashion, because of the increased π-HOMO energy in N-sulfinylamines and sulfurdiimides (Scheme 1-5). On the other hand the high sensitivity of certain RNSO species to moisture results in their hydrolysis, with the consequential formation of the respective transition metal complexes of sulfur dioxide.[23] The sensitivity to moisture depends on the exact coordination mode, which seems to reflect the strength of the complexation. The σ(S) pyramidal complexes react with water rapidly at 25 °C, whereas under these conditions, the hydrolysis of the σ(S) trigonal complexes is slow, and a temperature of up to 60 °C is needed for the reaction of the strongest π(N,S) complexes of RNSO–ML_n.[23] The above mentioned σ(S) pyramidal complexes are not reported for sulfurdiimides,[23] which might be ascribed to the lower charge on sulfur because of the lower electronegativity of the second nitrogen (as compared to oxygen) in these compounds.

The most complete coverage on the factors affecting binding motifs in these complexes is provided in Hill's review on the organo (transition) metallic chemistry of sulfur dioxide analogues.[23] As for all heterocumulenes compared, a higher electron density of the metal-ligand (ML_n) fragment increases the probability of the side-on π(N,S) interaction, because it represents the most effective way to alleviate the excess metal d-electron density. Consequently, this mode of binding is exhibited by d^8 and d^{10} transition metals in oxidation states of –1, 0 and +1.

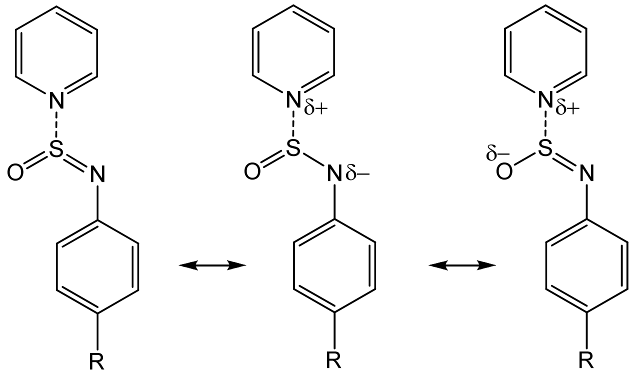


Scheme 1-5. Coordination modes of sulfur dioxide, N-sulfinylamines and sulfurdiimides in complexes with metal-ligands (ML_n).

Less electron rich d^6 and d^8 transition metals in higher oxidation states (+1 and +2) favour the σ(S)-trigonal mode of binding.[23] In this binding mode, the retrodative metal-ligand interaction is not as efficient as the side-on π(N, S), rendering σ-donation the most important interaction. The pyramidalization on S competes with the trigonal mode of coordination and is usually found in d^6-metal complexes with low-lying M–S antibonding orbitals of σ-symmetry.[23] The only known coordination of arsenic to the oxygen atom of (trifluoromethyl)sulfanyl-N-sulfinylamine (CF_3SNSO) in a σ(O) fashion was based on the crystal structure study of the CF_3SNSO complex with arsenic pentafluoride.[22]

From the above, it can be concluded that complexation of N-sulfinyl compounds with metals occurs predominantly to the sulfur atom or to the unsaturated N=S bond, where the coordination mode depends on the ability of the metal center to donate and accept the electron density in terms of relative energy and symmetry of the orbitals.[23,65] A similar effect of the basicity of water, dimethyl ether and amines on the strength of their charge transfer complexes with SO_2 was determined in multiple experimental and computational studies.[66-74] A roughly perpendicular orientation of the water oxygen or amine nitrogen on the sulfur atom with respect to the plane of the SO_2 molecule is suggestive of an n–π* charge-transfer interaction, albeit with significant electrostatic contribution to the binding.[67,68,73] An increased basicity of the donor is responsible for the increase in the charge transfer and, consequently, the strengthening of the complexes.[68,72,74,75]

In an earlier experimental study of the complexation of para-substituted phenyl-N-sulfinylamines (N-sulfinylanilines) with pyridine and triethylamine, the presence of an intermolecular S…N interaction was confirmed through analysis of their ^{17}O and ^{13}C chemical shifts.[40] Two sets of ^{17}O signals were reported for most N-sulfinylanilines in pyridine solution, which was explained by the presence of a mixture of free and pyridine-complexed RNSOs. The insensitivity of one signal to substitution was attributed to the presence of resonance structure **II** (Scheme 1-6), in which the SO part can no longer conjugate with the aromatic ring and, thus, does not exhibit a sensitivity to the para-substituent.



I **II** **III**

Scheme 1-6. Resonance structures of complexes of N-sulfinylanilines with pyridine.

In the NMR study, it was suggested that the para-substituent controls the complexation ability of N-sulfinylanilines.[40] For example, inclusion of the strong electron-donating substituent $(Me)_2N$ hindered the negative charge delocalization in **II** (Scheme 1-6), preventing the complexation with pyridine, while upon inclusion of the weaker OMe donor, both sets of signals were observed.[40] Similar effects in the deshielding of ^{17}O NMR chemical shifts upon complexation with pyridine were reported in our group.[76] But unlike Cerioni's work,[40] where only one signal, attributed to the fully complexed N-sulfinylaniline, was reported with the strongest electron-withdrawing substituent NO_2, both sets of signals are found.[76] This discrepancy was tentatively attributed to the differences in temperature dependence of the two sets of ^{17}O chemical shifts corresponding to the complexed (large $\Delta\delta/\Delta T$) and non-interacting (small $\Delta\delta/\Delta T$) species, and a possible accidental degeneracy of the two signals in the earlier study.[76]

In these complexation examples, ^{17}O signals other than those corresponding to N-sulfinylanilines were not detected,[40,76] and the interaction of N-sulfinylanilines with ternary amines is reversible. On the other hand, the interaction of N-sulfinylamines with dipolar bonds, such as C=O, C=N, S=O and P=O in a “quasi-Wittig” fashion and with proton-active compounds,[19,24,25] such as thiols, hydrogen halides, carboxylic acids, water and alcohols, does not stop at the stage of complexation. Similar to complexation and other types of reaction reported before, reaction occurs across the N=S bond of the N-sulfinyl species with formation of four-membered ring intermediates[25,77-79] in analogy to that presented in Scheme 1-2 for the transsulfinylation reaction.

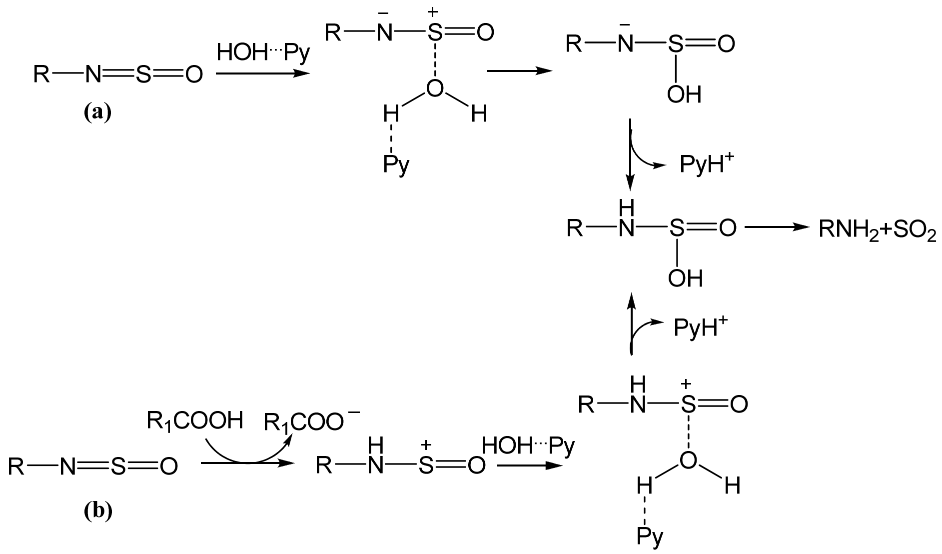
1.4. Hydrolysis of N-sulfinyl species

Hydrolysis and alcoholysis reactions, as the examples of the reaction with “proton-active” compounds, are expected to operate by a similar mechanism as presented in Scheme 1-2 for transsulfinylation reaction.[80] Reaction with water present a particular interest because the substituent on the N=S=O moiety can render the reactivity of N-sulfinyl species in a wide range, varying from explosive, reported for chloro-, bromo-, and iodo-N-sulfinylamines[81,82] to completely inert as exhibited by N-sulfinylhydrazines,[19] which for this reason have found an application in crop protection.[83-85] The carbonyl derivatives of N-sulfinylhydrazines (R–NH–NSO), N-sulfinylhydrazides (R–CO–NH–NSO) with one exception,[86] unlike the former, undergo hydrolysis, which was proposed to be effected by a possible keto-enol tautomerization in these species.[19] On the other hand, the carbonyl derivatives of N-sulfinylamines, N-sulfinylamides (R–CO–NSO), were reported to hydrolize quite readily.[37,87]

In general, the aliphatic compounds are reported to be more reactive with water than the aromatic, while the variation in reactivity due to substituents on N-sulfinylaniline was explored to some extend even at the early stages of investigation.[5-7,88] While it appears that electron-donating groups decrease, and electron-withdrawing groups increase, the reactivity of N-sulfinylamines with water, unfortunately, the presented examples often do not allow a clear distinction between electronic and steric effects. These findings imply that in the rate-determining steps of the hydrolysis the sulfur atom of the NSO group acts as an electrophile towards the nucleophilic water, as was suggested in the two experimental kinetic studies of the hydrolysis of N-sulfinylanilines reported to date.[17,89] As mentioned in Chapter I.2 on the structural features of N-sulfinylamines, the presence of an intense ($\log \varepsilon \approx 4.0$) absorption band in the UV-Vis spectra of aromatic N-sulfinylamines at approximately 330 nm, which shows sensitivity to substitution and does not overlap with bands from either the products (anilines and SO_2) or catalysts, allows to monitor the course of the reaction spectroscopically by its disappearance.[17,89]

The neutral hydrolysis of N-sulfinylaniline was found to be a slow process[89] with an activation energy of 9.88 kcal mol^{-1} for the 21-30 °C temperature range.[17] The possibility of autocatalysis from aniline, which is formed in the course of the reaction, casts doubts on the correctness of this value. At the same time, in the pseudo-first order reaction achieved by keeping the concentration of water in large excess, only a slight increase (not exceeding 5%) in reaction rate was found, which in fact can be attributed to the autocatalytic effect of aniline. Introduction of a methyl group in para-position of the aromatic ring decreased the rate of reaction even further as seen in the increase of the induction period from 4 to 10 h.[89]

The rate of the reaction can be significantly increased in the presence of pyridine (Py), with the mechanism presented in Scheme 1-7 along with the combined catalysis by pyridine and carboxylic acid.[89] In the base catalyzed reaction, the formation of the complex of water with pyridine increases the nucleophilic properties of water and therefore increases the rate of interaction of the water oxygen with sulfur in the rate-determining step. The formation of an unstable intermediate is followed by the fast protonation of nitrogen yielding sulfinamic acid, which decomposes with formation of the amine and sulfur dioxide. The third order (first with respect to each N-sulfinylaniline, water and pyridine) rate constant was determined to be 2.02, 2.96 and 4.2×10^{-3} mol^2 L^2 s^{-1} in the 20-40 °C range, resulting in an activation enthalpy $\Delta H^{\ddagger}$ of 5.7 kcal mol^{-1}.[89] The large negative activation entropy $\Delta S^{\ddagger}$ of –51 e.u., determined for the base-catalyzed reaction,[89] as well as –58 e.u. for neutral hydrolysis, suggests the need for proper orientation of the molecules in the TS.



Scheme 1-7. The hydrolysis of N-sulfinylaniline: a) base catalysis and b) combined catalysis by base and carboxylic acid.

Interestingly, the rate of reaction is even further increased in the presence of both pyridine and carboxylic acid.[89] The direct reaction of N-sulfinylaniline with acids was refuted under these reaction conditions,[90,91] but the increase in hydrolysis rate was attributed to the different mechanisms of the reaction, which is now initiated by the protonation of the NSO nitrogen, increasing the electrophilicity of sulfur and thus facilitating its attack by the "activated" complex of water and pyridine. The increase in the (water) isotope effect k_H/k_D from 1.73 to 2.23 for pyridine and the combined catalysis, respectively, seems to support the proposed mechanism of hydrolysis.[89]

There are only a few studies on the hydrolysis of N-sulfinyl species, while their alcoholysis, which occurs through a similar mechanism, was investigated more thoroughly.[8,11,13,80,92-97] In Chapter 1.5 we address the most important features of N-sulfinylamine hydrolysis/alcoholysis in comparison with closely related systems such as isocyanates and amides, whose reactivity was studied in great detail both experimentally and computationally.[98-104] Because of the large number of publications on the subject, only few are included in the discussion.

1.5. Hydrolysis of amides and isocyanates: experimental and computational perspectives

Much effort was brought to the investigation of the hydrolysis of amides because of the importance of this reaction for understanding of the peptide bond cleavage in living systems. The water assisted, base and acid catalyzed hydrolysis reactions of formamide as a prototype were studied at different theoretical levels, varying from semiempirical to density-functional theory and *ab initio* model chemistries, in the gas phase, with inclusion of a solvent field, as well as with molecular dynamics simulations.[99-101,103-105] For example, 66 ± 12, 78 ± 12 and 147 ± 12 kJ mol^{-1} barriers were determined for OH^{-}, H^{+} and water-assisted hydrolysis of methylacetamide using Car-Parrinello molecular dynamics simulations.[103]

At various levels of theory, the neutral hydrolysis, consistent with hydroxylation of the amide carbon, was determined to have a rather large energy requirement, 44 kcal mol^{-1} determined with MP2(full)/6-31G**//4-31G.[99] With the same model chemistry, the reaction barrier can be significantly reduced by preliminary protonation of nitrogen, increasing its pyramidalization, or oxygen atoms of the amide group, which decreases the barriers for the hydroxylation of carbon to 6.0 and 24 kcal mol^{-1}, respectively.[99,102]

Isocyanates, which exhibit cumulated bonding similar to N-sulfinyl species, react in hydrolyses in a similar fashion to both amide and N-sulfinyl species. With use of quantum chemical calculations, the reaction of isocyanic acid with one to three water molecules was modeled.[106] Unlike for amides, where preliminary protonation of either oxygen or nitrogen were proposed to be more efficient,[99] the concerted neutral hydrolysis of this smallest isocyanate showed the importance of an increasing number of water molecules treated explicitly for the proper description of the reaction. The effect of an increasing number of water molecules on a decreasing barrier to hydrolysis of amides, isocyanates and N-sulfinyl species was reported repeatedly in experimental and computational works.[94,106-109]

Ideally, in addition to a certain number of explicit solvent/reactant molecules, a calculation of a hydrolysis reaction should take solvent field effects into account. But despite reports that introduction of the electrostatic interaction of the solvent with a solute plus water changes the transition state geometries[100] and often decreases the activation barrier for the reaction,[102,105] the overall effect of a solvent field was less significant compared to the explicit inclusion of the solvent/reactant molecule in the reaction coordinate.[100,102,105]

To conclude, despite some general knowledge on the hydrolysis of N-sulfinyl species in the literature, there is no complete study on the factors causing the vastly different reactivity of N-sulfinyl compounds with water. Through a computational chemistry approach, in this thesis we plan to gain a deeper understanding of the nature of the reaction of N-sulfinyl species with water and to bring a quantitative meaning to the existent qualitative experimental results.

Chapter 2.

Objectives and organization of the thesis

The main goal of this thesis is to determine the factors leading to the very distinctive hydrolytic behavior of various classes of N-sulfinyl species (RNSO), which cover the full spectrum of reactivity from explosive to completely inert. For this purpose, computational studies on classes R–NSO, R–CO–NSO, R–NH–NSO and R–CO–NH–NSO are carried out to gain a detailed understanding of their hydrolysis and to add quantitative meaning to the existent qualitative experimental results.

The first task, as in any project, is to identify an appropriate method that yields reliable results in an efficient fashion. Thus, various computational methods and techniques need to be validated in order to find the most suitable model chemistry. Such model chemistry combines the correct reproduction of experimental geometries and hydrolytic reactivities, and therefore N-sulfinylaniline (PhNSO) represents the best choice for a model because its geometric parameters and quantitative, kinetic data for hydrolysis are available. Factors affecting the accuracy of prediction of complexation and reaction energies, such as basis set superposition errors and solvent field effects must be addressed.

Next, the appropriate number of water molecules to be included in the calculations needs to be established. Hence, the influence of the number of water molecules (one to five) on the strength of the initial complexation and the height of the reaction barrier must be determined. Again PhNSO is the appropriate model system due to the available kinetic data. In terms of the mechanism of the hydrolysis reaction, the proposed electrophilic attack of water towards the sulfur of the NSO moiety is to be validated, and the rate-determining step and preferred mode of attack, across S=O or N=S bonds, are to be established.

It is important to compare the results from the PhNSO calculations with those on the aliphatic N-sulfinylamines R–NSO with R = H, CH_3 and CF_3, whose hydrolytic reactivities are known qualitatively, to establish the substituent effect quantitatively. Equally important is to compare and contrast the hydrolytic behaviour of the N-sulfinylamines to that of the more well-known and structurally related isocyanates, R–NCO, with identical substituents. This comparison allows for a better understanding of the sensitivity of cumulated moieties to substitution, as the NSO group exhibits internal π-conjugation that is absent in the NCO group.

Finally, hydrolysis in the remaining classes of N-sulfinyl species needs to be addressed, and N-sulfinylhydrazides (R–CO–NH–NSO) deserve particular attention, because of the possibility of keto-enol tautomerization, which can affect their reactivity. It therefore needs to be established, through their relative stabilities and energetics of their various isomerization reactions, which isomers are energetically available for hydrolysis. Complexes and transition states for the initial step in the hydrolysis of all remaining classes of N-sulfinyl species (amides, hydrazines and hydrazides) need to be determined, and substituents R = H, CH_3, Ph are chosen again to capture aliphatic versus aromatic effects. The electronic structures of all N-sulfinyl species are to be determined in order to establish a link to their reactivity.

The organization of this manuscript-based thesis follows the order of the goals and tasks presented above. Thus, Chapter 3 presents the validation of various model chemistries, Chapter 4 our initial study on the hydrolysis of PhNSO, Chapter 5 its extension to the aliphatic RNSOs and the isocyanates. Before turning to the hydrolysis of the other N-sulfinyl classes, the isomerizations in the N-sulfinylhydrazides needed to be addressed and is presented in Chapter 6. Finally, Chapter 7 presents the hydrolysis of an even further extended series of N-sulfinylamines, of N-sulfinylhydrazines, -hydrazides and -amides, their electronic structures, and the link between electronic structure and hydrolytic reactivity. The general conclusions of this thesis are presented in Chapter 8.

For electronic and molecular structures, the Quantum Theory of Atoms in Molecules (QTAIM), Natural Bond Orbital (NBO) and Natural Resonance Theory (NRT) methods are used as needed. The important features of these techniques, relevant to this thesis, are covered in Appendix A. Appendices B, C and D contain additional information important for the discussion but not included in Chapters 5, 6 and 7, respectively. These data are published in the journal articles as supplementary information.

Chapter 3.

Methodology and choice of the model chemistry

3.1. Introduction

Since the accuracy of quantum-chemistry methods varies depending on the class of molecules and reactions studied, it is important to choose a proper model chemistry for the investigation of the reactivity of N-sulfinyl (R−N=S=O) compounds. Previous studies from our group suggest that the B3LYP/6-31+G(d) model chemistry provides a reliable description of the geometry of N-sulfinyl species.[49,110] However, because of the rather small basis set, this model might not be as accurate for the proper description of intermolecular pre-reaction complexes, which play an important role in the hydrolysis reaction.

It is known that quantum chemical calculations of intermolecular complexes often suffer from large basis set superposition errors (BSSE) when medium basis sets are employed.[111,112] In calculations of intermolecular complexes with a finite basis set, each molecule "borrows" the basis functions from nearby molecules to improve the description of its own wavefunction. As a result, the basis set size for each molecule becomes larger in the complex, compared to the isolated molecule, leading to an artificial lowering of the energy and therefore overestimated binding energies of complexes. For example, the BSSE in water dimer calculations from HF/3-21G is estimated to be as large as 4 kcal mol^{-1},[112] while the experimentally determined enthalpy of association in the water dimer is determined as only 5.2±1.5 kcal mol^{-1}.[113] The BSSE decreases with increasing basis set size, but a very large (larger than 4- and 5-zeta) basis set is required to completely eliminate it.[112] A more feasible approach to deal with the BSSE is the so-called counterpoise (CP) correction,[111,112] which is obtained by taking the difference in energy of a given molecule with and without empty (or "ghost") basis functions belonging to other molecules in the complex. Because the CP correction renders a calculation significantly more computationally expensive, it is important to select a basis set with a reasonably small BSSE, so that the CP correction can be avoided.

Another factor that needs assessing for the modeling of reactions, such as hydrolysis, in solution is the solvent effect. The bulk solvent is often incorporated by use of a solvent field, defined by its dielectric constant.[114] We tested several model chemistries for the isolated N-sulfinylaniline (Ph−NSO) and its complex with two water molecules, paying special attention to the BSSE and to solvation effects on the accuracy of the calculations.

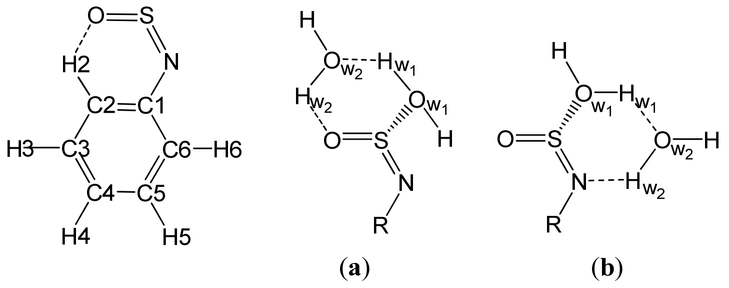
3.2. Computational details

Gaussian 98[115] and Gaussian 03[116] program packages were used for geometry optimizations and vibrational frequency calculations. Density functional theory calculations were performed with the Becke3[117] – Lee, Young and Parr (B3LYP) hybrid density functional.[118] In addition, *ab initio* calculations were performed with the Hartree-Fock method (HF) and the second-order Møller-Plesset perturbation theory with frozen core electrons [MP2(fc)].[119] Pople-style double- [6-31+G(d), 6-31+G(2d,2p)] and triple- [6-311++G(2d,2p)] zeta basis sets[119] as well as Dunning's augmented double-zeta correlation-consistent aug-cc-pVDZ basis set[120] were employed. The BSSE energy calculations and CP-corrected geometry optimizations were carried out as implemented in Gaussian 98 and 03.[115,116] For complexes of three molecules, the CP procedure involved calculation of each monomer individually (CP=3). The dependence of orientation of the water dimer with respect to the plane of the NSO moiety on the strength of the complexation and reaction barriers was modeled for the smallest N-sulfinylamine (HNSO), which also appeared to be a suitable system for the elucidation of the effects of the bulk solvent, which was studied for a water solvent field, characterized by the dielectric constant $\varepsilon=78.39$, using the polarizable continuum model (CPCM),[121] applied with full geometry optimization followed by frequency calculations.

3.3. Results and discussion

3.3.1. Geometries

In agreement with the data on other N-sulfinyl compounds reported to date,[10,12,15,20,36,45-47,122-126] the syn configuration of N-sulfinylaniline was found to be energetically favored by 6.0 to 7.7 kcal mol^{-1} over the anti configuration with all model chemistries employed. The geometric parameters for the syn configuration along with the results of previously reported calculations,[48,110] as well as the only available experimental parameters on the geometry of N-sulfinylaniline determined by X-ray diffraction[127] are summarized in Table 3-1, with atoms numbered according to Scheme 3-1.



Scheme 3-1. Atom numbering in N-sulfinylaniline and complexes of N-sulfinyl amines with one water molecule across the (a) S=O and (b) N=S bonds

A reasonable agreement between calculated and experimental geometries in terms of carbon-containing bonds and angles is obtained with all model chemistries, while the S=O and N=S bond lengths are quite significantly overestimated. Similar findings were reported earlier for other model chemistries.[110] The reason for this may be due to the fact that the bond lengths are defined differently in various experimental methods, which cause small deviations in the bond lengths resolution, with the gas phase electron diffraction method believed to be one of the most accurate. It also excludes the crystal field effects. Consequently, it would be the best technique for comparison of the results of quantum chemistry calculations of the molecules in the gas-phase. Unfortunately, electron diffraction studies failed due to the low vapour pressure of the compound.[48] The only exception is seen in results from the HF method, which, despite the small basis set, gives the closest agreement to the experimental data for the S=O, N=S and C1−N bonds due to a fortunate cancellation of errors. For B3LYP, the basis sets that contain a larger number of polarization functions on heavy atoms and hydrogen, such as (2d,2p), gives the smallest deviation from experimental results.

With all model chemistries, the presence of the blue-shifting C2−H2···O hydrogen bond,[110] characterized by contraction of the C2−H2 bond involved in the interaction by approximately 0.2-0.4 pm as compared to the other C−H bonds of the aromatic ring, was determined with the Quantum Theory of Atoms In Molecules.[51] The NSO angle, which is determined to be approximately 120° for most, including even sterically hindered N-sulfinyl species,[15,20,36,44-49] varies in the range of 119.3-120.4° in HF and B3LYP calculations, and is only slightly overestimated in the MP2 calculations. The angles around the nitrogen and carbon atoms are quite well reproduced with all model chemistries, and B3LYP with 6−31+(2d,2p) and 6−311++(2d,2p) basis sets gives the best agreement for NC1C2 and NC1C6 angles, with the former being larger due to the formation of the C2−H2…O interaction.

From the above, inclusion of polarization functions in the latter two basis sets as well as in Dunning's aug-cc-pVDZ basis set[120] seems to be necessary for a more accurate description of the weak bonding interactions, such as hydrogen bonds and the S···O interaction in complexes and transition states for the reaction of N-sulfinylaniline with water. Selected geometric parameters of intermolecular interactions, whose presence was confirmed through analyses of the electron density in the framework of QTAIM,[51] are summarized in Table 3-2 for the complex of N-sulfinylaniline with two water molecules across the S=O bond for optimized and CP-corrected geometries. The choice of a complex with two water molecules lies in the fact that a desirable S…O bonding interaction could not be determined for interaction with only one water molecule. As expected,[128] the application of the counterpoise correction does not alter the intramolecular bonding (the largest deviation is determined for the weak O…H2 interaction), but significantly lengthens the distances for the intermolecular weak interactions due to the reduction of the attraction between molecules. The substantial increase in the NSOO$_{w1}$ dihedral angle is also found with all model chemistries applied; this finding agrees well with the increased planarization in the H_2O…HF complex that was determined for the CP-corrected geometry.[128] As can be seen from Table 3-2, the smallest geometrical changes between optimized and CP-corrected geometries are found for B3LYP with aug-cc-pVDZ, 6-31+(2d,2p) and 6-311++(2d,2p) basis sets.

Table 3-1. Selected geometric parameters (bond lengths in pm and angles in degrees) of N-sulfinylaniline.

	Exp[a]	HF[a]	MP2		B3LYP				
		6-31 +G(d)	6-31 +G(d)[a]	6-31 +G(2d,2p)	6-31 +G(d)[a,b]	6-31 +G(d,p)	aug-cc-pVDZ	6-31 +G(2d,2p)	6-311 ++G(2d,2p)
S=O	145.84(10)	144.4	150.0	149.1	149.7	149.8	151.6	148.1	147.8
N=S	151.60(11)	149.2	156.2	155.3	154.8	154.9	156.5	153.4	153.1
C1−N	140.1(2)	140.1	140.8	140.5	139.4	139.4	139.4	139.3	139.3
C1−C2 [c]	140.59(14)	139.6	141.0	141.0	141.4	141.4	141.6	141.1	140.7
C2−H2		107.1	108.5	108.1	108.3	108.3	108.6	108.1	107.8
C3−H3 [d]		107.5	108.8	108.3	108.7	108.6	109.0	108.4	108.1
NSO	120.61(6)	119.3	121.1	121.6	119.8	119.8	119.5	120.4	120.3
C1NS	131.23(8)	133.2	129.5	130.0	131.7	131.6	130.2	132.3	132.4
NC1C2	124.23(10)	124.5	124.9	124.7	124.9	124.8	125.3	124.6	124.6
NC1C6	115.98(9)	115.6	114.9	115.3	115.6	115.6	115.3	115.9	116.0
C6C1C2[e]	119.80(10)	119.9	120.1	120.0	119.6	119.6	119.5	119.5	119.5
H2…O		234.9	231.6	232.4	233.7	232.8	228.8	235.4	235.2
C2H2O		123.5	126.3	126.9	126.1	126.2	127.0	125.8	125.8

[a] From ref. 48 (distances in the original paper were reported in Å) [b] From ref. 110. [c] The calculated C−C bond lengths vary in the range 138.2-141.6 pm, shown as an example for C1−C2. [d] As well as for all other C−H bonds except for C2−H2. [e] All angles around the other carbon atoms of the aromatic ring are computationally determined to be around 120°.

Table 3-2. Selected geometric parameters (distances in pm and angles in degrees) for intermolecular interactions in complexes of N-sulfinylaniline across the S=O bond, for regular and CP3-corrected[a] optimizations

	O…H2		S…O_{w1}		H_{w1}…O_{w2}		H_{w2}…O		$NSOO_{w1}$	
HF/6-31+G(d)	236.0	235.5	305.2	314.4	198.6	204.1	198.9	207.4	70.1	107.6
MP2(fc)/6-31+G(d)	241.9	242.2	297.0	308.6	191.4	200.5	192.8	202.2	78.4	85.4
MP2(fc)/6-31+G(2d,2p)	239.2	237.0	316.8	314.9	191.2	198.5	191.7	199.8	69.1	77.0
B3LYP/6-31+G(d)	234.2	233.4	299.7	311.6	185.6	189.8	187.7	192.7	101.9	114.4
B3LYP/6-31+G(d,p)	233.4	232.5	303.2	316.1	186.6	189.8	188.0	192.7	103.0	116.3
B3LYP/aug-cc-pVDZ	228.7	228.8	314.8	322.1	187.1	188.8	189.0	190.3	121.7	123.3
B3LYP/6-31+G(2d,2p)	235.8	235.4	314.6	323.6	188.8	190.0	192.1	193.4	109.8	118.7
B3LYP/6-311++G(2d,2p)	235.5	235.3	312.0	318.8	189.5	191.1	193.2	194.5	109.1	115.1

[a] Second column for each parameter.

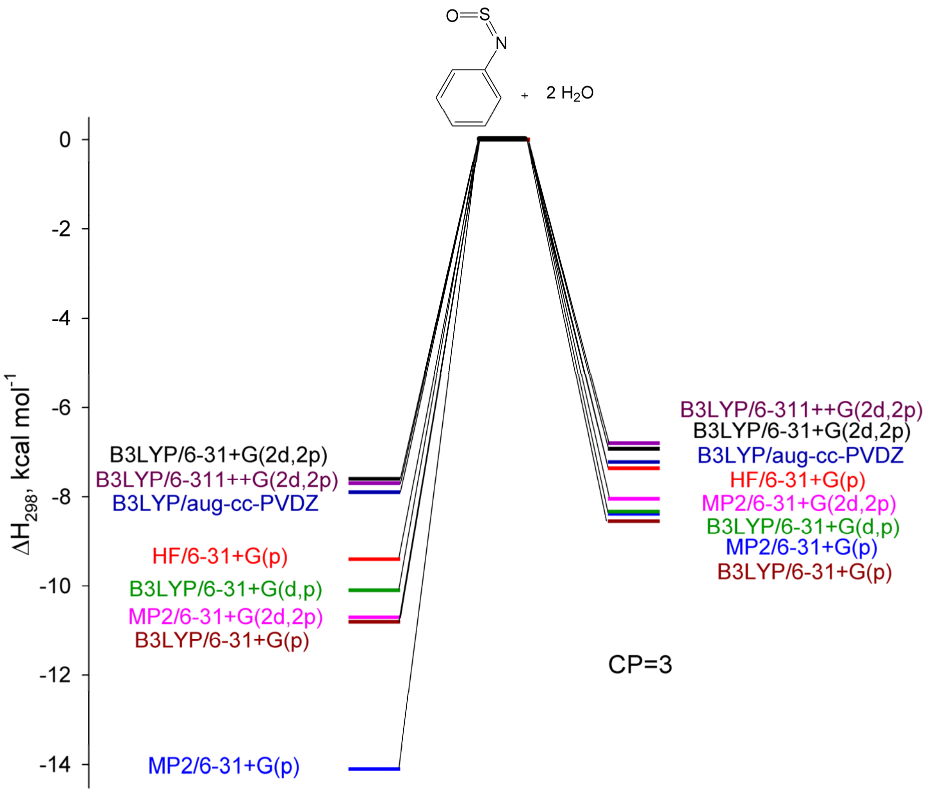


Figure 3-1. Binding enthalpies ΔH_{298} for the complex of N-sulfinylaniline with two water molecules for reaction across the S=O bond, calculated without (left) and with (right) counterpoise correction (CP = 3) with various model chemistries.

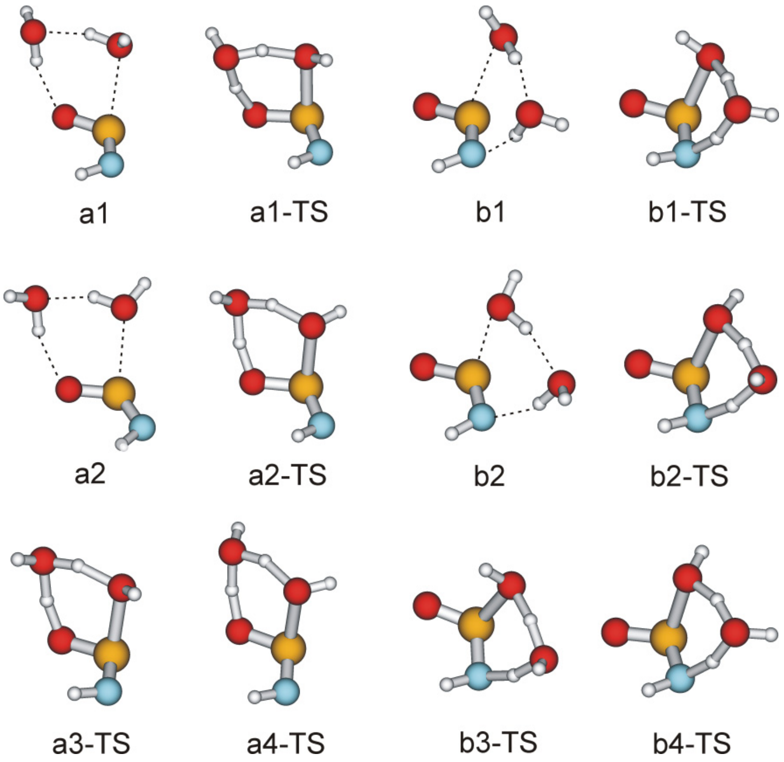
3.3.2. Energies

As can be seen from the results of Figure 3-1, the complexation energy depends on the model chemistry used, varying in the range of more than 6 kcal mol^{-1}. The poor performance for MP2/6-31+G(d) is probably due to the insufficiently large basis set. The counterpoise correction significantly narrows the spread, resulting in less than 2 kcal mol^{-1} difference, which is presented in graphical form in Figure 3-1. For the N-sulfinylaniline complex with two water molecules, the smallest difference of 0.7-0.9 kcal mol^{-1} between BSSE-corrected and uncorrected binding enthalpies is obtained with the same model chemistries that provide the least geometrical changes in the complexes, namely B3LYP in combination with aug-cc-pVDZ, 6-31+G(2d,2p) and 6-311++G(2d,2p). In addition, the activation barriers for the hydrolysis reaction with and without BSSE-correction are very close for the latter two basis sets, suggesting that either of them should be used in the studies of the hydrolytic behavior of N-sulfinyl species. Consequently, the B3LYP/6-31+G(2d,2p) model chemistry appears to be the most reasonable choice, due to its adequate accuracy in terms of geometries and enthalpies, combined with reasonably small computational expenses.

The chosen model chemistry [B3LYP/6-31+G(2d,2p)] was tested on its applicability in the prediction of the substituent effect in the hydrolysis of N-sulfinyl amines: for the unsubstituted HNSO, its higher reactivity compared to the aromatic analog was confirmed, and the results are summarized in Table 3-4 for reaction across S=O (**a**) and N=S (**b**) bonds, whose array of binding modes are given in Scheme 3-1. The effect of the conformation of the water dimer in complex formation with N-sulfinylamines on the relevant energies was investigated in detail for this smallest representative of N-sulfinyl species, HNSO.

Pre-reaction complexes were found for the staggered water dimer only. In these situations, one OH bond of the water interacting with sulfur sits over either S=O (**a**) or N=S (**b**) bonds. The second OH bond, not involved in H-bonding, is either parallel (**1**) with the second bond of the NSO group (N=S for **1**) or not (**2**) (Figure 3-2). These complexes are isoenthalpic (Table 3-4) and lead to similar activation barriers for hydrolysis as calculated based on complexation energies. There is a preference of less than 3 kcal mol^{-1} for reaction across the N=S bond. Because of the absence of complexes of the eclipsed water dimer (**3** and **4** in Figure

3-2), the activation enthalpies for transitions states **a3-TS**, **a4-TS**, **b3-TS** and **b4-TS** were calculated based on the energies of reactants and compared to the corresponding energies computed for the lowest energy activation barrier for corresponding mechanism in **a1-TS** and **b1-TS**. The increase in energy demand by maximum 1 kcal mol^{-1} (values in parentheses in Table 3-4) compared to the corresponding lowest energy reaction paths indicates that the orientation of the water molecules (both in the water dimer as well as with respect to the NSO group) is rather insignificant.



a1 a1-TS b1 b1-TS

a2 a2-TS b2 b2-TS

a3-TS a4-TS b3-TS b4-TS

Figure 3-2. Illustration of water attack onto S=O (**a**) and N=S (**b**) bonds: **1**, **2**, **3** and **4** represent different orientations of the water dimer with respect to the NSO group in HNSO. Weak bonding interactions in the complexes are depicted by dotted lines.

Table 3-3. Enthalpies for the preference of the syn over the anti configuration, complexation (ΔH_{298}, kcal mol^{-1}) and activation ($\Delta H^{\ddagger}_{298}$, kcal mol^{-1}), basis set superposition (BSSE,[a] kcal mol^{-1}) and BSSE-corrected enthalpies for the reaction of N-sulfinylaniline with two water molecules across the S=O bond.

Model chemistry	ΔH_{298} (anti-syn)	$-\Delta H_{298}$ compl.	$\Delta H^{\ddagger}_{298}$	BSSE, au	BSSE	$-\Delta H_{298}{}^{b}$ compl.	$\Delta H^{\ddagger}_{298}{}^{b}$
HF/6-31+G(d)	7.4	9.4	43.4	0.003253	2.0	7.4	41.4
MP2(fc)/6-31+G(d)	6.2	14.1	30.1	0.009113	5.7	8.4	24.0
MP2(fc)/6-31+G(2d,2p)	6.0	10.7	26.4	0.004226	2.7	8.0	23.6
B3LYP/6-31+G(d)	7.7	10.8	24.7	0.003592	2.3	8.5	22.5
B3LYP/6-31+G(d,p)	7.7	10.1	23.4	0.002819	1.8	8.3	21.6
B3LYP/aug-cc-pVDZ	6.6	7.9	22.4	0.001083	0.7	7.2	21.6
B3LYP/6-31+G(2d,2p)	7.0	7.6	24.3	0.001074	0.7	6.9	23.6
B3LYP/6-311++G(2d,2p)	7.0	7.7	25.3	0.001429	0.9	6.8	24.4

[a] Counterpoise correction (CP) = 3. [b] BSSE-corrected.

Table 3-4. Complexation (ΔH_{bind}, kcal mol^{-1}) and activation ($\Delta H^{\ddagger}$, kcal mol^{-1}) enthalpies for the reaction of HNSO with two water molecules across S=O (**a**) and N=S (**b**) bonds. Activation enthalpies, calculated based on reagents are shown in brackets.

Binding mode	Across S=O		Across N=S	
	a	**a-TS**	**b**	**b-TS**
1	-7.9	20.8	-7.2	18.3
		(12.9)		(11.1)
1'[a]	-0.9	18.3	-1.2	26.1
2	-8.0	21.0	-7.1	18.2
		(13.0)		(11.1)
3	-[b]	(13.9)	-[b]	(12.1)
4	-[b]	(13.8)	-[b]	(11.6)

[a] Were calculated with the polarizable continuum model (CPCM). [b] Complexes were not found.

3.3.3. Continuum solvation models

In the above, water was included in the calculations explicitly as the reagent in the concerted gas-phase reaction. However, in reality the hydrolysis reaction occurs in solution, where water also acts as a polar solvent, which may affect the course of the reaction. These solvent effects can be included in the calculations using one of the available continuum solvation models.[114] Unfortunately, the use of continuum solvation model makes calculations significantly more computationally expensive and may lead to various technical problems such as, for example, a slower convergence for geometry optimizations. In order to validate the importance of inclusion of a solvent field in the study of the hydrolysis of N-sulfinyl species, we employed CPCM[121] for the reaction of HNSO with two water molecules for **a1**, **a1-TS**, **b1** and **b1-TS** from Figure 3-2. These are defined as **1'** in Table 3-4, and their geometries are similar to those found in the gas phase.

The complexation and transition state enthalpies are included in Table 3-4, while the enthalpy profiles for the rate-determining step for both mechanisms of the reaction are shown in Figure 3-3 in comparison with those from the gas phase calculations. The complexation energies are weaker in solution by more that 6 kcal mol^{-1} compared to those in the gas phase because of the electrostatic interaction of the bulk solvent with the reacting complex; preference for complexation across the S=O bond is minimal in both cases.

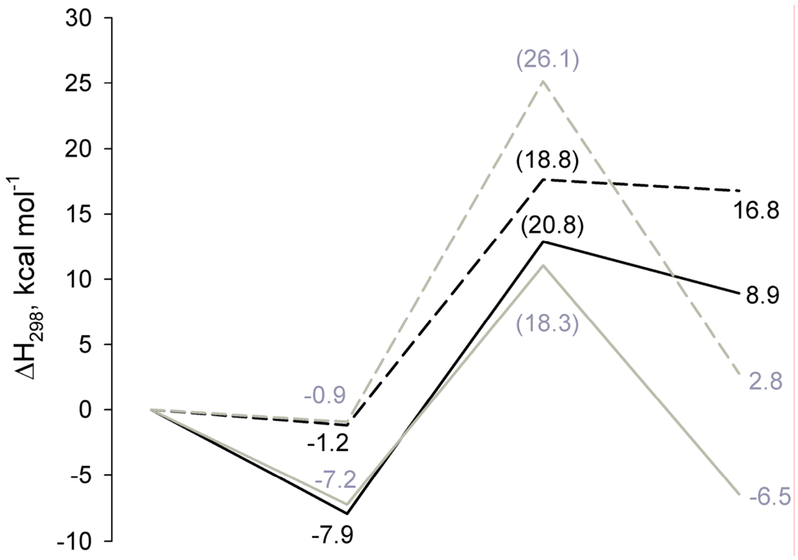


Figure 3-3. Enthalpy profiles for the rate-determining step of the reaction of HNSO with two water molecules across the S=O (black) or N=S (grey) bonds in the gas phase (solid lines) and in solution (dashed).

While the activation barrier for reaction across the S=O bond (black lines and values in Figure 3-3) decreases by 2.0 kcal mol^{-1}, the one for reaction across N=S increases by 7.8 kcal mol^{-1} in the solvent field compared to the gas phase. The influence of the solvent field can be further seen in comparison of the relative energies of the products of this first step, which are sulfurimidous and sulfuramidous acids complexes with one water molecule, for reaction across S=O and N=S bonds, respectively. Increases of 7.9 and 9.3 kcal mol^{-1}, respectively, were calculated going from the gas phase to the solvent field. An explanation can be found in the structural changes of the post-reaction complexes of the acids with water. Unlike for complexes and transition states, where the same mode of binding is observed in gas phase and solvent field calculations, one hydrogen bonding interaction is lost in the product complexes (Figure 3-3). In the bulk solvent the hydroxylation of sulfur with concerted protonation of either oxygen or nitrogen atoms of NSO group create the hydroxyl and amino groups in the products, for S=O and N=S reactions, correspondingly. These newly created OH and NH bonds play role of hydrogen bond donors towards oxygen atom of the second water, with lost of its proton interaction towards the hydroxyl oxygen. Inspite the disappearance of one intermolecular H-bond in each complex, which stabilized them better in a gas phase the complexation becomes even weaker in solution.

From the above, it is obvious that changes in energy upon solvation along the reaction coordinate are not uniform. These results are based on the use of water as the solvent. On the other hand, it is known from the rates of N-sulfinylamine hydrolysis and alcoholysis that while increases are found with increasing polarity of the solvent, the hydrogen bonding ability of the solvent plays a more crucial role.[94] Thus, in solvents unable to form hydrogen bonds with the solute, higher than first order rates in the solute were determined.[94] Therefore, it appears, similar to the many previous studies,[100,102,103,105,129] that the explicit treatment of the solvent molecules is more important for our study.

3.3.4. Conclusions

From studies on complexation of N-sulfinylamiline with two water molecules, B3LYP/6-31+G(2d,2p) was determined to be sufficiently accurate with respect to the BSSE. Seeing that it also is computationally inexpensive, we chose this model chemistry for following studies on the hydrolysis of N-sulfinyl species. Bulk solvent effects seem to play a less important role than the explicit inclusion of the solvent and can be neglected for the purposes of our studies.

Chapter 4.

Influence of the number of water molecules on the mechanism of N-sulfinylaniline hydrolysis[*]

4.1. Introduction

Our interest in the electronic and molecular structures of NSO species[49,110] is closely related to their reactivity. N-sulfinylamines (R–N=S=O) were first prepared by Michaelis in 1890[2] and their reaction with water was one on the first properties to be observed experimentally. While aromatic N-sulfinylamines are insoluble in water and hydrolyzed very slowly in it as well as in dilute acids, warm alkaline solutions or concentrated acids lead to their rapid hydrolysis.[5] Aromatic N-sulfinylamines in particular are widely employed in synthetic organic chemistry, as they readily undergo a variety of cycloaddition reactions to yield N,S-heterocycles (Diels-Alder reactions as both dienes and dienophiles,[130-132] 1,2-cycloadditions and 1,3-dipolar additions.[29,133] Common to all these reactions is the attack on sulfur of the NSO group, and hydrolysis can be considered as the prototype reaction. Therefore, an understanding of the initial steps of the hydrolysis reaction mechanism of N-sulfinylaniline is fundamental to its exploitation in similar reactions involving N-sulfinylamines.

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$$\mathrm{RNSO} + \mathrm{H_2O} \longrightarrow \mathrm{RNHS(O)OH} \longrightarrow \mathrm{RNH_2} + \mathrm{SO_2}$$

Scheme 4-1. Reaction of N-sulfinylamines with water.

The mechanism for hydrolysis of N-sulfinylamines is believed to proceed through nucleophilic addition of a water molecule to the NSO group with the formation of sulfinamic acid, followed by the acid's fast decomposition to sulfur dioxide and a primary amine (Scheme 4-1).[4] Aromatic N-sulfinylamines are known to be somewhat resistant towards water whereas aliphatic N-sulfinylamines hydrolyze more readily.[5] For N-sulfinylaniline (Ph–N=S=O), kinetics studies using ultraviolet spectroscopy showed neutral hydrolysis to be a slow process,[17,89] with an induction period of approximately four hours.[89] The reaction is complicated by autocatalysis from aniline, formed as a product of the reaction, which explains the relatively low activation energy of 9.88 kcal mol^{-1} in a 1:1 water/1,4-dioxane solution.[17] In the presence of pyridine as a base or with a combination of pyridine and a carboxylic acid the rate of reaction increases significantly.[89] General base catalysis was proposed for the hydrolysis in the presence of pyridine, where the formation of a pyridine–water complex increases the nucleophilic properties of water and facilitates its interaction with the electrophilic sulfur atom. This is proposed to be the rate-determining step of hydrolysis. It is a third order reaction, first order in each N-sulfinylaniline, water and pyridine, with an overall rate constant of $2.96 \times 10^{3}\ \mathrm{L^{2}\ mol^{-2}\ s^{-1}}$ and a low enthalpy of activation of 5.7 kcal mol^{-1} for the 20–40 °C temperature range.

For the combined catalysis by pyridine and a carboxylic acid, initial protonation of either nitrogen or oxygen atoms of the NSO group was predicted.[89] This would lead to an increase in the net positive charge on the sulfur atom and promote the addition of a water molecule to the NSO group. This acid catalysis is not part of the discussion in the present paper.

While literature data on the hydrolysis of N-sulfinyl compounds are limited,[17,89] the hydrolysis of their cumulated analogs, isocyanates (R–N=C=O), was studied intensively both experimentally[107,109,134] and computationally.[106] Based on their structural similarities, one might expect similar reactivities for these two classes of compounds. And while the NCO group is more or less linear whereas the NSO group is bent with a sulfur bond angle of 120.6º as determined from X-ray diffraction analysis,[52] the similar solvent kinetic isotope effects $k(H_2O)/k(D_2O)$ of 1.65 for PhNCO[107] and 1.73 for PhNSO[89] seem to support the idea of similar reactivities and maybe similar mechanisms in the hydrolysis of these compounds.

A second order dependence on water was found in the neutral hydrolysis of alkyl and aryl substituted isocyanates,[106,107,134] where one molecule acts as a general acid and the other as a general base. This is closely related to the base catalyzed hydrolysis of N-sulfinylaniline, if one water molecule is considered to take the role of the catalyst (pyridine). For the hydrolysis of 4-chlorophenyl isocyanate, however, a third order dependence with respect to water concentration was reported.[109] We therefore decided to explore the neutral hydrolysis of N-sulfinylaniline computationally to determine its mechanism and the number of water molecules involved.

4.2. Computational details

All geometry optimizations were performed with the Becke3[117] – Lee, Young and Parr (B3LYP) hybrid density functional[118] with the 6-31+G(2d,2p) basis set, using the

Gaussian 98 suite of programs.[115] This computational level best reproduces the observed geometry (X-ray analysis) of N-sulfinylaniline,[52] and the basis set superposition error[111] (BSSE) consists of less than 0.7 kcal mol^{-1} for the ternary complexes (counterpoise = 3, full geometry optimization).[*] All structures were optimized without constraints. The complexes and their transition states were studied in the gas phase, as it was found in similar studies of the hydrolysis of isocyanates[106] and amides[100] that the inclusion of the solvent as a dielectric continuum only leads to a small decrease in the activation barrier. Vibrational frequencies and zero-point vibrational energies (ZPVE) were obtained at the above level of theory. The identity of each transition state was additionally verified using the intrinsic reaction coordinate (IRC) method.[135,136] The total (E_{tot}) and ZPVE-corrected energies (E_{tot}+ZPVE) as well as the enthalpies of the complexes and their transition states are summarized in Table 4-1. Throughout the paper, we will report only the enthalpy term at standard state, unless stated otherwise. We chose enthalpies over Gibbs free energies because an enthalpy is available[89] for comparison. Furthermore, the entropy contribution ($-T\Delta S$) to the Gibbs free energy barrier, on average 5.8 kcal mol^{-1}, is practically independent of the number of water molecules: it varies from 5.1 to 6.5 kcal mol^{-1} without apparent pattern for 1–5 H_2O. Net atomic charges were obtained within the quantum theory of Atoms in Molecules[51] (QTAIM) with the AIMPAC module PROAIM.[137] The Natural Bond Orbital (NBO) program[138] (NBO 3.1) was used to study the charge transfer in the complexes.[139]

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[*] We used the counterpoise correction method to verify the applicability of our chosen level of theory, and the BSSEs obtained with full geometry optimization for three structures are shown in Table 4-1. Our results of the study of other methods (HF and MP2) with various basis sets will be summarized elsewhere.

4.3. Results and discussion

4.3.1. Approach to the problem

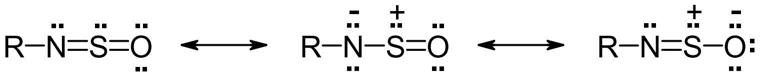
While the NSO group is commonly considered a heterocumulene and, from ^{17}O NMR and computational studies, the S=O bond is best described as a four-electron bond not unlike the carbonyl C=O bond, the electronic structure of N-sulfinyl species can be represented as a set of resonance structures, shown in Scheme 4-2. Obviously, a change of substituent on nitrogen can change the reactivity of the NSO group; nevertheless, sulfur is the most positive centre and either nitrogen or oxygen is considered as the negative end of the bond dipole. We chose to study the computationally expensive N-sulfinylaniline (**1**) (instead of the more common approach to substitute the phenyl group for a smaller methyl group or the H atom),[106] because it is the only compound for which quantitative experimental data are available, and for comparison with the reactivities of aliphatic N-sulfinyl species in a subsequent paper.

Table 4-1. Calculated total and zero-point vibrarional corrected energies as well as enthalpies at 298 K (au) of **1**, water, the water dimer and complexes **2–5** and their transition states for hydrolysis. Values in parentheses give counterpoise (CP) corrected energies.

	E_{tot}	E_{tot}+ZPVE	H_{298}
1	-759.811591	-759.711892	-759.703552
H_2O	-76.441069	-76.419706	-76.415926
$(H_2O)_2$	-152.890084	-152.843858	-152.837139
2a	-836.255744	-836.133041	-836.120484
2a-TS	-836.199402	-836.079012	-836.068877

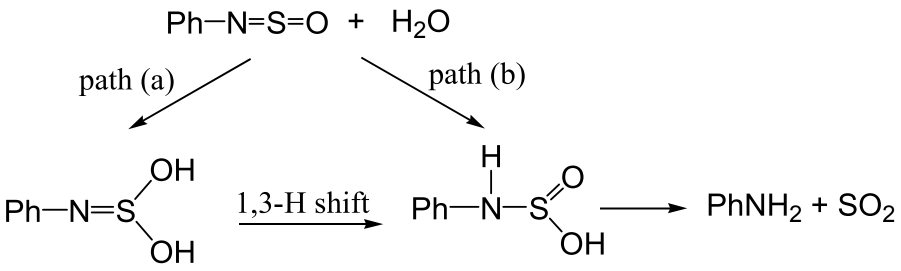
	E_{tot}	E_{tot}+ZPVE	H_{298}
2b-TS	-836.193196	-836.073030	-836.062605
3a	-912.710720	-912.562579 (-912.561490)[a]	-912.547481
3a-TS	-912.665029	-912.520710	-912.508745
3b	-912.708424	-912.560220 (-912.559117)[a]	-912.545030
3b-TS	-912.661079	-912.517559	-912.505502
4a	-989.164674	-988.991597	-988.973598
4a-TS	-989.120910	-988.952285	-988.937976
4b	-989.162650	-988.989247 (-988.987225)[b]	-988.971435
4b-TS	-989.120013	-988.954007	-988.939706
4c	-989.158246	-988.985327	-988.967235
4c-TSa	-989.115485	-988.946429	-988.931412
4c-TSb	-989.112714	-988.943772	-988.928953
5c	-1142.068493	-1141.844795	-1141.821378
5c-TSb	-1142.028754	-1141.811961	-1141.792257

[a] CP = 3, BSSE 0.7 kcal mol^{-1}. [b] CP = 4, BSSE 1.3 kcal mol^{-1}.



Scheme 4-2. Resonance structures of N-sulfinylamines.

The calculated net atomic charges of **1** confirm the idea of sulfur being the most electrophilic atom of the NSO group (Figure 4-1). Consequently, in a nucleophilic attack, the oxygen atom of the water molecule with a negative charge of –1.151 au is expected to attack the sulfur atom. A proton can then be transferred to either the oxygen (attack across the S=O bond, path (**a**)) or the nitrogen (attack across the N=S bond, path (**b**)) atom of the NSO group (Scheme 4-3), similar to hydrogen isocyanate hydrolysis.[106]



Scheme 4-3. Mechanisms of reaction of N-sulfinylaniline with water.

Reaction across the S=O bond includes two steps, the protonation of oxygen with formation of N-phenylsulfurimidic acid and a subsequent 1,3-hydrogen shift to form the intermediate N-phenylsulfinamic acid, which decomposes with formation of the final products, aniline and sulfur dioxide. Reaction across the N=S bond, on the other hand, is a one step process that yields N-phenylsulfinamic acid directly.

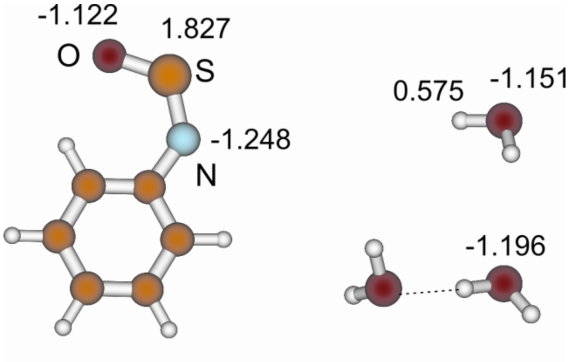


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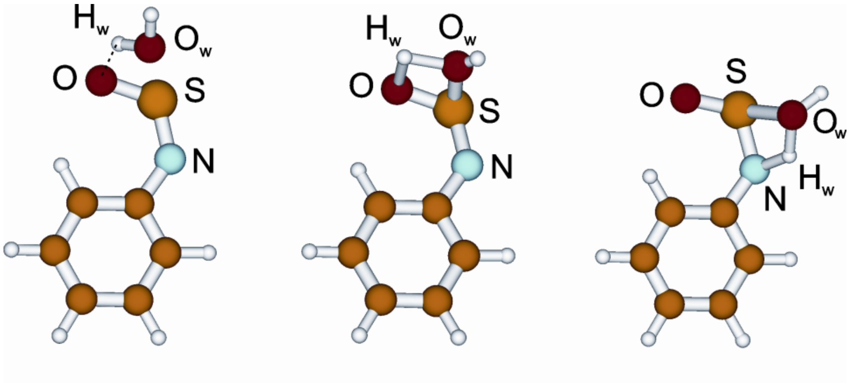
Figure 4-1. Selected calculated charges of atoms of interest in N-sulfinylaniline (**1**), water and the water dimer.

Structures from the interaction across the S=O bond are denoted with the letter “**a**”, those from the interaction across the N=S bond with the letter “**b**”. Structures with interactions across both S=O and N=S bonds are given the letter “**c**”. The subscript “**w**” is used for the designation of atoms that belong to water molecules. In the description of complexes with multiple water molecules, “H_{w1}” determines a hydrogen atom of the water molecule that interacts with the oxygen atom of the S=O bond, and “H_{w2}” a hydrogen atom of the water molecule that interacts with the nitrogen atom of the N=S bond.

In the following, we examine how the preference for reaction across the N=S or the S=O bond depends on the number of water molecules participating in the reaction. The complete reaction coordinate for the hydrolysis of **1** is presented for the participation of two water molecules.

4.3.2. Reaction of N-sulfinylaniline with one water molecule

Interaction with one water molecule is the simplest model in the study of the hydrolysis of N-sulfinylaniline (**1**). Even though the formation of a pre-reaction complex usually precedes the reaction, we were only able to locate complex **2a** with water situated on top of the S=O bond (Figure 4-2). Our search for **2b** with water on top of the N=S bond produced numerous hydrogen-bonded complexes, but there does not seem to be a stationary point on the potential energy surface for **2b**.



2a **2a-TS** **2b-TS**

Figure 4-2. Optimized complex **2a** for the interaction of **1** with one water molecule, and transition states **2a-TS** and **2b-TS** for the addition of water across the S=O and the N=S bond of **1**, respectively. Weak interactions in the transition states are given with solid lines.

Table 4-2. Selected geometrical parameters (distances in pm, angles in degrees) of N-sulfinylaniline (**1**) and its complexes with 1, 2, 3 and 5 water molecules, **2–5**. Values in parentheses show the change in the distances upon complexation with respect to **1**.

	1	**2a**	**3a**	**3b**	**4a**	**4b**	**4c**	**5c**
SO	148.1	148.7	149.2	147.7	149.2	147.4	148.7	148.5
		(+0.6)	(+1.1)	(-0.4)	(+1.1)	(-0.7)	(+0.6)	(+0.4)
NS	153.4	153.0	152.8	154.4	152.7	154.3	153.5	153.8
		(-0.4)	(-0.6)	(+1.0)	(-0.7)	(+0.9)	(+0.1)	(+0.4)
S…O$_w$		319.0	314.6	377.9	297.9	296.2	284.0	271.8
O…H$_{w1}$		240.4	192.0		195.9		197.6	189.2
N…H$_{w2}$				199.4		194.7	236.4	196.9
NSOO$_w$		101.9	109.8	131.2	105.0	107.0	106.8	109.3
NSOH$_{w1}$		104.3	116.8		128.1		95.8	103.8
OSNH$_{w2}$				177.2		170.2	122.0	171.8

The intermolecular distance between the sulfur atom and the oxygen atom of water (O_w) in **2a** is 319.0 pm (Table 4-2), with the water molecule forming a close to perpendicular alignment with the plane of **1** (the $NSOO_w$ dihedral angle is 101.9°). Even though this distance is less than 325.0 pm, which is the accepted value for the sum of the van der Waals radii of oxygen and sulfur atoms,[140] according to an analysis of the electron density within QTAIM, there is no interaction between these atoms. The complex **2a** is stabilized by a hydrogen bond with an $O \ldots H_w$ distance of 240.4 pm and an OH_wO_w angle of 130.8°. This non-ideal hydrogen bond geometry is in good agreement with the small stabilization energy of 0.6 kcal mol^{-1} upon complex formation (Figure 4-3). The perpendicular attack on sulfur is in stark contrast to the in-plane attack of water on the carbon atom in HNCO (16).

The activation enthalpy for the reaction of **1** with one water molecule is very high with 31.8 and 35.7 kcal mol^{-1} for transition states **2a-TS** and **2b-TS**, respectively (Figure 4-2 and Table 4-3). The barriers are calculated from the enthalpies of the reagents for lack of complex **2b** as a reference. The reaction across the S=O bond (path (**a**)) is favoured by 3.9 kcal mol^{-1}.

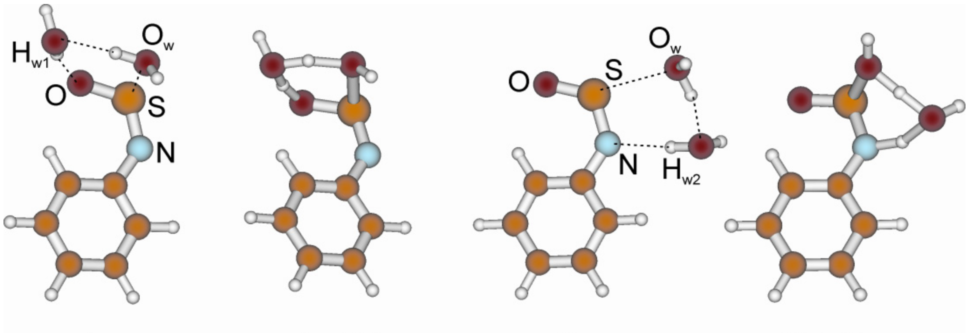
Table 4-3. Enthalpies (kcal mol^{-1}) of complex formation and activation at 298 K for **1** with 1, 2, 3 and 5 water molecules.

n H_2O	across S=O				across N=S			
		$-\Delta H_{bind}$		$\Delta H^{\neq}$		$-\Delta H_{bind}$		$\Delta H^{\neq}$
1	**2a**	0.6	**2a-TS**	32.4 (31.8)[b]	**2b**	–[a]	**2b-TS**	– (35.7)[b]
2	**3a**	7.6	**3a-TS**	24.3	**3b**	6.0	**3b-TS**	24.8
3	**4a**	14.0	**4a-TS**	22.4	**4b**	12.6	**4b-TS**	19.9
	4c	10.0	**4c-TSa**	22.5	**4c**	10.0	**4c-TSb**	24.0
5	**5c**	24.0			**5c**	24.0	**5c-TSb**	18.3

[a] Complex not found. [b] Based on the enthalpies of the reagents, **1** and water.

4.3.3. Reaction of N-sulfinylaniline with two water molecules

Introduction of a second water molecule allows the formation of a water dimer, which increases the nucleophilic properties of water towards the electrophilic sulfur. The negative charge on the oxygen atom of the original water molecule is increased by 0.045 au from –1.151 au in the monomer to –1.196 au in the dimer (Figure 4-1). Unlike in the interaction with one water molecule, both pre-reaction complexes **3a** and **3b** were located (Figure 4-3).



3a **3a-TS** **3b** **3b-TS**

Figure 4-3. Optimized complexes **3a** and **3b** for the interaction of **1** with the water dimer, and transition states **3a-TS** and **3b-TS**.

This is also different from HNCO hydrolysis, in that pre-reaction complexes of HNCO with water chains (dimers and trimers) were not found.[106] Selected geometrical parameters of **3a** and **3b** are shown in Table 4-2. Stabilization in both complexes is achieved through an S…O_w interaction along with hydrogen bond formation. The S…O_w interaction is mostly due to the electrostatic attraction between sulfur and water oxygen atoms, combined with some charge transfer from the lone pair of O_w into the antibonding orbital of the N=S bond ($\pi^*_{N=S}$), found for **3a** from an NBO analysis. As expected, complexation across the S=O bond primarily affects the SO bond length, and complexation across the N=S bond mainly influences the NS bond length. The lengthening of both bonds in their respective complexes to a similar degree coincides with the contraction of the second cumulated double bond (the changes in bond lengths from **1** are given in Table 4-2 for ease of comparison). But while **3a** exhibits the close to perpendicular arrangement between the plane of **1** and the water molecule complexed to sulfur that we also observed for **2a**, there is a much larger deviation from 90° found in **3b**. In addition, the S…O_w intermolecular distance in **3b** is significantly larger than that in **3a**, suggesting a non-ideal arrangement of its constituent fragments. These findings are nicely in accord with those for complexation with one water molecule and offer an explanation as to why **2b** could not be located. The requirements of a perpendicular attack of O_w on sulfur and an in-plane N…H_wO hydrogen bond (the $OSNH_{w2}$ dihedral in **3b** is close to 180°, Table 4-2) prevent the formation of **2b** and render **3b** somewhat strained. This interpretation is supported by the relative energies of **3a** and **3b**, with **3b** less stable by 1.6 kcal mol^{-1}. The formation of 6-membered cycles reduces the strain that exists in the 4-membered cycles of transition states **2a-TS** and **2b-TS** in the reaction of **1** with one water molecule. The full reaction coordinates for the reaction of N-sulfinylaniline (**1**) with two water molecules are given in Figure 4-4 for water addition across the S=O bond (path (**a**)) and in Figure 4-5 for addition across the N=S bond (path (**b**)).

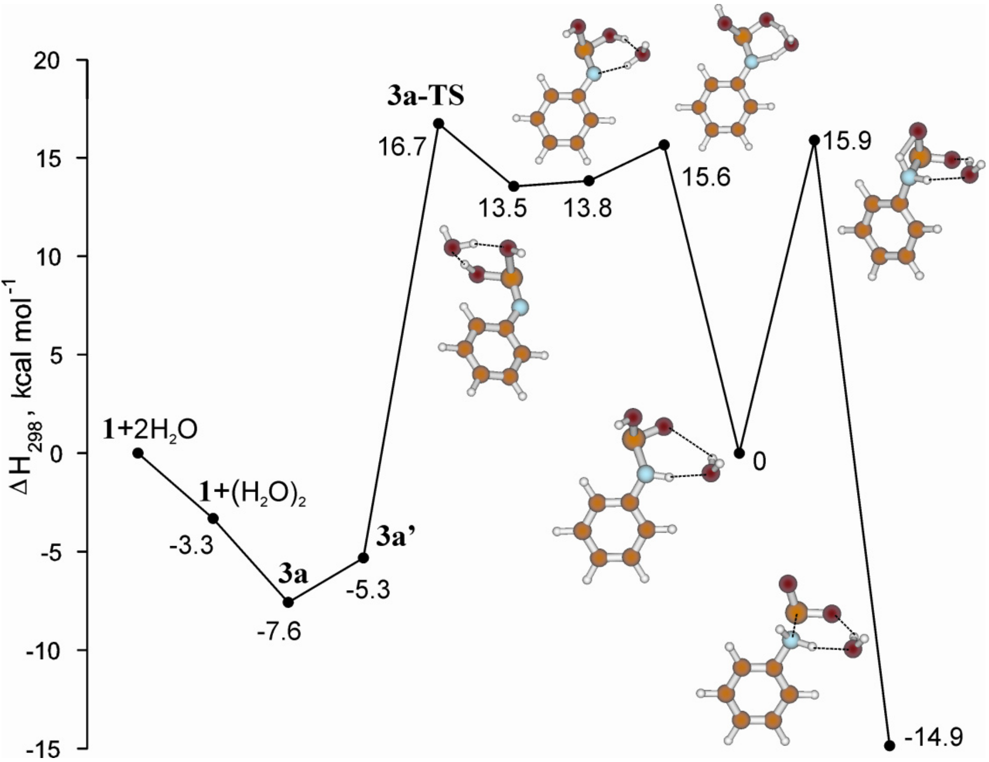


Figure 4-4. Enthalpy profile for the reaction of **1** with two water molecules, path (**a**), attack across the S=O bond.

The formation of **3a** is favourable by 7.6 kcal mol^{-1} with a stabilization of 4.3 kcal mol^{-1} in addition to the 3.3 kcal mol^{-1} of energy gain due to water dimer formation. The experimental enthalpy of association in the water dimer was found to be –3.59 ± 0.5 kcal mol^{-1} at 373 K.[113] As was proposed,[89] hydration of sulfur with protonation of oxygen of **1** is indeed the rate-determining step of the reaction. The activation enthalpy is 24.3 kcal mol^{-1}, a value that includes 2.3 kcal mol^{-1} due to the loss of planarity in **1** (**1** in **3a** is planar whereas in both the complex **3a’** and the transition state **3a-TS**, CCNS and CNSO torsional angles are 6.1 and 23.6°, respectively). The torsions allow a decrease of the $S\ldots O_w$ interatomic distance from 314.6 pm in **3a** to 299.4 pm in **3a’**, and this shortening of about 15 pm increases the strength of the interaction and facilitates the hydration of sulfur. Further along the reaction path, the water molecule in the primary reaction product (the complex of N-phenylsulfurimidic acid and water) changes its orientation, which allows it to abstract a proton from one hydroxyl group of N-phenylsulfurimidic acid and simultaneously protonate the acid’s nitrogen atom. This “water-assisted” 1,3-hydrogen shift[*] requires only 1.8 kcal mol^{-1} and yields the complex of N-phenylsulfinamic acid and water, in which the orientation of the water molecule cannot facilitate the protonation of nitrogen. Thus the unassisted decomposition of N-phenylsulfinamic acid into the complex of aniline, sulfur dioxide and water requires the large activation enthalpy of 15.9 kcal mol^{-1}. We find exactly the same value, 15.9 kcal mol^{-1}, for the enthalpy of activation for the decomposition of N-phenylsulfinamic acid in the absence of any water.

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[*] We of course only present a subset of possibilities of hydrogen bond formation on the potential energy surface for reaction of N-sulfinylaniline (**1**) with two water molecules. We believe that the chosen structures explain the formation of the final products and in some cases show the importance of the explicit treatment of water along the reaction pathway. Thus, we exclude, for example, the non-assisted 1,3-hydrogen shift in N-phenylsulfurimidic acid.

The formation of **3b** is less favourable than that of **3a**, as discussed above, and only shows a stabilization of 2.7 kcal mol^{-1} in addition to the stabilization from water dimer formation (Figure 4-5). The reaction of the water dimer with **1** again is the rate-determining step and an activation enthalpy of 24.8 kcal mol^{-1} is required, which is only 0.5 kcal mol^{-1} higher than (and therefore comparable with) that for the reaction across the S=O bond. As in Figure 4-4, this activation barrier includes 1.8 kcal mol^{-1} due to the torsion of the NSO group out of the plane of the aromatic ring (the CCNS and CNSO torsional angles of 46.0 and 7.9°, respectively, are similar in the complex **3b'** and in the transition state **3b-TS**). As in **3a'**, the $S\ldots O_w$ interaction is strengthened through a decrease in the intermolecular distance by 37 pm, from 377.9 pm in **3b** to 340.9 pm in **3b'**. Unlike **3a-TS** in Figure 4-4, **3b-TS** in Figure 4-5 yields the complex of N-phenylsulfinamic acid and water directly. Hydrogen bonding to the hydroxyl group of N-phenylsulfinamic acid allows for a reorientation of the water molecule that moves it into the ideal position for protonation of the nitrogen atom and facilitates the decomposition of the acid. In this water-assisted decomposition the activation barrier is decreased with respect to the non-assisted barrier in Figure 4-4 by more than 10 kcal mol^{-1} to a mere 5.5 kcal mol^{-1}. This finding, as well as the assistance of water in the 1,3-hydrogen shift, which was discussed in the previous mechanism (path (**a**), Figure 4-4), demonstrates the importance of the explicit treatment of water molecules in these hydrolysis reactions, a conclusion that was drawn earlier in amide[105,141] and isocyanate hydrolysis.[106]

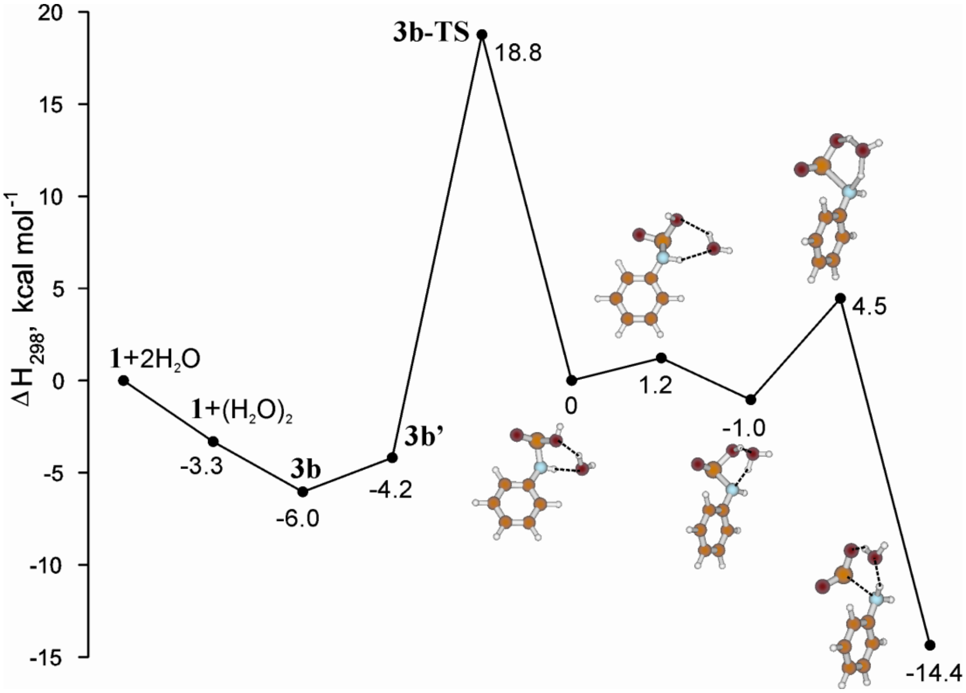

Figure 4-5. Enthalpy profile for the reaction of **1** with two water molecules, path(**b**), attack across the N=S bond.

The increase in the number of water molecules from one to two allows a decrease in the activation barriers for the hydrolysis reaction of approximately 8 to 11 kcal mol^{-1} (from 32.4 in **2a-TS** to 24.3 kcal mol^{-1} in **3a-TS**, and from 35.7[*] in **2b-TS** to 24.8 kcal mol^{-1} in **3b-TS**). This is at least partially due to the relief of strain on going from 4-membered cycles in **2a-TS** and **2b-TS** to the 6-membered cycles in **3a-TS** and **3b-TS**, as was mentioned earlier. The N=S bond demonstrates a higher sensitivity to this effect, because the hydroxyl group of the second water molecule now approaches **1** in the NSO plane (with a OSNH$_{w2}$ torsional angle of 177.2°, Table 4-2), where the nitrogen lone pair lies, confirming the idea of donor/acceptor directionality upon hydrogen bond formation.

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[*] As discussed above, this value is not based on the enthalpy of the pre-reaction complex, but rather on the enthalpies of the reactants, **1** and water.

Our finding about the almost equal probability of both mechanisms due to activation barriers of 24.3 kcal mol^{-1} for path (a) and 24.8 kcal mol^{-1} for path (**b**) seems quite different from the results for HNCO hydrolysis.[106] Calculations in the gas phase and in a solvent field based on the polarizable continuum model (PCM) with MP2/6-31G(d,p) along with other methods have shown that even though two water molecules are important for HNCO hydrolysis, in all cases studied (the presence of one, two and three water molecules was considered) reaction across the N=C bond is favoured. With two water molecules, for example, the activation energy decreases from 28 kcal mol^{-1} for reaction across the C=O bond to 11 kcal mol^{-1} for reaction across the N=C bond (values reported in the paper are E_{tot}+ZPVE, given in kJ mol^{-1}, and based on the corrected energies of the reactants). In the presence of a solvent field this difference becomes much smaller, though, 15 kcal mol^{-1} for reaction across C=O to 18 kcal mol^{-1} for reaction across N=C (single point energy calculations on the gas phase optimized geometries). To be able to compare results more directly, we also report ZPVE corrected energies in Table 4-1. From these, we obtain an activation energy of 19.2 kcal mol^{-1} for reaction across S=O and 21.1 kcal mol^{-1} for that across N=S, both based on the corrected energies for **1** and two water molecules. Obviously, the direct comparison is limited by the different substituents (phenyl in **1** and hydrogen in HNCO), and further analysis of the difference between RNSO and RNCO hydrolysis will only be reported in our forthcoming paper on substituent effects in the reactivity of NSO species.[*]

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[*] A change in mechanism seems to be a common trait in the hydrolysis of NSO species with electron donating substituents. For HNSO, the transition states for reaction with one water molecule are isoenthalpic, and the different mechanisms for CCl_3NSO hydrolysis do not seem to exhibit a dependence of preference on the number of water molecules.

4.3.4. Reaction of N-sulfinylaniline with three and five water molecules

Compared to the reaction of N-sulfinylaniline with one and two water molecules, water trimer complexation to **1** in **4a** and **4b** (Figure 4-6) further increases the flexibility of the systems due to formation of 8-membered cycles. As can be seen from Table 4-2, the lengths and, consequently, the strengths of the S=O and N=S bonds do not differ much in complexes of **1** with two (**3a, 3b**) and three (**4a, 4b**) water molecules. But inclusion of the third water molecule significantly strengthens the weak $S \ldots O_w$ interaction. The effect is especially pronounced for complexation of the water trimer across the N=S bond. The $S \ldots O_w$ intermolecular distance decreases by 81.7 pm, from 377.9 pm in **3b** to 296.2 pm in **4b** (Table 4-2). For complexation towards the S=O bond this effect is less pronounced, but still important, as the $S \ldots O_w$ distance decreases by 16.7 pm going from **3a** to **4a**. Along with this, a contraction of the $N \ldots H_{w2}$ hydrogen bond by 4.7 pm is found going from **3b** to **4b**. In contrast, comparing **3a** and **4a**, the $O \ldots H_{w1}$ hydrogen bond distance increases by 3.4 pm.

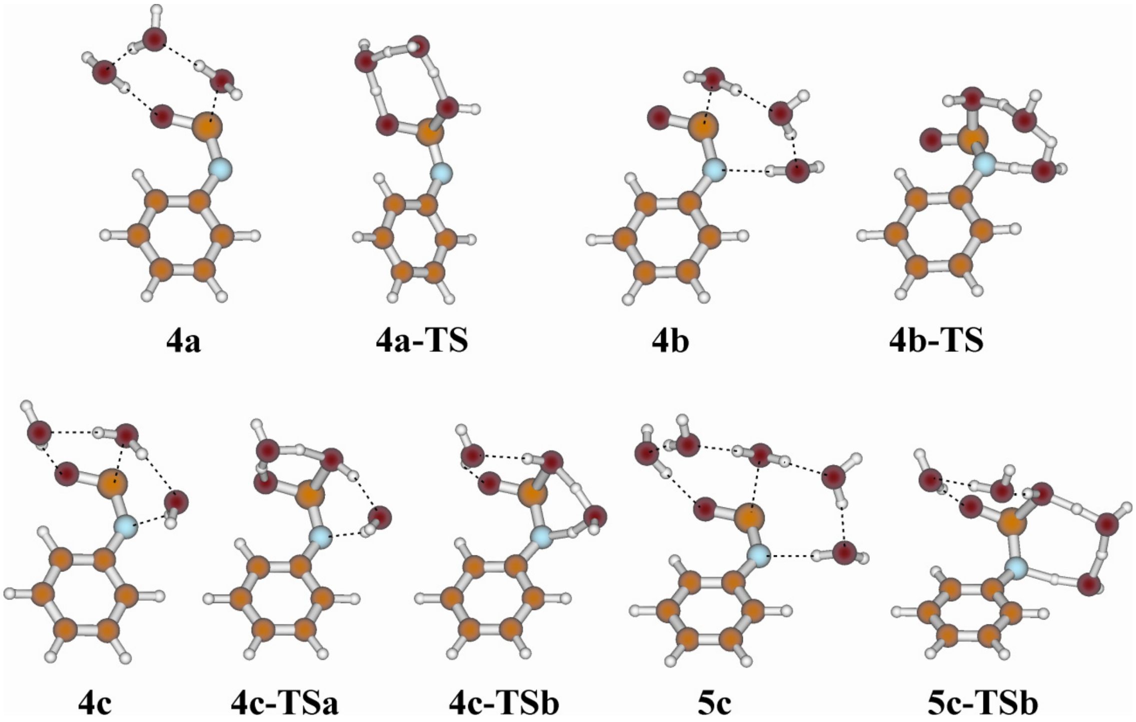

Figure 4-6. Optimized structures **4a**, **4b, 4c** and **5c** for the interaction of **1** with three and five water molecules, and transition states **4a-TS**, **4b-TS, 4c-TSa, 4c-TSb** and **5c-TSb** for hydrolysis.

The strengthening of the S…O_w intermolecular interaction in complexes **4a** and **4b** further decreases the activation barrier for hydrolysis by approximately 2 to 5 kcal mol^{-1} for the two pathways (from 24.3 in **3a-TS** to 22.4 kcal mol^{-1} in **4a-TS** for the reaction across the S=O bond, and from 24.8 in **3b-TS** to 19.9 kcal mol^{-1} in **4b-TS** for the reaction across the N=S bond (Table 4-3). The one-step mechanism, reaction across the N=S bond, is now favoured by 2.5 kcal mol^{-1}, as two requirements, "perpendicular" attack on sulfur ($NSOO_w$ torsional angle 107.0°) and in-plane protonation of nitrogen ($OSNH_{w2}$ torsional angle 170.2°) are fulfilled without apparent strain.

The two different attacks on the NSO group are combined in **4c**, where hydrogen bonding to both nitrogen and oxygen atoms of the NSO group assists in the strengthening of the S…O_w interaction, which is 12.2 and 13.9 pm shorter than in **4a** and **4b**, respectively (Table 4-2). But both hydrogen bonding interactions are weaker in **4c** than in either **4a** or **4b**. The increase in the O…H_{w1} distance in **4c** from **4a** by 1.7 pm is considered to be insignificant, and this is reflected in the enthalpy barrier of 22.5 kcal mol^{-1} for reaction via **4c-TSa**, which is similar to the activation enthalpy of 22.4 kcal mol^{-1} for **4a-TS**. In contrast, the increase in the N…H_{w2} intermolecular distance in **4c** from **4b** by 41.7 pm, together with a less favourable $OSNH_{w2}$ dihedral angle of 122.0º in **4c**, contributes to **4c-TSb** being less stable than **4b-TS** and increases the activation barrier by 4.1 kcal mol^{-1}.

As can be seen from Figure 4-3 and Figure 4-6, the structures for **4c-TSa** and **4c-TSb** are very similar to those obtained for reaction of **1** with two water molecules, **3a-TS** and **3b-TS**. The third water molecule in complex **4c** and consequently in **4c-TSa(b)** might be seen as a bystander that does not react directly with **1**, yet it participates through hydrogen bond formation, which weakens both S=O and N=S bonds (Table 4-2). The elongation of these bonds from those in **1** is less efficient than in **3a** and **3b** and consists of 0.6 pm for the S=O and 0.1 pm for the N=S bond in **4c**, but the weakening of the bonds of the NSO group is accompanied by a significant shortening of the S…O_w intermolecular distance in **4c** by 30.6 and 93.9 pm from **3a** and **3b**, respectively, which facilitates hydrolysis. This is reflected in a decrease in the activation barrier (by 2.2 kcal mol^{-1} in **4c-TSa** compared to **3a-TS**, and by 0.8 kcal mol^{-1} in **4c-TSb** compared to **3b-TS**).

Complex **5c** (Figure 4-6) represents the combination of **4a(b)** and **4c** in that both points of attack to the NSO group are connected as in **4c**, but the strain in **4c** is removed by the inclusion of water molecules, similar to **4a** and **4b**. The S…O_w intermolecular distance of 271.8 pm in **5c** is found to be the shortest among all complexes studied. The O…H_{w1} distance in **5c** is shorter than in both **4a** and **4c**, whereas the N…H_{w2} interaction is much shorter (by 39.5 pm) in **5c** than in **4c**, but longer by 2.2 pm compared to **4b**. The increase in the number of water molecules up to five further decreases the activation enthalpy for the hydrolysis reaction (only the reaction across the N=S bond was studied), but the barrier through **5c-TSb** is only 1.6 kcal mol^{-1} smaller than that in the corresponding reaction with three water molecules, **4c-TSb**.

Our results from the study of the influence of the number of water molecules in the hydrolysis of N-sulfinylaniline (**1**) are summarized in Figure 4-7, which shows the decrease in the activation enthalpy with an increase in the number of water molecules for both pathways, reaction across the S=O and the N=S bond. For the reaction across N=S with one water molecule, the grey zone in Figure 4-7, see the discussed above.[5] The reaction barriers with one water molecule are prohibitively large, and so two water molecules are important for hydrolysis, as is suggested by the solvent isotope effect.[89] Similar conclusions were drawn in the computational study of HNCO hydrolysis.[106] However, there is a crossover in mechanism at this point, and participation of a third water molecule only benefits the reaction across the N=S bond, in contrast to HNCO hydrolysis.[106] Such a third order dependence on water concentration has been proposed for the hydrolysis of the related 4-chlorophenyl isocyanate.[109] Figure 4-7 also suggests that the values for the enthalpy barriers are more or less converged for both pathways (with three water molecules for attack across S=O and five water molecules for that across N=S) and that larger numbers of water molecules need not be considered. The "converged" values for the activation enthalpy of about 23 kcal mol^{-1} for path (a) and 18 kcal mol^{-1} for path (b) are obviously still much higher than the experimentally determined values[89] of 9.88[17] and 5.7 kcal mol^{-1}. But as both experimental barriers were determined for a catalyzed hydrolysis (autocatalysis from aniline in the former case, pyridine catalysis in the latter), this is not surprising.

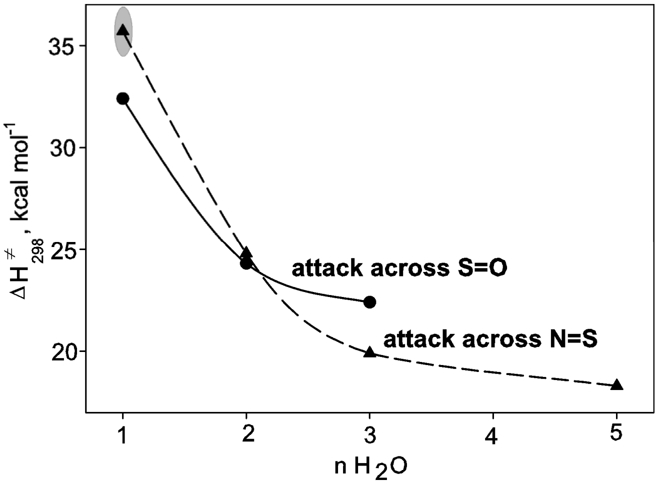

Figure 4-7. Dependence of the activation barrier of the hydrolysis reaction on the number of water molecules. See text for the grey zone.

4.4. Conclusions

We have presented a computational study on complexes of N-sulfinylaniline (Ph–N=S=O, **1**) with one to three and five water molecules and on the mechanism of neutral hydrolysis of **1**. While the complex of **1** with one water molecule does not possess an interaction between the sulfur atom and the water oxygen atom, water chains of two, three and five molecules led to increasingly strong S…O interactions. In these complexes, water attacks on sulfur close to perpendicular to the NSO plane.

Two mechanisms have been investigated for reaction of **1** with one to three water molecules, hydration of the sulfur atom with protonation of either oxygen or nitrogen atoms of the NSO group. The full reaction coordinate was probed for hydrolysis with two water molecules, and S…O interaction with proton transfer from water is found to be the rate-determining step in both mechanisms. Unrealistically high activation barriers are found for reaction with one water molecule, and two water molecules are important for hydrolysis. This is in good agreement with the first order dependence in both water and base that was observed for the base catalyzed reaction, if one water molecule is considered to take the role of the base. Reaction across the S=O bond is preferred with one water molecule, whereas an increase in the number of water molecules leads to a change in mechanism. For two water molecules, both mechanisms are equally probable; for three water molecules reaction across the N=S bond is favoured. As expected, the calculated enthalpies of activation for the neutral hydrolysis reaction are several kcal mol^{-1} larger than the experimentally determined barriers for the base catalyzed reaction.

The results presented here have revealed differences between PhNSO and HNCO, the smallest member of the related isocyanates, in both complexation with water and mechanism for hydrolysis with an increasing number of water molecules. We are currently investigating this further with a study of substituent effects in N-sulfinylamine hydrolysis.

Chapter 5.

Hydrolysis of *N*-sulfinylamines and isocyanates: A computational comparison[*]

5.1. Introduction

N-Sulfinylamines, R–N=S=O, were synthesized for the first time more than a century ago[2] and have since found wide application in synthetic organic chemistry. Various reactions resulting in the formation of N,S-heterocycles have been explored, including 1,2-cyclo-, 1,3-dipolar- and 1,4-cycloaddition reactions, where N-sulfinylamines can act as dienes and dienophiles,[24,60] as well as reactions with "active" hydrogen atoms.[24] When handling a compound, one of the first properties of interest is often its reactivity with water. Curiously, therefore, while the synthetic value of N-sulfinylamines has been well explored, their hydrolysis, a seemingly straightforward reaction, is not well understood. In particular, the fact that the substituent R has a dramatic effect on the reactivity of compounds R–N=S=O with water[19,24] has not been investigated extensively. While the aliphatic N-sulfinylamines are reported to hydrolyze readily, the aromatic compounds and N-sulfinylhydrazides (R–CO–NH–N=S=O) are less moisture-sensitive, and N-sulfinylhydrazines (R–NH–N=S=O) do not react with water.[19] Many of these general observations are unfortunately not supported by quantitative data,

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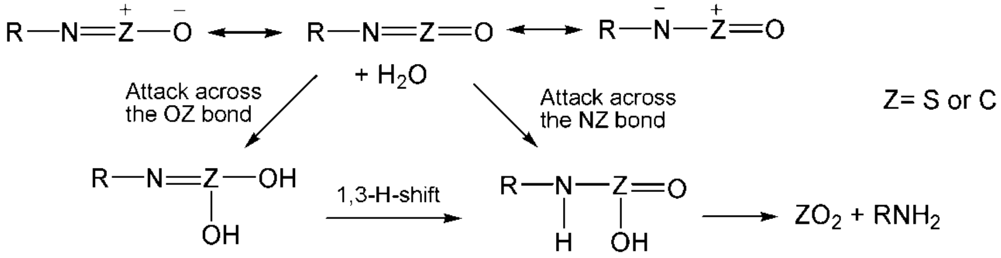
and there are only a few kinetic studies on the hydrolysis of aromatic N-sulfinylamines.[17,89] Consequently, an understanding of the effect of the substituent on the reactivity of N-sulfinyl species with water is desirable.

While data from the related and more thoroughly studied alcoholysis reaction could be used for reference,[24,25,92-94] another interesting prospective for comparison is offered in the form of the much better known isocyanates, R–N=C=O. At first glance, both N-sulfinylamines and isocyanates possess terminal cumulated double bonds[142,143] and similar resonance structures[60,142] as shown in Scheme 5-1, where Z is either sulfur or carbon, and could therefore be expected to show similar reactivity. On the other hand and in contrast to N-sulfinylamines, for isocyanates the aromatic compounds were shown to be more reactive than the aliphatic compounds.[143,144]



Scheme 5-1. Mechanisms of reaction with water of N-sulfinylamines and isocyanates.

With a few exceptions,[27,142,145] the known reactions of N-sulfinylamines and isocyanates proceed through interaction across the N=S or N=C bond, and if both π and σ bonds are broken, this results in the evolution of SO_2 or CO_2, respectively.[60] This is the case in their hydrolyses, where primary amines are formed as products (Scheme 5-1). The neutral hydrolysis is a slow process for both N-sulfinylamines and isocyanates but the reaction can be catalyzed by both acids and bases. In the base catalyzed reaction, the complexation of a tertiary amine to water increases the nucleophilicity of the water molecule and thus facilitates the hydroxylation of the sulfur or carbon atom, with hydroxylation being the rate-determining step of the reaction.[89,146] In this respect, the importance of the formation of dimeric and trimeric agglomerates of water or alcohol molecules has been described,[94,107-109] and the participation of chains of water molecules in hydrolysis reactions is supported by the rate increase in non-coordinating solvents.[89,146] The similarity of the hydrolyses of N-sulfinylamines and isocyanates seems to be established from a rough comparison of available kinetic parameters, even though a thorough comparison is impossible due to the lack of identical experimental conditions. The enthalpies of activation of 5.7 and 5.9 kcal mol^{-1}, along with activation entropies of –51 and –58 e.u., determined for the base-catalyzed hydrolysis[89] and methanolysis,[93] respectively, of N-sulfinylaniline (Ph–NSO) do not differ much from the values of 8.2 kcal mol^{-1} and –44.5 e.u. given for the non-catalyzed methanolysis of *p*-chlorophenyl isocyanate.[146] The nearly identical kinetic isotope effects k_H/k_D of 1.73[89] and 1.65[107] seem to further support the like reactivity of these two classes of compounds.

The mechanism for hydrolysis was proposed to consist of hydroxylation of sulfur or carbon and protonation of the NSO or NCO group (Scheme 5-1).[89,108] This was confirmed in computational studies for the hydrolysis of N-sulfinylaniline with 1-5 water molecules[147] and for isocyanic acid in the presence of 1-3 water molecules.[106] In fact, two mechanisms are possible, a one-step reaction across the N=S or N=C bond and a two-step reaction across the S=O or C=O bond with formation of sulfurimidic or carbonimidic acid and subsequent 1,3-hydrogen shift to give the unstable sulfinamic or carbamic acids, respectively (Scheme 5-1). Interestingly, while both mechanisms are feasible for N-sulfinylaniline,[147] isocyanic acid predominantly reacts through the N=C bond.[106] After all the similarities in reactivity listed above, such a dissimilarity is not entirely unexpected, though, because the two cumulated systems are electronically rather different. While the two π bonds in the NSO group are parallel and are best described as a conjugated system,[39,40] those in the NCO group are orthogonal,[146] but the effect of this difference in electronic structure on the reactivity toward water is not immediately obvious.

In this paper, we present the comparative study of the hydrolysis of substituted N-sulfinylamines and isocyanates with 1-3 water molecules to determine the relative reactivity within and between these classes of compounds, the preferred mechanism as well as any substituent effect on the activation energy or mechanism that would account for the experimental findings.

5.2. Computational details

All calculations were performed with the Becke3[117] – Lee, Young and Parr[118] hybrid density functional (B3LYP)[148] with the 6-31+G(2d,2p) basis set, using the Gaussian 98[115] and Gaussian 03[116] suites of programs. We have chosen this model chemistry based on its very good performance in the reproduction of experimentally observed geometries and dipole moments of N-sulfinylamines[12,36,44,53,122] and isocyanates.[149-153] The accuracy of the calculations was verified by the counterpoise correction (CP) method,[111] in that basis set superposition errors of less than 0.7 and 1.3 kcal mol^{-1} were determined with geometry optimization for the ternary (CP = 3) and quaternary (CP = 4) complexes of N-sulfinylaniline with two and three water molecules, respectively.[147] All geometries were fully optimized. In several cases, geometrical constraints were used in preliminary optimizations, followed by the release of all constraints and a tight optimization. The nature of saddle points was verified by frequency calculations.

We chose to use gas phase calculations throughout because although it is known that the rates of hydrolysis or alcoholysis reactions of N-sulfinylamines[89,94] and isocyanates[146] increase with increasing solvent polarity, the specific interactions of the reactant with the solvent are believed to have a more significant effect on the reaction rate and on the number of participating water molecules.[89,94,108,146]

To be consistent with our previous paper on the hydrolysis of N-sulfinylaniline,[147] we will use the enthalpy term (ΔH_{298} and $\Delta H^{\ddagger}_{298,}$ kcal mol^{-1}) throughout. The electronic and zero-point energy (unscaled) corrected energies, the enthalpies of the modeled molecules, complexes and transition states, as well as the free energies, where these were used in estimations of rate constants, are summarized in Table B-1 of Appendix B. The entropy contribution -TΔS for hydrolysis of the N-sulfinylamines, averaged for the different substituents and based on the pre-reaction complexes, consists of 5.9 kcal mol^{-1}, independent of the number of water molecules. However, when based on the energies of the reactants rather than the complexes, the entropy contribution to the reaction barrier, averaged for both N-sulfinylamines and isocyanates, was determined to be additive, with 11.5, 22.9 and 33.1 kcal mol^{-1} for one, two and three water molecules, respectively.

Atomic charges and weak bonding interactions in the molecules, complexes and transition states (TS) were determined from the electron density within the quantum theory of Atoms in Molecules (QTAIM),[51] using the AIMPAC series of programs.[137] Only the relevant results are included in the present paper.

5.3.Results and discussion

5.3.1. General considerations

With a similar computational approach to that used in the study of the hydrolysis of N-sulfinylaniline (**IV**),[147] here we present the results for the reaction of N-sulfinylamines **I–III** and isocyanates **V–VIII** with one, two and three water molecules; results for **IV** are included for comparison. We chose substituents H (**I** and **V**), CF_3 (**II** and **VI**), CH_3 (**III** and **VII**) and Ph (**IV** and **VIII**) for their distinctively varying electron-donating, electron-withdrawing and conjugating ability, aiming to gain insight into the effect of substituents in the hydrolysis reaction of these two classes of compounds.

Despite the fact that the formation of sulfinamic (for N-sulfinylamines) and carbamic (for isocyanates) acids is not the final stage of the hydrolysis, for the determination of the reactivity we only present calculations for the rate-determining step of the reactions. Given the possibility of two reaction mechanisms, we use “**a**” for the reaction across the S=O or C=O bond and “**b**” for the reaction across the N=S or N=C bond throughout this paper. The number of participating water molecules precedes the letter “**a**” or “**b**” in the identification of the species. The subscript “**w**” is used for the description of atoms belonging to water molecules involved in the interaction with the NSO and NCO groups.

5.4. Hydrolysis of N-sulfinylamines

5.4.1. N-sulfinylamines

Selected geometrical parameters, dipole moments and atomic charges of N-sulfinylamines **I–IV** are summarized in Table 5-1, the structures are shown in Figure 5-1. Unlike the almost linear isocyano group, the N-sulfinyl moiety is bent with an NSO angle of about 120°, and while both syn and anti configurations are possible, this paper deals with the more stable syn configuration.[53,122] Our report on the substituent effect on the preference of syn over anti configurations will be presented elsewhere. N-sulfinylamines **I–IV** have a planar H–N–S–O or C–N–S–O skeleton. For N-sulfinylaniline (**IV**) this leads to conjugation of the N=S=O group with the aromatic ring,[42,57,154] and the oxygen atom is found to interact with an ortho hydrogen atom on the ring.[110] Figure 5-1 shows that **II** and **III** exhibit different conformations, a C–H bond in **III** being aligned with the S=O bond in a favourable interaction of bond dipoles, whereas such an alignment is avoided for a C–F bond in **II**. The conformation given for **III** in Figure 5-1 was confirmed experimentally, although the barrier for rotation of the CH_3 group was reported to be only 335±15 cal mol^{-1}.[36] Table 5-1 shows that calculated dipole moments agree qualitatively with measured values.

Table 5-1. Selected geometrical parameters (bond lengths in pm, angles in degrees), dipole moments (μ, Debye) and atomic charges (q, au) of N-sulfinylamines **I–IV**.

	I	**II**	**III**	**IV**
S=O	146.9	146.1	147.5	148.1
	(145.1±0.5)[a]		(146.6±0.4)[b]	(145.84)[c]
N=S	152.4	153.0	152.6	153.4
	(151.2±0.5)[a]		(152.5±0.4)[b]	(151.60)[c]
H–N or C–N	102.4	142.5	145.5	139.3
	(102.9±1.0)[a]		(142.1±0.5)[b]	(140.12)[c]
NSO	120.0	120.3	119.6	120.4
	(120.4±0.5)[a]		(117.0±2)[b]	(120.61)[c]
HNS or CNS	115.7	126.3	124.5	132.3
	(115.8±1)[a]		(126.0±2)[b]	(131.23)[c]
μ	0.88	1.92	1.84	2.69
	(0.911±0.003)[a]		(1.70±0.02)[d]	(2.30±0.06)[e]
q(O)	-1.115	-1.077	-1.127	-1.121
q(S)	1.942	1.983	1.878	1.828
q(N)	-1.240	-1.153	-1.191	-1.249
q(H or C)	0.414	2.014	0.399	0.374

Experimental results are shown in parentheses: [a] From ref. 44 where distances are reported in Å. [b] From ref. 122 where distances are reported in Å. [c] From ref. 53 where distances are reported in Å. [d] From ref. 36. [e] From ref. 12.

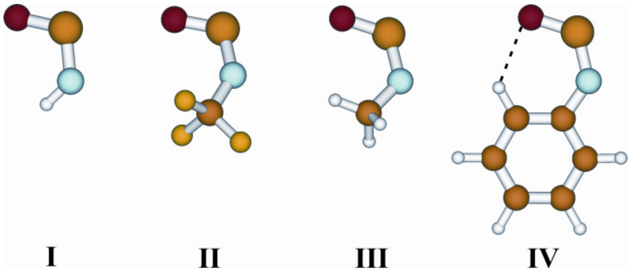


Figure 5-1. Optimized N-sulfinylamines **I**–**IV**. The C–H…O interaction in **IV** is shown by the dotted line.

A comparison of computational and available experimental geometrical parameters from Table 5-1 shows good agreement. With increasing electron-donating ability of the substituent, with **I** taken as the standard, a distinct elongation of the S=O bond is observed. In contrast, the variation in the N=S bond length is less pronounced, because nitrogen as the transmitter of the substituent effect shows a higher sensitivity to the combination of electronic and steric characteristics of the substituent. This can also be seen from the dramatic widening of the CNS bond angle in **II**–**IV** compared to that in HNS of **I**, with a maximum increase of 16.6° found for **IV**. The large bond angle on nitrogen in **IV** might, in part, be due to steric congestion, though. In that respect, it is interesting to note that **IV** prefers a widening of the nitrogen bond angle (about 8° calculated from that in **III**) to a twist about the C–N bond, which would lead to a reduction in strength of both π-conjugation and C–H…O interaction.

The difference in electron demand of the substituents is also seen from the variation of the atomic charges within the NSO moiety. With increasing electron-donating ability of the substituent, going from **II** to **IV**, the positive charge on sulfur decreases. We will show below that this is important for the susceptibility of the sulfur atom to attack by water. The charges on nitrogen and oxygen are less affected and become more negative with increasing electron-donating ability of the substituent. The slightly smaller charge on oxygen in **IV** as compared to **III** could be attributed to the intramolecular C–H…O interaction that this oxygen is involved in.[110]

5.4.2. Reaction with one water molecule

In line with our previous results on N-sulfinylaniline (**IV**),[147] for **I–III** we were able to locate pre-reaction complexes for reaction across the S=O bond. Similar to **IV**,[147] the attack by water occurs in a close to perpendicular orientation to the plane of the NSO group, and the $NSOO_w$ improper dihedral angle varies from 102 to 114°, depending on the substrate. Any attempts to find the minima for one water molecule complexed toward the N=S bond (path **b**) were unsuccessful due to the fact that perpendicular attack of the oxygen atom of water (O_w) toward the sulfur atom and simultaneous in-plane O_w–H_w…N hydrogen bonding to the nitrogen lone pair are hardly possible. Because of this lack of comparison (we were also unable to locate any pre-reaction complexes for the isocyanates), complexes of N-sulfinylamines with one water molecule are not discussed further and their geometries are presented in Table B-2 of Appendix B.

In the following, the reaction with one water molecule is discussed in detail for **I** as the prototype. An account for **IV** has been given,[147] yet the results are included in Table 5-2 for comparison with those for **I–III**. As mentioned above, we will focus on the initial steps of the hydrolysis reaction, the formation of sulfinamic acid directly (reaction across N=S, path **b**) or via sulfurimidic acid (reaction across S=O, path **a**) with subsequent 1,3-hydrogen shift (Figure 5-2). The highly strained 4-membered-ring transition state structures, **I-1a-TS** and **I-1b-TS** in Figure 5-2, result in the unrealistically high activation enthalpies of 29.8 and 30.3 kcal mol^{-1} (Table 5-2) for the reaction across the S=O and the N=S bond, respectively. The 1,3-hydrogen shift in sulfurimidic acid in path **a** leading to sulfinamic acid requires 21.9 kcal mol^{-1}, but this barrier can be dramatically reduced by the inclusion of a second water molecule. Thus, a decrease in the activation enthalpy from 15.9 to 5.5 kcal mol^{-1} upon participation of a second water molecule was shown for the 1,3-hydrogen shift in the hydrolysis of **IV**.[147] As a final note on Figure 5-2, two enantiomeric N-sulfinamic acids are formed from the two mechanisms, but as this is not important in the present context, only one structure is shown.

Table 5-2. Activation enthalpies[a] ($\Delta H^{\ddagger}_{298}$, kcal mol^{-1}) for the reaction of N-sulfinylamines **I-IV** with 1-3 water molecules across the S=O (**a**) and N=S (**b**) bond, and for consecutive 1,3-hydrogen shift[b] in the reaction across the S=O bond.

	I		**II**		**III**		**IV**	
nH_2O	**a**	**b**	**a**	**b**	**a**	**b**	**a**	**b**
1	29.8	30.3	28.6	28.9	30.5	32.5	31.8	35.7
	(31.0)		(30.4)		(31.4)		(32.4)	
	[21.9]		[20.4]		[20.2]		[16.9]	
2	12.9	11.1	10.8	11.3	15.0	14.2	16.7	18.8
	(20.8)	(18.3)	(19.7)	(19.1)	(22.9)	(21.1)	(24.3)	(24.8)
3	4.1	0.9	-3.0	-1.3	6.8	2.6	8.4	7.3
	(19.2)	(15.7)	(13.0)	(14.8)	(21.9)	(16.3)	(22.4)	(19.9)

[a] Reaction barriers are based on the enthalpies of the reactants. Results based on the enthalpies of the complexes are shown in parentheses. [b] Given in square brackets.

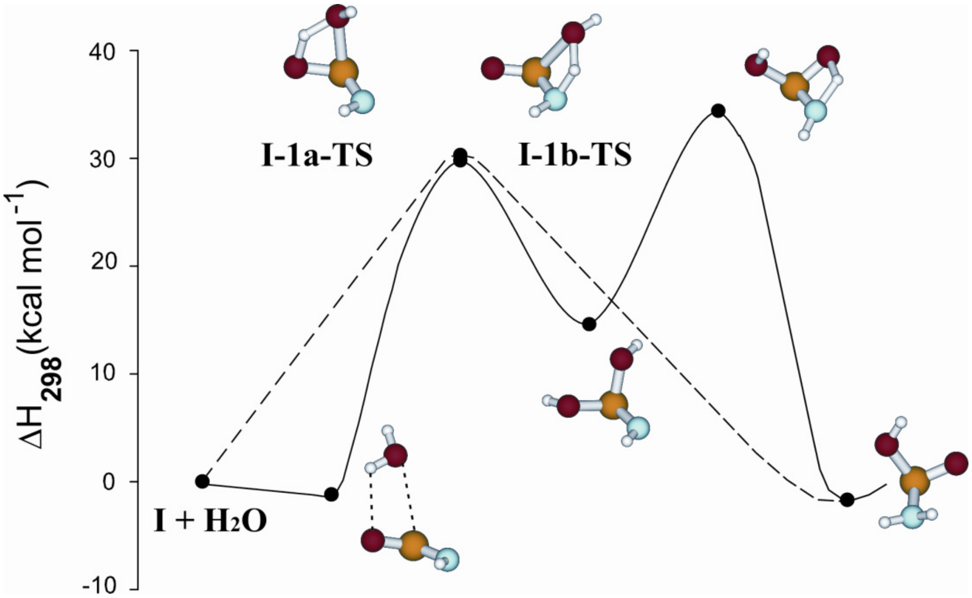
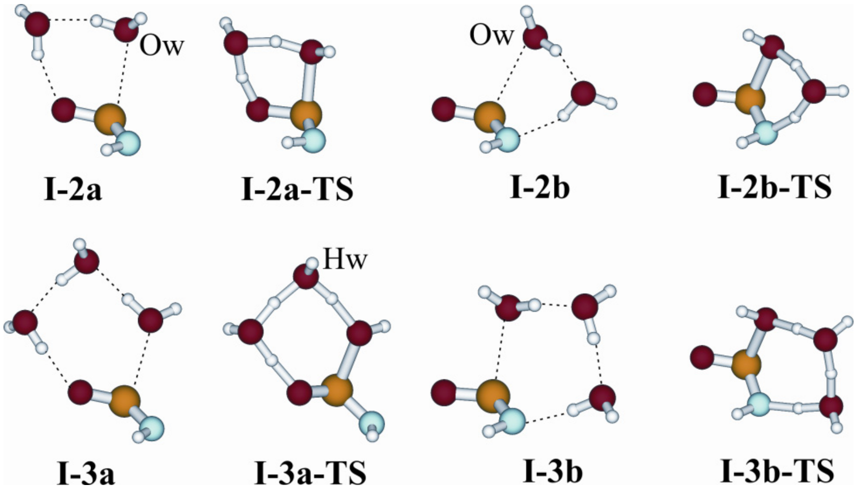


Figure 5-2. Enthalpy profile for the formation of sulfinamic acid in the reaction of N-sulfinylamine **I** with one water molecule. The solid line shows attack across the S=O, the dashed line that across the N=S bond. Weak interactions in the complex are shown with dotted lines.

For N-sulfinylamines **I–IV**, the hydroxylation of sulfur and concurrent protonation of nitrogen or oxygen is the rate-determining step of the hydrolysis reaction. The subsequent 1,3-hydrogen shift in sulfurimidic acid is much less energetically demanding. Table 5-2 shows that in the reaction with one water molecule attack across the S=O bond (path **a**) is always favoured; however, the preference for this path becomes smaller with increasing electron-withdrawing ability of the substituent. The large reaction barriers in all cases agree well with the high strain in the 4-membered-ring transition states and suggest the necessity of increasing the number of water molecules that participate in the reaction for a more accurate description of the hydrolysis reaction, as was done earlier for N-sulfinylaniline.[147]

5.4.3. Reaction with two and three water molecules

The pre-reaction complexes with two and three water molecules forming a chain were located for N-sulfinylamines **I–IV**. A staggered orientation of water molecules with respect to each other in the ternary complexes is favoured over an eclipsed arrangement by approximately 0.2 kcal mol^{-1}. The representative structures of the complexes and transition states for the simplest N-sulfinylamine **I** are shown in Figure 5-3. Those for **II** and **III** are similar, as are those for **IV**, which have been reported.[147]



I-2a **I-2a-TS** **I-2b** **I-2b-TS**

I-3a **I-3a-TS** **I-3b** **I-3b-TS**

Figure 5-3. Optimized complexes and transition states for the reaction of N-sulfinylamine **I** with two and three water molecules (reaction across the S=O (**a**) and N=S bond (**b**)). Weak interactions in the complexes are shown with dotted lines.

Table 5-3 summarizes selected geometrical parameters for pre-reaction complexes and transition states of the rate-determining step of the reaction of N-sulfinylamines **I–IV** with two water molecules, based on our previous result of the “two-water-molecule” model being sufficiently descriptive and less computationally expensive than the model with three water molecules.[147] The geometrical parameters for reaction with three water molecules are summarized in Table B-3 of Appendix B because of the similarity between the two models. As can be seen from the $NSOO_w$ improper dihedral angles, the interaction in all cases occurs in a close to perpendicular orientation of the water molecule and the NSO group. In accord with attack on sulfur, and concomitant rehybridization, the bond angle on sulfur (NSO) in the complexes decreases by 1.1-1.8°, in the transition states by up to 8.0°. Geometry changes in the complexes and transition states from those of the non-interacting species are given in Table 5-3 in parentheses.

Table 5-3. Selected geometrical parameters (bond lengths in pm, angles in degrees) of complexes and transition states in the reaction of N-sulfinylamines **I–IV** with two water molecules across the S=O (**a**) and N=S (**b**) bonds.[a]

	I				**II**				**III**				**IV**			
	a	**a-TS**	**b**	**b-TS**	**a**	**a-TS**	**b**	**b-TS**	**a**	**a-TS**	**b**	**b-TS**	**a**	**a-TS**	**b**	**b-TS**
S=O	147.9	155.9	146.6	146.8	147.0	154.0	145.9	145.7	148.6	156.9	147.2	146.7	149.2	157.1	147.7	146.1
	(1.0)	(9.0)	(-0.3)	(-0.1)	(0.9)	(7.9)	(-0.2)	(-0.4)	(1.1)	(9.4)	(-0.3)	(-0.8)	(1.1)	(9.0)	(-0.4)	(-2.0)
N=S	152.2	152.3	153.3	159.7	152.7	152.9	154.2	161.7	152.1	151.7	153.4	159.3	152.8	151.9	154.4	160.0
	(-0.2)	(-0.1)	(0.9)	(7.3)	(-0.3)	(-0.1)	(1.2)	(8.7)	(-0.5)	(-0.9)	(0.8)	(6.7)	(-0.6)	(-1.5)	(1.0)	(6.6)
H–N or	102.4	102.2	102.4	102.2	142.1	140.5	141.9	141.3	145.4	145.6	145.8	146.7	139.3	140.0	139.7	142.2
C–N	(0.0)	(-0.2)	(0.0)	(-0.2)	(-0.4)	(-2.0)	(-0.6)	(-1.2)	(-0.1)	(0.1)	(0.3)	(1.2)	(0.0)	(0.7)	(0.4)	(2.9)
NSO	118.4	113.8	118.2	112.0	118.9	114.4	118.5	113.9	118.4	114.0	118.0	112.4	119.2	115.9	119.3	114.3
	(-1.6)	(-6.2)	(-1.8)	(-8.0)	(-1.4)	(-5.9)	(-1.8)	(-6.4)	(-1.2)	(-5.6)	(-1.6)	(-7.2)	(-1.2)	(-4.5)	(-1.1)	(-6.1)
HNS or	115.5	115.3	114.8	110.9	126.5	126.0	125.2	122.1	124.9	125.7	123.8	121.0	133.2	134.6	131.8	127.0
CNS	(-0.2)	(-0.4)	(-0.9)	(-4.8)	(0.2)	(-0.3)	(-1.1)	(-4.2)	(0.4)	(1.2)	(-0.7)	(-3.5)	(0.9)	(2.3)	(-0.5)	(-5.3)
S…O$_w$	290.1	205.0	298.0	210.1	273.6	198.6	269.8	203.1	305.2	210.9	335.5	217.9	314.6	212.0	377.9	219.7
NSOO$_w$	109.3	110.5	106.4	104.3	104.3	108.7	105.6	101.2	105.8	111.3	115.5	104.8	109.8	110.7	131.2	101.1

[a] The deviation of geometrical parameters in the transition states from the geometries of the non-interacting N-sulfinylamines are shown in parentheses.

One of the main geometrical features for both paths consists of a pronounced elongation of the bond across which the complexation and following reaction occurs, along with a small contraction of the other cumulated bond. These changes exhibit but a small substituent effect: while in general elongation of the S=O bond is more pronounced, for **II** with its electron-withdrawing CF_3 substituent elongation is more pronounced for the N=S bond.

In contrast, the S…O_w distance in the complexes and transition states appreciably correlates with the electron-donating/withdrawing ability of the substituent. Thus, the strong electron-withdrawing substituent in **II** enhances the electrophilicity of sulfur, which consequently forms the tightest complexes with water for both mechanisms. The conjugating phenyl group in **IV** leads to the weakest complexes and loosest transition states. From the different possible descriptors for the electrophilicity of an atom,[*] we have chosen the charge on sulfur (Table 5-1) as the most straightforward to be a measure of the susceptibility of the N-sulfinylamines toward nucleophilic attack by water. Figure 5-4 presents the relationship between the charge on sulfur of the non-interacting N-sulfinylamines and the S…O_w distance in the transition state of the reactions with two water molecules, which is the obvious choice for comparison between mechanisms "**a**" and "**b**" and for later comparison with the reactivity of the isocyanates, due to the absence of pre-reaction complexes for the latter. Although the type of correlation (linear or exponential; the data points have simply been traced) is unclear for this small series, the trend is obvious: an increase in the electrophilicity of sulfur leads to a shorter S…O_w distance and therefore a stronger interaction in the transition state.

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[*] Other descriptors for the electrophilicity have been suggested, such as the quadrupole moment[155] and Fukui functions.[156]

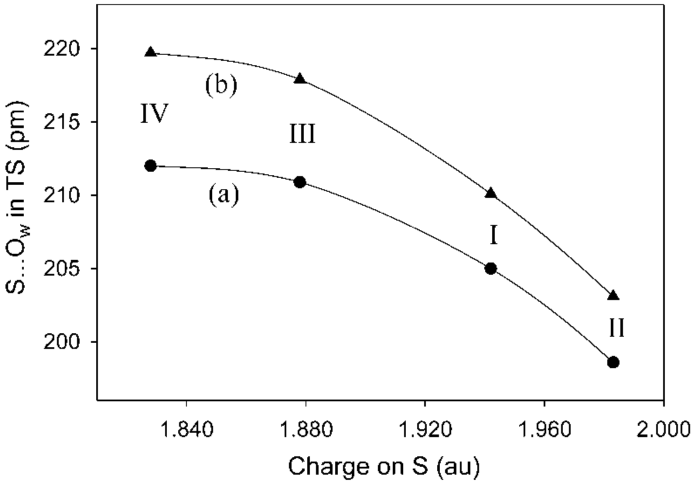

Figure 5-4. Dependence of the S…O_w intermolecular distance in the transition state of the reaction of **I–IV** with two water molecules on the charge on sulfur. Reaction across (**a**) the S=O (●) and (**b**) the N=S (▲) bond. Data points have been traced.

5.4.4. Summary and conclusions on N-sulfinylamine hydrolysis

Figure 5-5 shows the dependence of the reaction barrier of the hydrolysis of N-sulfinylamines **I–IV** on the number of water molecules for reaction across the S=O bond only. The graphical representation of the results for reaction across the N=S bond is very similar, with the exact values summarized in Table 5-2. For the solid lines in Figure 5-5, based on the enthalpies of the reactants, it is immediately obvious that the activation enthalpy drops significantly as the number of water molecules is increased. In general, the addition of the second water molecule has a larger effect than that of the third. This is only different for **II** with its CF_3 substituent, which causes the overall largest changes. The comparatively larger decrease in the reaction barrier for **II-3a-TS** might be explained by the presence of one additional hydrogen-bonding interaction between the dangling hydrogen of the central water molecule (equivalent to H_w in Figure 5-3) and a fluorine atom of the CF_3 group, with a concurrent conformational change about the C–N bond on going from **II** to **II-3a-TS**. This additional O_wH_w…F interaction is not present in the complex **II-3a**, and so the smaller activation enthalpy for **II-3a-TS** is found irrespective of the chosen reference (cf. the dashed line in Figure 5-5).

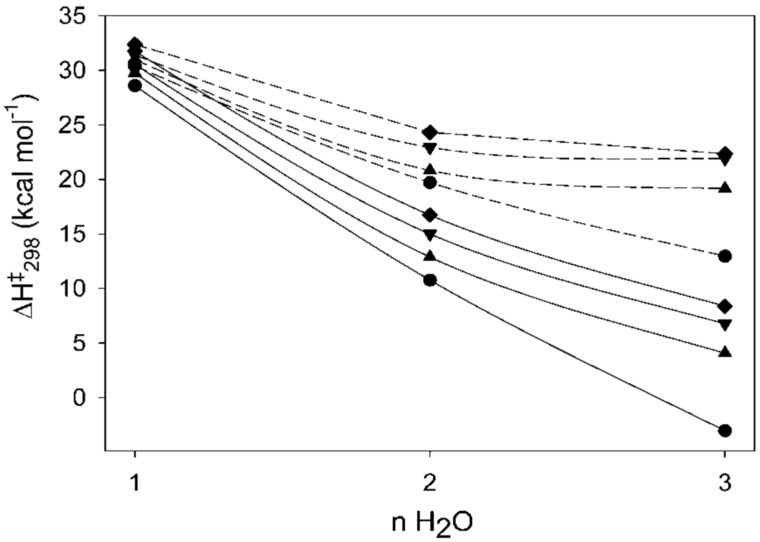

Figure 5-5. Dependence of the reaction barrier for hydrolysis of N-sulfinylamines **I–IV** for attack across the S=O bond (path **a**) on the number of water molecules. Activation enthalpies based on the enthalpies of the reactants are shown by solid lines, those based on the enthalpies of the complexes are shown by dashed lines. Data points have been traced for easier comparison of the trends. (H ▲, CF_3 ●, CH_3 ▼, Ph ◆).

The progression of the dashed lines in Figure 5-5, because the data are based on the enthalpies of the complexes, is in fact more relevant to our discussion. The overall changes are smaller than those discussed above, and there already seems to be a leveling-off for addition of the third water molecule, as the reaction barrier decreases by only 1–7 kcal mol^{-1}, with the largest change for **II** for the reason already discussed. These findings confirm the necessity and sufficiency of the "two-water-molecule" model for the proper description of N-sulfinylamine hydrolysis.

Two additional conclusions can be drawn. Firstly, a higher activation enthalpy for the hydrolysis of N-sulfinylaniline (**IV**) than that for N-sulfinylmethylamine (**III**) agrees well with the qualitative experimental observation of a higher reactivity of aliphatic N-sulfinylamines toward water.[24] In fact, our free energies allow one to estimate a rate constant increase of about one to three orders of magnitude on going from **IV** to **III** (free energies are provided in Table B-2 of the Appendix B). Secondly, with an average difference of about 2.1 kcal mol^{-1}, the preference for either mechanism is not pronounced, and which mechanism is preferred computationally can depend on whether energies of activation energies or of pre-reaction complexes are used for the determination of the barriers, at least for reaction with one water molecule. We will present the factors that determine the reactivity of the N-sulfinylamines after a detailed analysis of the hydrolysis of isocyanates.

5.5. Hydrolysis of Isocyanates

5.5.1. Isocyanates

Figure 5-6 shows that, in contrast to the angular NSO group in N-sulfinylamines, isocyanates **V–VIII** possess a more or less linear NCO group, as has been reported from numerous experimental and computational studies.[106,149] Selected geometrical data for **V–VIII** are presented in

Table 5-4. The NCO bond angle in **V–VIII** varies insignificantly in the range of 172.8-173.8°, whereas the bond angle on nitrogen varies widely with the substituent, in line with the findings for **I–IV** above. The substituent effect on the variation of the N=C and C=O bond lengths is not pronounced and, unlike in the N-sulfinylamines, where an increase in electron-donating ability of the substituent results in the elongation of both cumulated bonds of the N=S=O group, an elongation of the C=O combined with a contraction of the N=C bond is found for the isocyanates. Geometrical parameters in

Table 5-4 suggest that methyl and phenyl substituents in **VII** and **VIII**, respectively, exert a similar effect on the N=C=O group, in line with the negligible conjugation energy between the N=C bond and the substituent on nitrogen found earlier for methyl, ethyl and phenyl isocyanates.[146] The available experimental data agree quite well with our calculated results, with the exception of the underestimated dipole moment of HNCO (**V**). The difficulties with interpreting the large difference between the dipole moments of methyl isocyanate (**VII**) and isocyanic acid (**V**) were addressed earlier, and the significant variation in the nitrogen bond angle was given as a possible reason for the difference.[151]

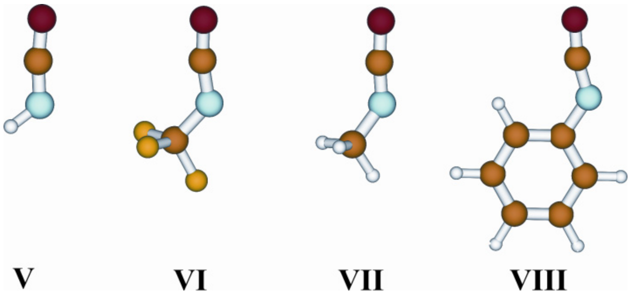

Figure 5-6. Optimized isocyanates **V–VIII**

Table 5-4. Selected geometrical parameters (bond lengths in pm, angles in degrees), dipole moments (μ, Debye) and atomic charges (q, au) of isocyanates **V–VIII**.

	V	**VI**	**VII**	**VIII**
C=O	116.8	116.1	117.7	117.3
	(119±3)[a]		(118±3)[a]	(117.1)[b]
N=C	121.6	121.8	120.2	120.6
	(119±3)[a]		(119±3)[a]	(120.7)[b]
H–N or C–N	100.8	140.4	144.4	140.0
	(101)[a]		(147)[a]	(137.0)[b]
NCO	172.8	173.4	173.7	173.8
HNC or CNC	124.5	129.8	138.4	139.1
	(125)[a]		(125±5)[a]	(140.6)[b]
			(140.0)[c]	
μ	2.16	0.49	3.03	2.56
	(1.59)[d]		(2.81)[c]	(2.3)[e]
q(O)	-1.146	-1.112	-1.151	-1.137
q(C)	1.958	1.999	1.976	1.974
q(N)	-1.286	-1.184	-1.317	-1.345
q(H or C)	0.473	2.065	0.479	0.409

Experimental results are shown in parentheses: [a] From ref. 149 where distances are reported in Å. [b] From ref. 150 where distances are reported in Å. [c] From ref. 151. [d] From ref. 152. [e] From ref. 153.

As was found for **II**, with the largest positive charge on sulfur, the trifluoromethyl-substituted **VI** possesses the largest positive charge on the NCO carbon. The charges on sulfur in **I–IV**, though, vary more widely in the range of 0.155 au compared to the 0.041 au range for carbon in **V–VIII**. In addition, the loss of positive charge (0.050 au) on sulfur in **IV** from that in **III** is larger than that (0.002 au) on carbon in **VIII** from that in **VII**, further corroborating the idea of a similar effect of methyl and phenyl substitution on the NCO group. The charges on nitrogen and oxygen in two classes of compounds are generally comparable, and more negative for the isocyanates, as expected.

5.5.2. Reaction with one water molecule

Similar to the results of the computational work of Raspoet et al. on the hydrolysis of isocyanic acid (**V**),[106] we did not find any pre-reaction complexes for the reaction of isocyanates **V–VIII** with either one, two or three water molecules. Consequently, all reaction barriers for this part of our study are based on the enthalpies of the reactants. Unlike N-sulfinylamines, whose attack by water occur perpendicular to the plane of the NSO group, isocyanates react with water in the plane of the NCO group, where the nucleophilic attack of oxygen O_w on the carbon atom is concerted with the protonation of either nitrogen or oxygen.

Again, we only deal with the first stage of the hydrolysis, and the discussion of the mechanism in the presence of one water molecule is based on the simplest isocyanate model compound, isocyanic acid (**V**). Even though the computational analysis of the hydrolysis of **V** (optimized with the HF/6-31G(d,p) model chemistry, single point energies with MP2/6-311++G(d,p) and QCISD(T)/6-31G(d,p) and with use of Onsager and polarized continuum models have been reported,[106] we include **V** here for comparison. Irrespective of the model chemistry used, the outcome for the hydrolysis of **V** in the presence of one water molecule is essentially the same: as for the N-sulfinylamines, the high strain of the 4-membered-ring transition state results in an unrealistically large value for the activation enthalpy (energy).[106,*] The enthalpy profile for both mechanisms is presented in Figure 5-7.

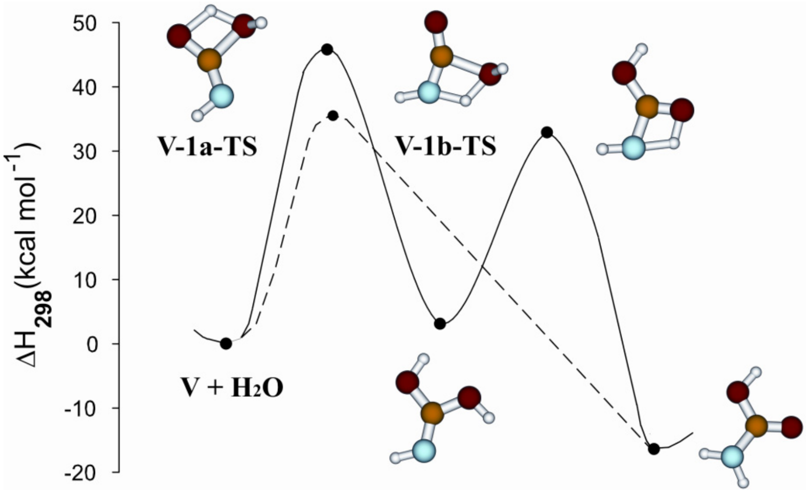

Figure 5-7. Enthalpy profile for the formation of carbamic acid in the reaction of isocyanic acid (**V**) with one water molecule. The solid line shows attack across the C=O, the dashed line that across the N=C bond.

The activation enthalpy for the one-step reaction across the N=C bond (path **b**), which yields carbamic acid directly, is found to be 35.5 kcal mol^{-1} and compares favourably to the reaction barrier of 36.8 kcal mol^{-1} calculated with QCISD(T)/6-31G(d,p).[106,*] The reaction across the C=O bond (path **a**) requires the significantly higher activation enthalpy of 45.8 kcal mol^{-1}, and yields an intermediate carbonimidic acid, which further undergoes a 1,3-hydrogen shift with an activation enthalpy of 29.7 kcal

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[*] In the original paper, activation barriers are described as zero-point vibrational corrected energies and are given in kJ mol^{-1}. Zero-point energy corrections were taken from HF/6-31G(d,p) calculations and scaled by a factor of 0.9.

mol^{-1}. These barriers were earlier found to be 46.1 and 31.5 kcal mol^{-1}, respectively.[106,48] In analogy to the hydrolysis of N-sulfinylamines, the hydroxylation of carbon is the rate-determining step of isocyanate hydrolysis. Table 5-5 presents the reaction barriers for the hydrolyses of **V-VIII** and reveals an interesting substituent effect. Unlike for N-sulfinylamines, the replacement of hydrogen in **V** by a methyl or phenyl group does not change the activation enthalpy for the reaction across the C=O bond and decreases it by only 1.6-1.7 kcal mol^{-1} for the reaction across the N=C bond. Only the strong electron-withdrawing CF_3 group in **VI** leads to a more substantial decrease in the activation enthalpies of both mechanisms. This will be rationalized in a following section. For isocyanates **V–VIII**, reaction across the N=C bond is always favoured by about 10 kcal mol^{-1}. We also note that while the reaction barriers for the 1,3-hydrogen shift in the sulfurimidic acids increase in the series CF_3, H, CH_3 and Ph, the corresponding barriers for the carbonimidic acids become smaller.

5.5.3. Reaction with two and three water molecules

As in the case of the N-sulfinylamines, we chose the isocyanate/water-dimer system as the necessary and sufficient model for a comparison of the geometrical features of the transition states and for a proper description of the hydrolysis reaction, a conclusion which was drawn before for **V**.[106] Table 5-3 summarizes the selected geometrical parameters of the transition structures for the reaction of isocyanates **V-VIII** with two water molecules; those for the reaction with three water molecules can be found in Table B-4 of Appendix B. In all cases, the reaction again occurs in the plane of the NCO group, as can be seen from the improper torsional angles $NCOO_w$ (Table 5-6).

Table 5-5. Activation enthalpies[a] ($\Delta H^{\ddagger}_{298}$, kcal mol^{-1}) for the reaction of isocyanates **V–VIII** with 1-3 water molecules across the C=O (**a**) and N=C (**b**) bonds, based on the enthalpies of reactants, and for consecutive 1,3-hydrogen shift[b] in the reaction across the C=O Bond.

	V		**VI**		**VII**		**VIII**	
nH_2O	**a**	**b**	**a**	**b**	**a**	**b**	**a**	**b**
1	45.8 [29.7]	35.5	42.1 [30.2]	32.8	45.5 [27.6]	33.8	45.6 [24.7]	33.9
2	19.4	12.9	12.2	8.0	19.3	12.9	18.9	13.2
3	7.4	3.0	-1.7	-3.3	7.2	3.4	6.4	3.9

[a] Reaction barriers are based on the enthalpies of the reactants. [b] Given in square brackets.

The most interesting feature in Table 5-6 is the significant decrease in the NCO and CNC or HNC bond angles, by 32 and 16° on average, respectively, upon formation of the transition states, leading to a shortening of the distance between the oxygen of the NCO group and atoms of the substituent R. In the case of **VIII,** this results in the appearance of a weak intramolecular C–H…O interaction between an *ortho*-hydrogen of the phenyl ring and the oxygen of the NCO moiety, confirmed through topological analyses of the electron densities and given as dotted lines in Figure 5-8. The C–H…O interactions in N-sulfinylaniline (**IV**)[110] and in the transition states for phenyl isocyanate (**VIII**) hydrolysis are best described as blue-shifting (or anti-) hydrogen bonds, characterized by the contraction of the interacting C–H bond from 108.3 to 108.0-108.1 pm in all cases, including the reaction of **VIII** with one water molecule, which was not specified above. The distances between the *ortho*-hydrogen and the oxygen atom of the NCO group and the CH…O angles resulting from these weak interactions also resemble those in **IV** and are very similar for complexes and transition states for the reactions of **IV** and **VIII** with two and three water molecules (presented in Table B-3 and Table B-4 of the Appendix B).

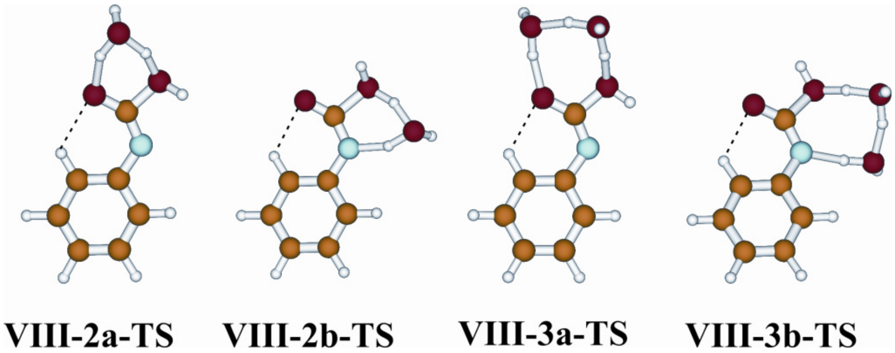

Figure 5-8. Optimized transition states for the reaction of phenylisocyanate (**VIII**) with two and three water molecules for reaction across the S=O (**a**) and the N=S bond (**b**). Weak interactions determined from electron densities are shown as dotted lines.

The attack of the water dimer across the C=O or the N=C bond causes elongation of that bond. No obvious effect of the substituent is found in the series of the isocyanates **V–VIII**, however, unlike for N-sulfinylamines with their simultaneous contraction of the second cumulated bond, a lengthening for that bond is observed for all isocyanates. The extent of this elongation varies, depending on the mechanism of hydrolysis and therefore on which bond lengthens: for attack across the C=O bond (path **a**) it consists of 5.1-6.2 pm, while for attack across the N=C bond (path **b**) it is half that and varies in the range of 1.9-3.1 pm.

Table 5-6. Selected geometrical parameters (bond lengths in pm, angles in degrees) of transition states in the reaction of isocyanates **V–VIII** with two water molecules across the C=O (**a**) and N=C (**b**) bonds.[a]

	V		**VI**		**VII**		**VIII**	
	a-TS	**b-TS**	**a-TS**	**b-TS**	**a-TS**	**b-TS**	**a-TS**	**b-TS**
C=O	125.4	119.6	123.5	119.2	125.8	119.6	125.3	119.7
	(8.6)	(2.8)	(7.4)	(3.1)	(8.1)	(1.9)	(8.0)	(2.4)
N=C	126.7	129.7	128.0	131.2	126.1	129.0	126.8	129.8
	(5.1)	(8.1)	(6.2)	(9.4)	(5.9)	(8.8)	(6.2)	(9.2)
H–N	101.7	101.3	139.5	139.8	145.8	146.3	140.7	141.3
or C–N	(0.9)	(0.5)	(-0.9)	(-0.6)	(1.4)	(1.9)	(0.7)	(1.3)
NCO	140.6	143.2	139.7	141.0	140.0	142.9	140.6	143.1
	(-32.2)	(-29.6)	(-33.7)	(-32.4)	(-33.7)	(-30.8)	(-33.2)	(-30.7)
HNC or	110.2	111.7	118.6	118.1	117.5	116.3	123.2	121.8
CNC	(-14.3)	(-12.8)	(-11.2)	(-11.7)	(-20.9)	(-22.1)	(-15.9)	(-17.3)
$C\ldots O_w$	154.0	163.2	151.3	156.9	154.2	165.3	153.2	162.7
$NCOO_w$	179.6	179.8	179.6	179.6	179.3	179.7	179.4	179.9

[a] The deviation of geometrical parameters in the transition states from those of the non-interacting isocyanates is shown in parentheses.

The spread of the charge on carbon is much smaller than that of sulfur in the N-sulfinylamines, as mentioned above, and even though a certain trend between the intermolecular distance and the charge on carbon is observed, it is less affected by the electron-donating/withdrawing ability of the substituent. The dependence of the $C\ldots O_w$

distance in the transition state on the charge on carbon in the non-interacting isocyanates is presented in Figure B-1 of the Appendix B.

5.5.4. Summary and conclusions on isocyanate hydrolysis

The increase in the number of water molecules again releases the strain of the 4-membered-ring transition states in the reaction with one water, consequently decreasing the activation enthalpies for isocyanate hydrolysis dramatically, which is given in numerical form in Table 5-5 and in graphical representation in Figure B-2 of the Appendix B for the reaction across the C=O bond. The dependence on the number of water molecules for the reaction across the N=C bond is essentially the same and presented in Figure 5-9 for the comparison of the hydrolyses of N-sulfinylamines and isocyanates. For both mechanisms considered, the reaction barrier shows almost no sensitivity to the substituent in **V, VII** and **VIII**, and the attack across the N=C bond is favoured. A significant decrease in activation enthalpy, by approximately 5–9 kcal mol^{-1}, is found for **VI** with its strongly electron-withdrawing CF_3 group. Because the activation energies are only based on the enthalpies of the activation energies and not on the (lower-energy) pre-reaction complexes, they even drop to negative values in the reaction with three water molecules, as was the case for **II** (cf. Table 5-2). Finally, from the free energies a rate constant increase for **VI** of about three to five orders of magnitude over those for the other isocyanates can be estimated (free energies provided in Table B-1 of the Appendix B).

A detailed comparison of the reactivity of N-sulfinylamines and isocyanates toward water is presented in the final section.

5.6. Comparison of the hydrolyses of N-sulfinylamines and isocyanates

The results of this study confirm a certain similarity of the reactivities of N-sulfinylamines and isocyanates toward water, based on a comparison of the activation enthalpies for their hydrolyses, summarized in Table 5-2 and Table 5-5 and presented in graphical form in Figure 5-9. It can be seen that the reaction barriers, based on the enthalpies of the reactants for the reaction with 1-3 water molecules across the N=S or N=C bond (Figure 5-9) essentially lie within the same range, with individual data points providing some spread. Unfortunately, as stated above, the more appropriate pre-reaction-complex-based activation enthalpies cannot be employed in this comparison. As expected, an increasing number of water molecules decrease the activation enthalpy, on average by 17.4 and 23.9 kcal mol^{-1} for addition of the second water and by 10.7 and 11.3 kcal mol^{-1} for addition of the third water molecule for N-sulfinylamines and isocyanates, respectively. While a gradual decrease of the reaction barrier with increasing electron-withdrawing ability of the substituent was found for N-sulfinylamines **I–IV**, only the strongly electron-withdrawing trifluoromethyl group in **VI** has a major influence on isocyanate reactivity.

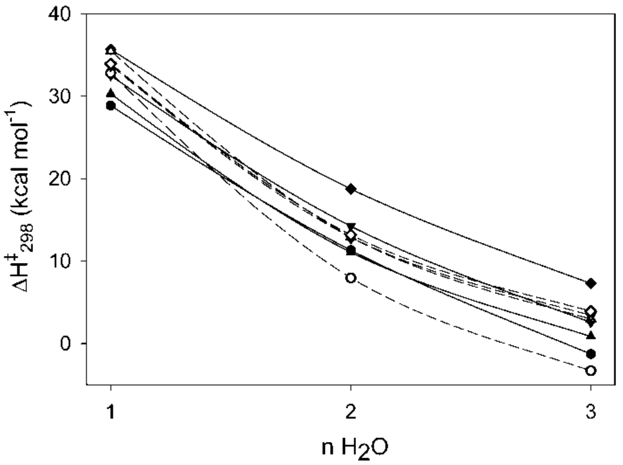

Figure 5-9. Dependence of the activation enthalpy for hydrolysis of N-sulfinylamines **I–IV** on the number of water molecules (solid lines: H ▲, CF_3 ●, CH_3▼, Ph ◆) and isocyanates **V–VIII** (dashed lines: H △, CF_3 ○, CH_3 ▽, Ph ◇) in the reaction across the N=S or the N=C bond (path **b**). Data points have been traced for easier comparison of the trends.

To gain further insight into this differing reactivity, we correlate the activation enthalpy for the reaction with two water molecules with the charge on the electrophilic centre of **I-VIII** in Figure 5-10. As nucleophilic attack of water on sulfur or carbon is the rate-determining step of hydrolysis, the reactivity could be governed by the charge of this reactive centre. Figure 5-10 shows that this is indeed the case. The sulfur atom of the N-sulfinylamines **I–IV** possesses a high sensitivity to the nature of the substituent, which results in a large variation in its charge. A reasonably linear correlation that includes reactions across both the N=S and S=O bonds is found. Even though Figure 5-10 displays relative linearity only for path **a** and a distinct curvature for path **b**, the correlation with both mechanisms simultaneously seems justified because the preference for either mechanism is not pronounced and is affected by the substituent, the number of water molecules and the reference employed for the determination of the activation energies, as described above. Overall, an increase in electron-withdrawing ability of the substituent causes an increase in the electrophilicity of the sulfur atom and its susceptibility to hydroxylation, consequently decreasing the reaction barrier for hydrolysis of the N-sulfinylamines.

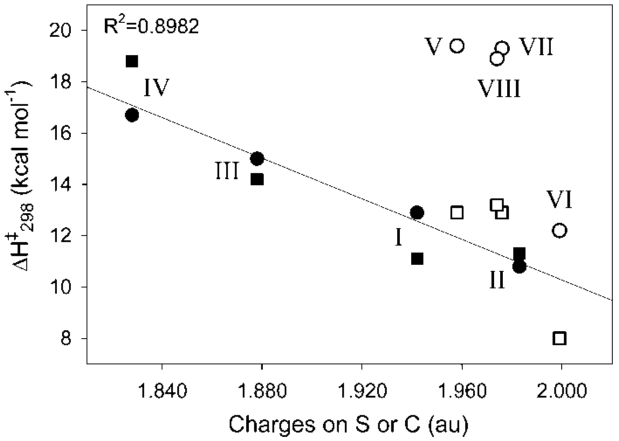

Figure 5-10. Dependence of the activation enthalpy for the reaction with two water molecules on the charge on sulfur (**I**–**IV**) and carbon (**V**–**VIII**): Reaction across the S=O (path **a**, ●) and the N=S bond (path **b**, ■) for **I**–**IV**; reaction across the C=O (path **a**, ○) and the N=S bond (path **b**, □) for **V**–**VIII**. Activation enthalpies are based on the enthalpies of the reactants.

The charge on carbon of the isocyanates **V–VIII** also correlates with the activation enthalpy for their hydrolysis. The insignificant variation of the charge in **V**, **VII** and **VIII** results in negligible changes in their reactivity toward water, whereas trifluoromethyl isocyanate (**VI**), possessing the largest positive charge on carbon in the series, demonstrates an enhanced electrophilicity and hydrolyzes more readily. A linear regression has not been performed due to the poor spread in the data.

A comparison of data from Table 5-2 and Table 5-5 indicates that while both mechanisms **a** and **b** are feasible for N-sulfinylamines, the attack across the N=C bond is clearly favoured by isocyanates. This preference, noted earlier for isocyanic acid (**V**), was explained as being "due to the more extended concentration of electron density", a result obtained from Fukui functions, although a Mulliken population analysis predicted oxygen to be twice more negative than nitrogen, which bore the small charge of –0.17 au.[106] In other work,[146] and in contrast, a comparison of molecular and bond dipoles in a series of isocyanates was used to propose that nitrogen is more negative than oxygen in **V**. The calculated charges presented in Table 5-1 and

Table 5-4 show that the nitrogen atom indeed possesses a more negative charge than oxygen in both N-sulfinylamines **I–IV** and isocyanates **V–VIII**, with a more substantial difference in isocyanates **VII** and **VIII**. This agrees well with the distinct preference for reaction across the N=C bond found for isocyanates, but requires some comments for seeming outliers in N-sulfinylamine reactivity. Thus, firstly, for the RNSO species, the transition state for reaction with one water molecule across the N=S bond, because of the requirements of perpendicular interaction toward sulfur and in-plane orientation to the nitrogen lone pair, is so highly strained that the reaction across the S=O bond becomes preferred. And secondly, reaction of **II** with three water molecules across the S=O bond is facilitated by an additional hydrogen bond stabilizing this transition state.

The rate-limiting step in the concerted hydrolysis reaction involves the hydroxylation of sulfur in **I-IV** or carbon in **V-VIII** along with the protonation of either nitrogen or oxygen atoms. It may, therefore, not seem surprising that the actual pathway (**a** or **b**) taken also follows the proton affinities of these atoms. The proton affinities calculated from the 0 K-enthalpies[157] are given in Table B-5 of the Apendix B. In general for **I-VIII**, the proton affinity for nitrogen is larger than that for oxygen, and the difference in proton affinities for these atoms (ΔPA) for isocyanates **V–VIII** is twice that for an N-sulfinylamines **I–III**. This again explains the observed reactivity. Finally, while ΔPA for the phenyl-substituted **VIII** is in line with those for the other isocyanates, for N-sulfinylaniline (**IV**) the nitrogen and oxygen atoms exhibit an about equal affinity for protonation, in accord with the observed lack of preference for either mechanism and the fact that conjugation with the phenyl ring in **IV** extends over all atoms of the NSO group.

5.7. Conclusions

The "two-water molecule" model is found to be adequate for the proper description of the hydrolysis of N-sulfinylamines **I-IV** and isocyanates **V-VIII**. Despite the overall similar reactivity of these two classes of compounds, reaction across both the N=S and S=O bonds are feasible for N-sulfinylamines, while the reaction across the N=C bond is strongly favoured for isocyanates. This dissimilarity is rooted in the different proton affinities of the nitrogen and oxygen atoms in the NSO and NCO groups. N-sulfinylamines exhibit a pronounced sensitivity to substitution, and the smaller reaction barrier encountered with a more electron-withdrawing substituent agrees well with the experimentally determined higher reactivity of the aliphatic species as compared to aromatic N-sulfinylamines. The similar reactivity of aromatic and aliphatic isocyanates agrees with the previously reported close to zero conjugation energy between the substituent and the NCO group in aliphatic and phenyl isocyanates, although an increase in reactivity can be achieved through a strongly electron-withdrawing (CF_3) substituent. The correlations found between the charge on sulfur and carbon with the $S\ldots O_w$ and $C\ldots O_w$ intramolecular distances in the transition state and, consequently, with the activation enthalpy for hydrolysis of N-sulfinylamines and isocyanates, suggests that these atomic charges could be used as a measure of electrophilicity of the reactive center in future studies. With estimated ranges of gas phase rate constants of $10^{-18} – 10^{-12}$ s^{-1} for N-sulfinylamines and $10^{-19} – 10^{-11}$ s^{-1} for isocyanates within even the small series covered here, this could prove a welcome aid for experimentalists.

Chapter 6.

N-sulfinylhydrazides: Configurational isomerization from a computational point of view[*]

6.1. Introduction

Since the time of their discovery,[2] N-sulfinylhydrazides (R–CO–NH–N=S=O) as well as other related N-sulfinyl (R–N=S=O) species have found a wide application in synthetic organic chemistry. N-sulfinylamines are reported to be excellent reagents for cycloaddition reactions leading to four-, five- and six-membered heterocycles.[19,32,59,60,132,158-160] They are known to react with dipolar bonds such as C=O, C=N, C=S, S=O and P=O, and with proton-active compounds such as water, alcohols, amines and hydrogen halides.[24,25] In the latter set of reactions,[161] hydrolysis is of particular interest as the substituent dictates the reactivity of the N=S=O group in a wide range, varying from explosive[81] through moderate[89] to complete inertness.[19] For example, while N-sulfinylhydrazines (R–NH–N=S=O) do not exhibit sensitivity towards water, their carbonyl derivatives, N-sulfinylhydrazides (R–CO–NH–N=S=O), with one exception, were reported to react quite readily with water.[19] Consequently, the inclusion of the carbonyl group alters the reactivity of these N-sulfinyl species significantly. This behavior is not entirely unexpected, because the N=S=O group is known to enter into

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[*] To be submitted as E.V. Ivanova and H.M. Muchall, *Journal of Physical Chemistry A,* 2010

conjugation with available π-systems,[18,20,38,47,48,154,162] and, thus, the reactivity of both can be mutually affected. In this respect, certain characteristics for amides might be transferable to N-sulfinylhydrazides, but unfortunately their electronic structures, which influence their reactivity, are not reported to date.

Being a building block of proteins and enzymes and recently reported to be involved in DNA mutation,[163-165] the nature and reactivity of the amide group have attracted much attention in the past few decades. The understanding of the effect of the substituent on the amide moiety is, thus, of utmost importance from both the chemical and biochemical point of view. It was reported that the trans conformation, with carbonyl oxygen and amine hydrogen on opposite sides of the C–N bond, is strongly favoured over the cis conformation in monosubstituted amides, while steric factors lead to dramatic changes in the equilibrium for disubstituted amides.[166] The n_N-π conjugation results in the partial double bond character of the C–N bond and is thus responsible for its hindered torsion. This feature is one of the most extensively studied, both experimentally and computationally.[167-179] The barrier for restricted rotation around the C–N bond was determined to lie in the range of about 15-20 kcal mol^{-1}, determined as enthalpy, free or activation energy in various amides[166,168-175] and thioamides.[179]

Despite the fact that most amide derivatives are found to exist predominantly in the amide form,[166,180-183] the possibility of amido-imide (keto-enol) tautomerization cannot be completely rejected, because the stabilization of the imido form through complexation with metal ligands is known in the literature.[184] The possibility of keto-enol tautomerization in N-sulfinylhydrazides was thus alluded to in earlier experimental studies, however without detail of its effect on their reactivity.[19]

The higher stability of the keto over the enol form of amides was also reported in several computational studies.[141,185-188] Thus, for example, formamide is 12-13.5 kcal mol^{-1} more stable, compared to formamidic acid, with the activation barrier for intramolecular proton transfer calculated to be 45.6-48.9 kcal mol^{-1} at various levels of theory.[141,185,186] For explicit solvation, the activation barrier decreases to 20.8 and 18.3 kcal mol^{-1} for inclusion of one and two water molecules, respectively.[141] Moreover, complexation with water increases the stability of formamidic acid, compared to the corresponding complexes of formamide, by 1 to 2 kcal mol^{-1}.[141] As can be seen, while the activation barriers changes significantly, the change in stability of the unfavourable enol is almost too small to lead to a change in its population in the equilibrium.

In our studies of the hydrolysis of N-sulfinyl species[147,189] and following from the preceding, it is of high importance to determine which isomers of N-sulfinylhydrazines are energetically accessible. Thus, to gain further insight into the effect of the NSO functionality directly attached to the amide group on their chemical reactivity, in this paper we present the study of the electronic structure, relative stability and isomerization barriers for N-sulfinylhydrazides, substituent effects and effect of water on their rotational and keto-enol tautomerization barriers in comparison with reported amide transformations.

6.2. Methodology and computational details

The Becke3[117] – Lee, Young and Parr[118] hybrid density functional (B3LYP)[148] with the 6-31+G(2d,2p) basis set were employed in all calculations, using the Gaussian 03 suite of programs.[116] Four configurations/conformers of each N-sulfinylhydrazide, transition states (TS) for their interconversion, complexes with water and transition states for keto-enol tautomerization were fully optimized. In several cases, preliminary geometry constraints were applied, followed by the release of all constraints and tight geometry optimization. All optimizations were followed by vibrational frequency calculations, and all transition states were characterized by the presence of one imaginary frequency. Intrinsic reaction coordinate (IRC)[135,136] analyses were performed on selected transition states to validate the minimum energy reaction pathways.

The gas phase calculations within the chosen model chemistry provide a very good correlation between calculated and experimentally observed geometries and dipole moments for N-sulfinylamines and isocyanates.[189] To further validate the choice of model chemistry, and because of the lack of quantitative data on structure and reactivity of N-sulfinylhydrazides, results on formamide, studied with experimental X-ray[190] and electron[191] diffractions and with microwave spectroscopy,[192-194] were reproduced with our model chemistry. In addition, its isomerization was calculated and compared with results on N-sulfinylhydrazides.

The enthalpy term (ΔH_{298} and $\Delta H^{\ddagger}_{298}$) was used throughout for consistency with our previous studies.[147,189] The electronic, unscaled zero-point corrected energies and enthalpies of the modeled molecules, complexes and transition states are summarized in Table C-1 of Appendix C. Inter- and intramolecular bonding interactions were identified and analyzed within Bader's quantum theory of Atoms in Molecules (QTAIM),[51] using the AIM2000 program.[195] Orbital interactions were identified with the use of the Natural Bond Orbital (NBO) analysis of Weinhold.[196]

6.3. Results and discussion

6.3.1. Structures of N-sulfinylhydrazides 1 – 3

Because of our interest in the substituent effect on the hydrolysis of N-sulfinyl species and because of the lack of results on their electronic structures, N-sulfinylhydrazides (R–CO–NH–NSO) with R = H (**1**), Me (**2**) and Ph (**3**) were included in this study. Each syn-N-sulfinylhydrazide (syn with respect to S=O and N–N bonds) is best described by the equilibrium of four configurations; their optimized structures are shown in Figure 6-1. Additional higher-energy configurations of the N-sulfinylhydrazides, as they arise from isomerization around the N=S (leading to anti configurations) and the N–N_h bond (leading to sickle configurations), are not considered here. Throughout the paper, letters **K** and **E** are used for keto and enol tautomers, respectively, and subscripts **E** and **Z** for identification of their conformation with respect to the NNCO moiety. The subscript **h** is used to define atoms belonging to the hydrazide moiety, **R** for the atoms of the substituent (R = H, Me or Ph) as illustrated in Figure 6-1 for **1-K**$_\mathbf{Z}$, and **w** for atoms of water.

Because of the ability of the N=S=O group to conjugate with available *p*-orbitals or π-systems,[18,20,38,47,48,197] its direct attachment to the planar CONH group[198] leads to the planarity of the entire O−S−N−N_h−C_h−O_h skeleton in all configurations of **1** and **2**, and in **3-E**$_\mathbf{Z}$. The aromatic **3-K**$_\mathbf{Z}$, **3-K**$_\mathbf{E}$ and **3-E**$_\mathbf{E}$, on the other hand, possess a twist of the N_h–C_h−C_R=C dihedral angle equal to 22.7, 30.8 and 27.8°, respectively. Similar to the findings for formimidic acid (NHC(OH)H),[185] all enols of N-sulfinylhydrazides favour the E (s-cis) conformation of the O_h–H_h with respect to the C_h=N_h bond (Figure 6-1).

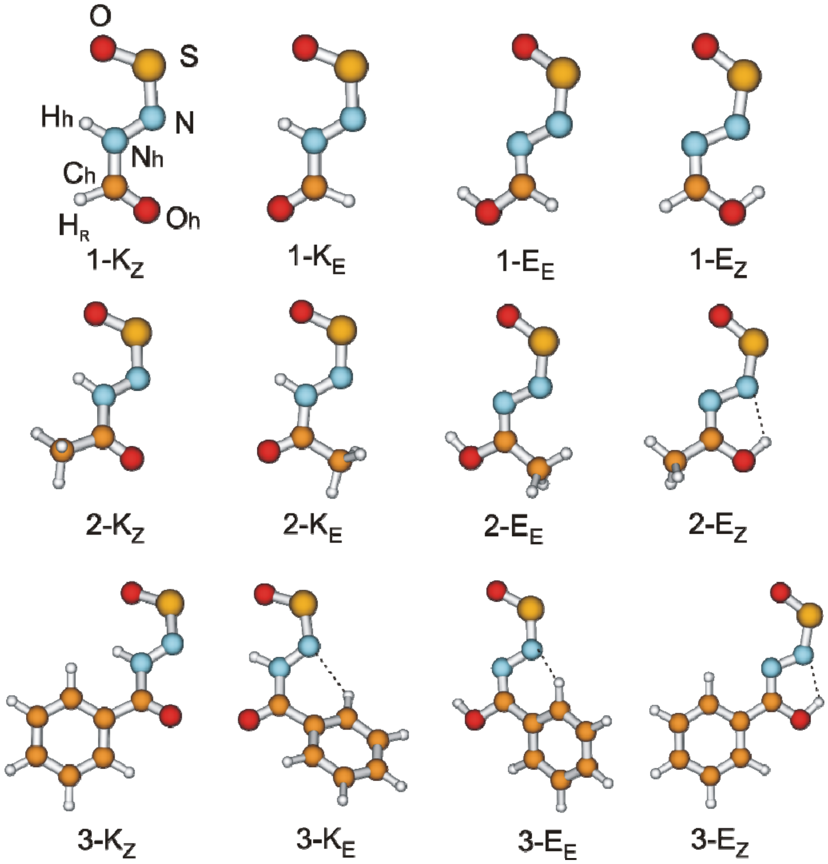


Figure 6-1. Optimized structures of four isomers of N-sulfinylhydrazides **1 – 3**. Intramolecular weak bonding interactions are shown with dotted lines.

The calculated relative enthalpies of the keto and enol forms of N-sulfinylhydrazides **1 – 3** are shown in Figure 6-2. Unlike in N-methylformamide (H–CO–NHCH$_3$) and formohydrazide (H–CO–NHNH$_2$), where the Z-configuration (with CH$_3$ or NH$_2$ group and O atom on the same side of the C–N bond, i.e., s-cis) is found to be more favourable than the E-form, the E-keto tautomers of N-sulfinylhydrazides are determined to be the lowest energy species, and their enthalpy is set as relative zero in Figure 6-2. As can be seen from Figure 6-2, the enol tautomers are much higher in enthalpy, in line with results from numerous studies performed computationally for formamide.[141,185-187] The different stabilities of keto and enol forms can be attributed to the different types of orbital interactions. For N-sulfinylhydrazides, while the *p*-hybridized lone pair of the hydrazide nitrogen conjugates with both the carbonyl $\pi^*(C_h=O_h)$ orbital and the NSO $\pi^*(N=S)$ orbital in the keto forms, in the enol forms a $\pi(N_h=C_h) \rightarrow \pi^*(N=S)$ interaction and an interaction of the sp^2-hybridized hydrazide nitrogen lone pair with available σ^* orbitals (from C_hO_h for Z and C_hH_R (C_hC_R) for E-configurations) is found. The amount of the charge transfer (or delocalization), determined through NBO analyses with results summarized in Table 6-2, is significantly larger in the keto tautomers, resulting in their higher stability.

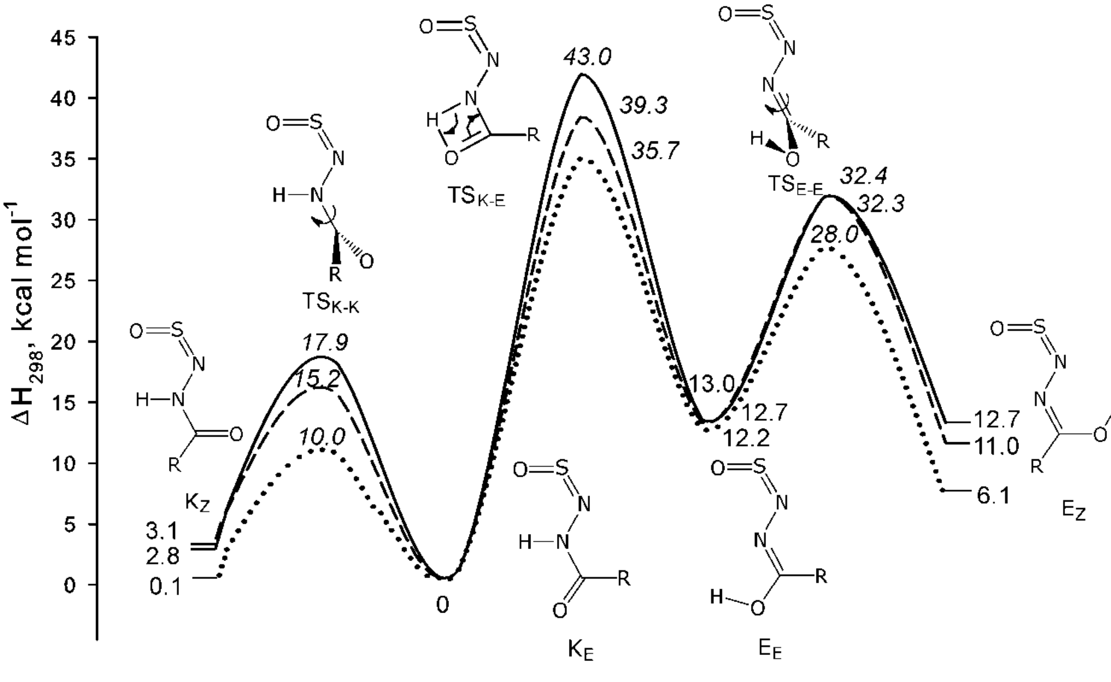


Figure 6-2. Relative stabilities and interconversion barriers for different configurations of N-sulfinylhydrazides **1** – **3** (**1** solid, **2** dashed, **3** dotted line).

The importance of the different types of orbital interactions can be seen further in the comparison of the enthalpy differences in pairs of E and Z conformations of each pair of tautomers. As can be deduced from Figure 6-2, the keto preference equal to 13.0, 12.7 and 12.2 kcal mol^{-1} in the E-pairs is notably larger than that in the Z-pairs (9.9, 7.9 and 6.0 kcal mol^{-1}). The analysis of data from Table 6-2 gives a good explanation, presented below, of these findings.

The amount of charge transfer does not differ much for E and Z configurations of the keto tautomers and agrees well with the small difference in their stabilities. The phenyl-N-sulfinylhydrazide (**3**) presents a particular interest in this respect. Thus, while Z ketones are less favourable than their E rotamers for **1** and **2**, the difference vanishes in **3**.

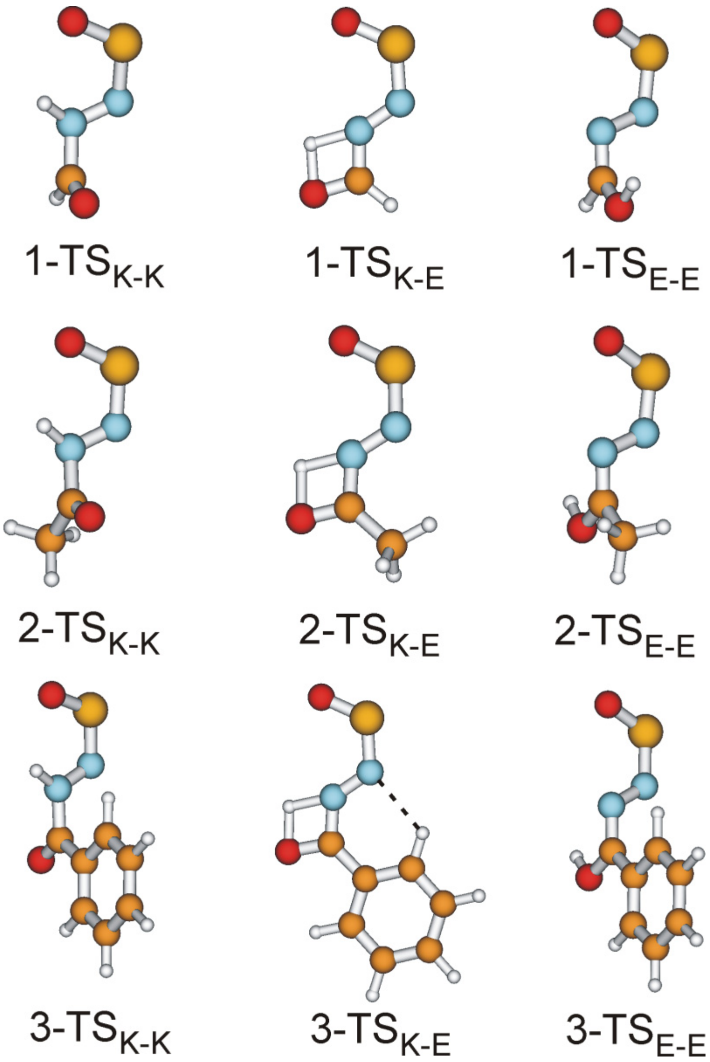
The amount of conjugation in Z enol tautomers, on the other hand, is slightly larger compared to that in the E-configurations, as can be seen from the amount of orbital interactons $\pi(N{=}C)\rightarrow\pi^*(N{=}S)$ and $n(O_h)\rightarrow\pi^*(N_h{=}C_h)$, summarized in Table 6-2. In addition, the $n(N)\rightarrow\sigma^*(O_hH_h)$ interaction in the Z-enols increases in going from H to Ph, resulting in the formation of O_hH_h…N interactions (shown in Figure 6-1 by dotted lines) in **2-E$_Z$** and **3-E$_Z$**, which is supported by an analysis of the electron density in the frame of the Atoms in Molecules theory, and is in line with the observed geometric changes (Table 6-1). The increasing enthalpy difference between the E and Z conformations of 1.7 and 6.1 kcal mol^{-1} from Me to Ph substituent is explained by the extended π-conjugation between the hydrazide moiety and aromatic ring in the latter case.

N=S and S=O bond lengths do not differ much for Z and E conformations in pairs of enol and keto forms of each N-sulfinylhydrazide and slightly increase with increasing electron-donating ability of the substituent, highlighting the extent of the conjugation

(Table 6-2 and Table 6-3). In accordance, contraction of the N–N_h bond and elongation of the corresponding N–C_h (or N=C_h) and C_h–O_h (or C_h=O_h) bonds are observed going from **1** to **2** and **3**.

When compared between tautomers, N=S and S=O bonds in the enol forms are shorter than those in the keto forms by 0.9 and 1.8 pm, respectively (average for all three species), again in accord with extensive conjugation and with the length of the N_h=C_h double bond in the enols, which is about 10 pm shorter on average than that of the partial N_h–C_h double bond in the keto forms. The NSO and SNN_h angles are more open in the enols; NSO angles of 113.5-113.8° for the keto tautomers are very close to those of 113.6 and 114.0° reported in experimental studies of dimerization of aromatic N-sulfinylhydrazines with X-ray[199] and neutron diffraction[54] techniques, respectively. This similarity is not at all unexpected and supports the notion that the keto forms of N-sulfinylhydrazides can be regarded as carbonyl derivatives of N-sulfinylhydrazines. On the other hand, the NSO angles for the enol forms, varying in the range from 118.8° to 119.7°, are very close to the average value of 120° determined for various aromatic and aliphatic N-sulfinyl amines both experimentally and computationally.[14,20,44,45,47,53,122]

Finally, the dipole moments (μ) of the N-sulfinylhydrazide enols are larger than those of the keto forms, but differences of 0.17 to 0.86 D are small, and therefore stabilization in aqueous solution should be comparable from simple polarity considerations. This is in contrast to the very different stabilization in solution that was proposed for formamide/formamidic acid and 2-pyridone/2-hydroxypyridine equilibria, where the dipole moments of the keto forms were found to be more than 3 D larger than those of the enols.[187]



1-TS$_{K\text{-}K}$ 1-TS$_{K\text{-}E}$ 1-TS$_{E\text{-}E}$

2-TS$_{K\text{-}K}$ 2-TS$_{K\text{-}E}$ 2-TS$_{E\text{-}E}$

3-TS$_{K\text{-}K}$ 3-TS$_{K\text{-}E}$ 3-TS$_{E\text{-}E}$

Figure 6-3. Optimized structures of transition states for rotation and tautomerization in N-sulfinylhydrazides **1-3**. The $C_o{-}H_o{\cdots}N$ interaction in **3-TS$_{K\text{-}E}$** is shown by a dashed line.

Table 6-2. Selected orbital interactions in keto and enol tautomers of N-sulfinylhydrazides **1–3**.

	Keto				Enol			
	$n(N_h)\rightarrow \pi^*(N{=}S)$	$n(N_h)\rightarrow \pi^*(C_h{=}O_h)$	$n(O_h)\rightarrow \sigma^*(N_hC_h)$	$n(O_h)\rightarrow \sigma^*(C_hH_R)$	$\pi(N{=}C)\rightarrow \pi^*(N{=}S)$	$n(N_h)\rightarrow \sigma^*(C_hO_h)$	$n(O_h)\rightarrow \pi^*(N_h{=}C_h)$	$n(N)\rightarrow \sigma^*(O_hH_h)$
1-K$_Z$	60.36	46.47	32.03	21.92				
1-K$_E$	63.72	45.47	30.10	21.08				
1-E$_Z$					21.84	14.52	48.83	5.89
1-E$_E$					20.90	11.50	44.94	
2-K$_Z$	62.80	44.12	34.85	20.93				
2-K$_E$	68.28	44.16	31.33	20.13				
2-E$_Z$					24.37	16.11	49.36	7.86
2-E$_E$					22.46	13.85	43.82	
3-K$_Z$	62.42	42.42	33.95	20.85[a]				
3-K$_E$	62.35	41.37	29.58	20.10				
3-E$_Z$					26.81	15.41	47.46	8.60
3-E$_E$					23.18	5.19 14.94[b]	41.23	

[a] $n(O_h)\rightarrow\sigma^*(C_hC_R)$. [b] $n(N_h)\rightarrow\sigma^*(C_hC_R)$.

Table 6-3. Selected geometric parameters (distances in pm, angles in degrees) and dipole moments (μ in D) of N-sulfinylhydrazides **1 – 3**.

	1				**2**				**3**			
	K_Z	**K_E**	**E_Z**	**E_E**	**K_Z**	**K_E**	**E_Z**	**E_E**	**K_Z**	**K_E**	**E_Z**	**E_E**
S=O	148.7	148.5	147.0	147.3	149.0	148.7	147.2	147.5	149.1	148.8	147.4	147.6
N=S	156.7	157.0	155.8	155.9	156.8	157.3	155.9	156.0	156.9	157.4	156.6	156.4
$N–N_h$	133.6	133.5	137.6	137.2	133.3	133.1	137.1	136.4	133.1	133.1	135.8	135.5
$N_h–C_h$ or $N_h=C_h$	139.2	138.8	129.5	128.5	140.6	140.2	130.4	129.6	140.7	140.6	131.2	130.2
$C_h=O_h$ or $C_h–O_h$	120.1	120.6	132.6	132.7	120.5	121.1	133.2	133.7	121.0	121.6	133.3	134.3
$O_h–H_h$			97.6	97.1			97.8	97.2			97.8	97.1
NSO	113.8	113.8	119.5	119.7	113.7	113.7	119.3	119.7	113.5	113.7	118.8	119.6
SNN_h	117.7	118.6	121.0	120.0	117.8	118.5	121.4	120.2	117.5	118.3	121.3	120.0
$N_hC_hC_RC_o$[a]									22.7	30.8		27.8
$C_o–H_o$[a]										108.1		107.9
$N^{\cdots}H_o$[a] or $N^{\cdots}H_h$							200.6			245.2	197.9	239.4
μ	2.03	2.37	2.89	2.72	2.59	3.08	3.22	3.55	3.46	3.90	3.63	4.39

[a] The subscript “o” defines the *ortho* C and H atoms of the aromatic ring involved in weak interactions.

6.3.2. Isomerization of N-sulfinylhydrazides 1 – 3: Rotation and tautomerization

All isomerization barriers are calculated with respect to the lowest energy configuration for each individual reaction and shown in Figure 6-2. The structures of the rotational transition states $\mathbf{TS_{K\text{-}K}}$ (for interconversion of keto forms) and $\mathbf{TS_{E\text{-}E}}$ (for interconversion of enol forms) and of those for tautomerization $\mathbf{TS_{K\text{-}E}}$ are displayed in Figure 6-3. In the transition states for tautomerization, due to the short distances, the partial bonds to the shifting hydrogen atom are shown as cylinders.

6.3.2.a. Isomerization of keto tautomers

Rotation about the $N_h{-}C_h$ bond in the ketones requires 17.9 (**1**), 15.2 (**2**) and 10.0 (**3**) kcal mol^{-1} (Figure 6-2). These barriers fit well with the range of about 15-20 kcal mol^{-1} determined for the restricted rotation around the C−N bonds in various amides.[168-175] A similarly strong dependence on substitution, where electron-donating substituents lower while electron-withdrawing substituents raise the torsional barrier, was reported for substituted amides and thioamides.[179]

Selected geometric parameters for all transition states are summarized in Table 6-4. The most important geometric change upon torsion in the keto isomers, which is also found in amides,[173] is the significant elongation of the $C_h{-}N_h$ bond. In the 90° rotational transition state, the lengthening of the $N_h{-}C_h$ bond consists of 6-7 pm, while the corresponding contraction of the $C_h{=}O_h$ bond is expectedly smaller, about 1 pm. The increasing lengths of S=O and N=S bonds in the keto rotational transition states correspond with the decreasing NSO and N_hNS angles. All of these features are consistent with a loss of conjugation. While the N−N$_h$ bond is almost unaffected, the N$_h$ atom is pyramidalized, which can be seen from the sum of its bond angles, equal to 358° for N-sulfinylhydrazide **1** and 348° for each **2** and **3**. Pyramidalization is not dramatic because of the residual n(N$_h$)→π*(NS) conjugation (about 35 kcal mol^{1}, as compared to 60-68 kcal mol^{-1} in Table 6-2).

Table 6-4. Selected geometric parameters (bond lengths in pm, angles in degrees) of transitions states for rotation and tautomerization of N-sulfinylhydrazides **1-3**.

	1			**2**			**3**		
	TS$_{K\text{-}K}$	**TS$_{E\text{-}E}$**	**TS$_{K\text{-}E}$**	**TS$_{K\text{-}K}$**	**TS$_{E\text{-}E}$**	**TS$_{K\text{-}E}$**	**TS$_{K\text{-}K}$**	**TS$_{E\text{-}E}$**	**TS$_{K\text{-}E}$**
S=O	149.2	148.7	147.7	149.4	149.0	147.9	149.5	149.0	148.1
N=S	157.6	159.8	156.8	157.8	160.0	157.0	157.7	160.2	157.4
N−N$_h$	133.7	127.9	133.8	133.4	127.8	133.4	133.4	127.6	132.8
N$_h$–C$_h$	145.5	124.9	135.2	147.3	125.5	134.0	146.9	126.0	133.2
C$_h$–O$_h$	119.3	135.1	127.0	119.7	136.1	127.6	120.4	136.2	128.4
C$_h$–H$_R$ or C$_h$–C$_R$	109.9	109.0	108.6	149.8	150.0	148.1	147.7	147.6	145.8
NSO	112.3	115.5	117.6	112.3	115.3	117.5	112.4	115.5	117.4
SNN$_h$	117.2	122.4	120.6	117.4	122.0	120.9	117.5	122.6	120.6
NN$_h$H$_h$	116.1	−	160.9	115.6	−	160.7	115.5	−	158.1
NN$_h$C$_h$	117.8	156.0	124.5	115.4	156.0	124.2	115.6	156.0	126.8
C$_h$N$_h$H$_R$ or C$_h$N$_h$C$_R$	123.7	−	74.6	117.1	−	75.1	116.6	−	75.1

6.3.2.b. Isomerization of enol tautomers

The calculated enthalpies of activation for interconversion of the more stable Z to the E enol isomers are somewhat larger than those for the keto forms. Barriers of 19.6 (**1**), 21.3 (**2**) and 21.9 (**3**) kcal mol^{-1} were calculated (represented by values of 32.4, 32.3 and 28.0 kcal mol^{-1} in Figure 6-1, i.e., relative to $\mathbf{K_E}$). Selected geometric parameters for the rotational transition states of the enol isomers **1-3** are summarized in Table 6-4. Transition states $\mathbf{TS_{E\text{-}E}}$ for **1** and **2** were obtained by initially constraining the NN_hC_h angle at 156° (value as found in the optimized $\mathbf{3\text{-}TS_{E\text{-}E}}$). The increase in NN_hC_h angle of 39.5-45.0° in the transition states compared to the initial enol isomers is consistent with the change in the hydrazide nitrogen lone pair from *sp*^{2}-type to *p*-type, and leads to a smaller than expected activation barrier for rotation.

Unlike in the keto forms, in $\mathbf{TS_{E\text{-}E}}$ of **1-3** the C_hN_hNSO skeleton is planar with substantial lengthening of the $N{-}N_h$ bond (9.7 (**1**), 8.6 (**2**) and 7.9 (**3**) pm), which becomes less prominent for the electron-donating substituents. The lengthening of the C_hN_h bond is even smaller and varies in the range of 3.6-5.2 pm. Elongation of the S=O bond is less pronounced, and that of the N=S bond is more pronounced, than found for twisting in the keto tautomers. All those findings are in line with the significant changes in orbital interactions in the transition state for the rotation comparing to enols; where the appearance of significant contribution of the $n(N_h) \rightarrow \pi^*(NS)$ orbital interaction replaces the existing $\pi\rightarrow\pi^*$ and $n\rightarrow\sigma^*$ conjugative interaction in isolated enols (Table 6-2).

6.3.2.c . Tautomerization of N-sulfinylhydrazides and explicit effect of water

The in-plane keto-enol tautomerization (transition state structures shown in Table 6-4) requires the high activation enthalpy of 43.0 (**1**), 39.3 (**2**) and 35.7 (**3**) kcal mol^{-1}

(Figure 6-2), exhibiting a decrease with increasing electron-donating ability of the substituent.

In the transition states for tautomerization, C_hO_h and N_hH_h bonds elongate while N_hC_h shortens, with a corresponding decrease in the $N_hC_hO_h$ angle, going from 106.6 (**1**) to 104.9 (**2**) and 103.4° (**3**), which implies an increase in proton mobility in this order (Table 6-3). In **3**, both $\mathbf{K_E}$ and $\mathbf{E_E}$ possess intramolecular blue-shifting hydrogen bonds (Figure 6-1), and the contraction of $N–N_h$ and $C_h–C_R$ bonds $\mathbf{TS_{K\text{-}E}}$ results in their strengthening, with $C_oH_{o\ldots}N$ distance and C_oH_oN angle calculated to be 236.9 pm and 121.7°, respectively.

The strain in the four-membered ring transition states is responsible for the high reaction barriers, suggesting a low probability of keto-enol tautomerization of N-sulfinylhydrazides in the gas phase. On the other hand, the catalytic effect of water has been described in detail for various types of reactions, including amide isomerizations[141,186,200] and hydrolyses.[18,99,101,105] We also reported the decrease in activation barrier for the hydrolysis of N-sulfinylamines and isocyanates upon an increase in the number of participating water molecules.[147,189] Consequently, to determine the solvent effect on the tautomeric equilibrium of N-sulfinylhydrazides, we modeled this reaction in the presence of one and two water molecules for isomerization of **1** only, because **2** and **3** are not expected to behave differently.

The structures of the complexes and transition states of explicitly solvated $\mathbf{1\text{-}TS_{K\text{-}E}}$ are shown in Figure 6-4, while selected geometric parameters are listed in Table C-2 of the Apendix C, including the corresponding data for the isolated **1** for comparison.

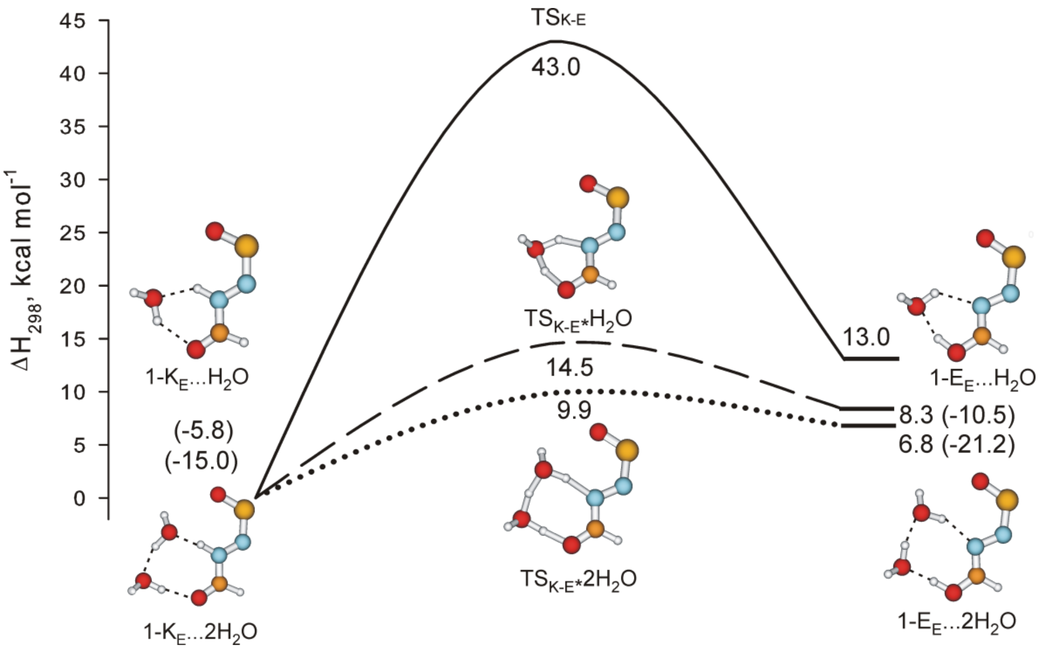


Figure 6-4. Relative stabilities of complexes and keto-enol tautomerization barriers for N-sulfinylhydrazide **1**: isolated (solid line), hydrated (dashed line) and dihydrated (dotted line).

Similar to amide tautomerization,[141,186] the addition of water significantly stabilizes the enol in comparison to the keto form. Binding energies of 5.8 and 15.0 kcal mol^{-1} (complex of the keto form plus one and two water molecules, respectively) and 10.5 and 21.2 kcal mol^{-1} (for the enol form), given in Figure 6-4 by the negative numbers in parentheses, are calculated. The higher basicity of nitrogen compared to oxygen renders the former a better hydrogen bond acceptor and leads to the more stable complexes. At the same time, the higher acidity of the hydroxyl O_h–H_h, compared to the amino N_h–H_h group, results in the stronger O_w–H_w...N_h interaction in the enol complexes.

As expected, the explicit inclusion of water molecules, with formation of six- and eight-membered rings, decreases the activation enthalpies for keto-enol tautomerization dramatically (Figure 6-4). Activation enthalpies in Figure 6-4 are calculated based on the keto form or its complex. Equally importantly, the enol tautomers become energetically less unfavourable upon complexation with water, with the enthalpy difference between keto and enol forms of **1** decreasing from 13.0 kcal mol^{-1} in the isolated species to 6.8 kcal mol^{-1} in the dihydrated species (Figure 6-4). For formamide, shown in Figure C-1 of Appendix C, the stabilization of the enol form is less efficient, resulting in a decrease in keto-enol enthalpy difference from 12.8 (isolated) to 10.3 (two water molecules) kcal mol^{-1} only. Moreover, the activation enthalpies for formamide keto-enol tautomerization are calculated to be 17.1 and 13.9 kcal mol^{-1} in complexation with one and two water molecules, respectively, are therefore lowered less than for N-sulfinylhydrazides.

Both, the smaller activation barriers for hydrolysis and the higher stability of the enol form of N-sulfinylhydrazides, as compared to the amido-imide situation in amides, suggest the higher possibility of the existence of the enolic form of N-sulfinylhydrazides in solution. This, in turn, leads to the conclusion that enol isomers must not be neglected in studies of the hydrolytic reactivity of N-sulfinylhydrazides. In fact, in Chapter 7 we show that the enol tautomers of N-sulfinylhydrazides hydrolyze far more readily than the keto tautomers.

6.4. Summary and conclusions

The relative stabilities of four configurational isomers of N-sulfinylhydrazides and their isomerization barriers were determined. The isolated keto tautomers are energetically significantly more favourable than the corresponding enols. The effects of conjugation and hydrogen bonding in relation to the stability of the isolated isomers as well as their isomerization barriers were discussed. The barrier for rotation around the N_h–C_h (partial double) bond in ketones was found to decrease with an increasing electron-donating ability of the substituent. In contrast, rotation around the true C_h=N_h double bond in enols, found to involve a change in hybridization on the hydrazide nitrogen and determined to be higher in energy, exhibits an increase with increasing electron-donating ability of the substituent, but this effect is less pronounced. As expected, the barriers for keto-enol tautomerization of N-sulfinylhydrazides are found to be large in the gas phase. Explicit water molecules in the reaction coordinate for keto-enol tautomerization not only decrease the reaction barrier but also substantially increase the stability of the enol complexes, thus increasing their importance in the hydrolytic reactivity of N-sulfinylhydrazides.

Chapter 7.

From inert to explosive: The hydrolytic reactivity of R–NSO compounds understood.

A computational study[*]

7.1. Introduction

The history of discovery of N-sulfinylamines (R−N=S=O), sometimes referred to as N-thionyl-,[9,10] N-sulphinyl-,[12,14-16] -imines,[16,20] -imides[9] or iminooxosulfuranes[23] can be traced back to the 1890s, when they were synthesized and first investigated by Michaelis and co-workers.[2,3] Since then, N-sulfinylamines have found wide application in cycloaddition reactions, which with a few exceptions[142] occur across the N=S bond. [2+2], [2+4] and 1,3-dipolar cycloadditions are the most common reactions of N-sulfinylamines, which in Diels-Alder additions can play the role of either diene or dienophile.[60]

A synthetically less useful but nevertheless important set of reactions characteristic for N-sulfinylamines is that with proton-active compounds,[24] such as water, alcohols, thiols and hydrogen halides (Scheme 7-1).

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$$\mathrm{R{-}N{=}S{=}O} + 2\,\mathrm{HX} \longrightarrow \mathrm{RNH_2} + \mathrm{SOX_2}$$

Scheme 7-1. N-sulfinylamines reactions with proton-active compounds.

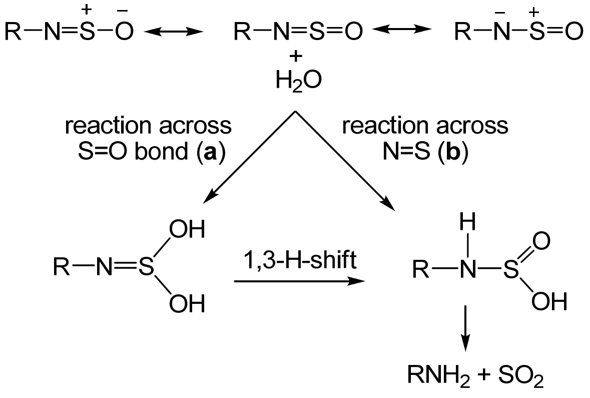
Within this set, hydrolysis represents a particular interest because, depending on the substituent R attached to the N=S=O group, the reactivity with water varies dramatically. Thus, for example, chloro-N-sulfinylamine (R = Cl) reacts explosively with water,[81] while aromatic N-sulfinylamines (e.g., R = Ph) hydrolyze more slowly,[24] and aromatic N-sulfinylhydrazines (e.g., R = Ph–NH) are stable towards water.[19,25] Besides the general interest in this intriguing trend, the importance of understanding the exceptional inactivity of N-sulfinylhydrazines towards moisture stems from their activity as acaricides and pesticides[83,85,201] and from their potential application as anti-cancer agents.[202] N-sulfinylamides (R−CO−N=S=O) and -hydrazides (R−CO−NH−N=S=O), with one exception,[86,87] and even though there is no quantitative comparison of their reactivity with other N-sulfinyl species, are also known to react rapidly with water.[19,86,87] Interestingly, whereas amides and hydrazides hydrolyze through nucleophilic attack of water on the carbonyl carbon,[99,100,102,203] their sulfinyl derivatives follow the same mechanism of hydrolysis as N-sulfinylamines.

Even though more than 600 N-sulfinyl compounds are known,[126] only several aromatic N-sulfinylamines,[12,18,20,36,44,45,47,52,122,123,154,204,205] –hydrazines,[54,199] mono- (R−S−NSO) and disulfides (R−S−S−NSO)[206-208] were structurally characterized and their reactivity analyzed to some extend. While it appears that steric hindrance leads to kinetic stabilization,[5,209] attempts to determine electronic effects of substitution on an aromatic ring were not always conclusive due to the presence of multiple substituents.[5-7,88]

Quantitatively, the introduction of a methyl group in *para*-position of N-sulfinylaniline caused a decrease in the rate constant of its uncatalyzed hydrolysis, with the induction period increasing from 4 to 10 h,[89] suggesting that electron-donating substituents stabilize N-sulfinylamines towards water. Accordingly, electron-withdrawing substituents have the opposite effect and increase the rate of the hydrolysis reaction.[17]

While the neutral hydrolysis of N-sulfinylaniline is a relatively slow process that requires an activation energy of 9.88 kcal mol^{-1},[17] the reaction can be catalyzed by both acids and bases. In the presence of pyridine, for example, hydrolysis is first order in each N-sulfinylaniline, water and pyridine, and proceeds with an activation enthalpy of 5.7 kcal mol^{-1}.[89] For both neutral and pyridine-catalyzed hydrolyses, the low activation entropies of –58 and –51 e.u.,[89] respectively, imply the need for proper orientation of the reacting molecules. It was proposed that water acts as a nucleophile in the rate-determining step of the reaction, with the water oxygen attacking the sulfur atom of the NSO moiety, similar to alcoholysis.[13,57,58,95] Consequently, the complexation of pyridine with water (or an alcohol) increases the nucleophilicity of the latter towards the electrophilic sulfur and thus facilitates the hydrolysis of N-sulfinylamines.[89,96]

Because only two kinetic studies of the hydrolysis of N-sulfinylanilines have been reported to date,[17,89] we have evaluated the mechanism of hydrolysis of several substituted N-sulfinylamines computationally (Chapter 4 and Chapter 5).[147,189] Reaction can occur across the S=O or the N=S bond, according to the resonance structure representation (**I** and **II**, Scheme 7-2) and the concerted hydroxylation of sulfur and protonation of either oxygen or nitrogen of the NSO group is indeed the rate-determining step of the reaction.[147,189] The two-water-molecule model was found to be sufficient for the description of the hydrolysis, and the reaction barriers decrease with increasing electron-withdrawing ability of the substituent (Chapter 5).[189]



Scheme 7-2. Mechanisms of reaction of N-sulfinyl species with water.

While this constitutes a promising initial conclusion, it was obtained for CF_3–N=S=O only (Chapter 5),[189] and general conclusions for the change in hydrolytic behavior of the extended R–N=S=O series[19,24,25,81] (amines, hydrazines, hydrazides, amides) cannot be drawn. Thus, a division into classes is necessary to address the structure-reactivity issues of N-sulfinyl compounds.

In this paper, similarities and differences in the electronic structures of the four classes of N-sulfinyl species introduced above are analyzed in relation to their reactivity with water in order to bring a quantitative meaning to the existing qualitative experimental results. Because of the lack of data on the aliphatic compounds in general and to compare the reactivity within each class, hydrogen, methyl and phenyl substituents for each N-sulfinylamine, -hydrazine, -hydrazide and -amide are included in this study. We begin by describing the effect of the substituent on the geometries and structures of each class of compounds and follow this with the study of the two possible reaction mechanisms of N-sulfinyl species with water in relation to their electronic structure and its effect on the hydrolysis rate.

7.2. Computational details and methodology

All calculations were performed with the Becke3[117] – Lee, Young and Parr[118] hybrid density functional (B3LYP)[148] with the 6-31+G(2d,2p) basis set, using the Gaussian 98[115] and Gaussian 03[116] suites of programs. The reliable performance of this model chemistry in the study of N-sulfinyl species was suggested from a strong correlation between calculated and experimentally observed geometries and dipole moments of N-sulfinylamines and of isocyanates[189] and in the reproduction of isomerization barriers of formamide.[210]

It was shown that the explicit inclusion of two water molecules in the gas-phase calculations of N-sulfinylamines or isocyanates is sufficient for the proper description of their hydrolysis (Chapter 5).[189] This is in agreement with the experimental findings that specific interactions between the reactants and the solvent molecules influence the reaction rates to a greater degree than the solvent polarity. It was shown that while increasing solvent polarity leads to an increase in the rate of hydrolysis (as well as that of alcoholysis) of N-sulfinylamines and isocyanates, even weakly polar solvents that cannot hydrogen-bond can accelerate the rates of reaction by increasing the concentration of complexes of catalyst with water or alcohol, or of complexes between water/alcohol molecules themselves.[89,94,146]

The parent molecules and their complexes and transition states with water were fully optimized. Some geometric constraints in terms of frozen distances or dihedral angles were applied in preliminary optimizations for some complexes and transition states of N-sulfinylhydrazines, several -hydrazides and -amides with water; these were followed by the release of all constraints and tight geometry optimizations. The order of saddle points was determined through vibrational frequency calculations. Despite the possibility of configurational isomers for N-sulfinyl compounds, only the most energetically favorable syn configuration is considered here.[10,12,15,20,36,45-47,122-126] The intrinsic reaction coordinate (IRC)[135,136] procedure was applied to selected transition states to verify the nature of the potential energy surface for a proposed reaction path.

The enthalpy term (ΔH_{298} and $\Delta H^{\ddagger}_{298,}$ kcal mol^{-1}) is used throughout for consistency with our previous papers (Chapter 4 and Chapter 5).[147,189] The electronic, unscaled zero-point corrected energies and enthalpies of the modeled molecules, complexes and transition states are summarized in Table D-1 of Appendix D. The averaged entropy contribution $-T\Delta S$ is determined to be about 5 kcal mol^{-1} for reactions across both the N=S and S=O bonds for various N-sulfinyl species, as can be seen from the correlation in Figure D-1 of Appendix D.

Weak bonding interactions within molecules, in their complexes and transition states, and all atomic charges were determined from electron density analyses within the quantum theory of Atoms in Molecules (QTAIM),[51] using the AIMPAC series of programs,[137] but only the relevant results are included here. It is worth mentioning that apart from AIM charges, Natural Bond Orbital (NBO) charges can be used as well in the analyses, with qualitatively the same result, whereas Mulliken charges cannot be used (Figure D-2 of the Supporting information). The nature of orbital interactions and the degree of electron delocalization in the parent molecules and the transition states were evaluated using the NBO analysis of Weinhold and co-workers.[196] The Natural Resonance Theory (NRT)[211] approach was applied for the determination of the contribution of various resonance structures to the overall electronic structure.

The following abbreviations are used for each N-sulfinyl class: **SAn** for amines, **SAd** for amides, **SHn** for hydrazines, and **SHd-K** and **SHd-E** for keto and enol forms, respectively, of hydrazides. Hydrogen, methyl and phenyl substituents are indicated with a preceding **H**, **Me** or **Ph**, respectively. The subscript "R" defines the atom directly attached to an NSO group, "r" the other the atoms of the substituent important for discussion, "N" the hydrogen atom of a hydrazine or hydrazide moiety, "o" the *ortho*-hydrogen and -carbon atoms of a phenyl ring involved in weak bonding interactions and finally "w" the oxygen and hydrogen atoms belonging to water molecules.

7.3. Results and discussion

7.3.1. Geometry and electronic structure of various N-sulfinyl species

7.3.1.a. N-Sulfinylamines (R–NSO)

These are the most extensively studied N-sulfinyl species. X-ray, IR and Raman, UV, microwave and NMR spectroscopy techniques,[10,12,15,36,44-46,122-126,154] as well as various theoretical model chemistries[20,47,48,52,53] have been employed for the determination of their structural characteristics. Geometric parameters and substituent effects on the activation enthalpy for the hydrolysis of N-sulfinylamines with R = H, Me, Ph and CF_3 were discussed in detail in our previous paper in comparison to the corresponding substituted isocyanates (Chapter 5).[189] Consequently, to avoid repetition, only the features important in the current context are addressed here. A graphical representation of the optimized N-sulfinylaniline (Ph–NSO, **PhSAn**) is given in Figure 7-1, along with those of the corresponding aromatic representatives of the other N-sulfinyl classes.

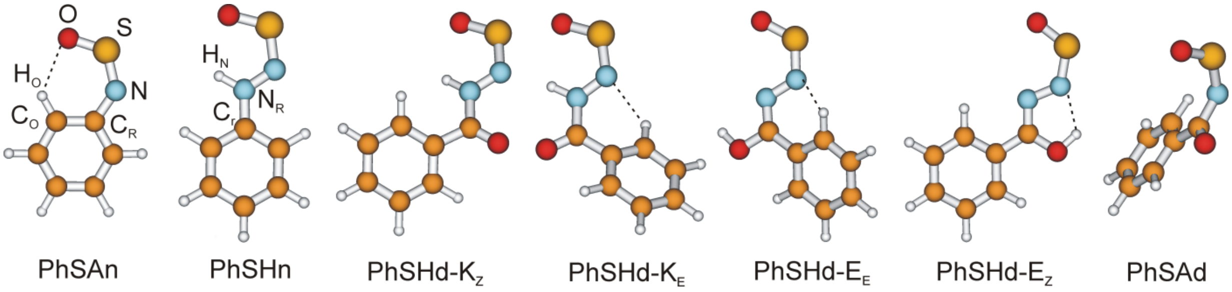


Figure 7-1. Optimized phenyl-N-sulfinyl species: amine (**PhSAn**), hydrazine (**PhSHn**), hydrazide (**PhSHd**) and amide (**PhSAd**).

The three N-sulfinylamines of interest, H–NSO (**HSAn**), Me–NSO (**MeSAn**) and Ph–NSO (**PhSAn**), are planar, with the N=S=O group bent at about 120°; this also holds for other reported N-sulfinylamines without steric hindrance.[15,20,36,44-49] The bent gives rise to weak interactions upon substitution. In accord with experimental findings,[122] one C_R–H_r bond in **MeSAn** is aligned with the S=O bond due to a favorable bond dipole interaction, and the reported experimentally determined rotational barrier around the C_R–N bond of 335±15 cal mol^{-1} [36] agrees well with the 0.31 kcal mol^{-1} we obtained as ZPVE-corrected electronic energy with B3LYP/6-31+G(2d,2p). In **PhSAn**, as in all other aromatic N-sulfinylamines that are not substituted in *ortho*-position, the NSO group is co-planar and enters in conjugation with the aromatic ring.[12,15,39,47] The proximity of the NSO oxygen atom to an *ortho*-hydrogen of the ring, which was proposed to decrease the barrier for the C_RN bond internal rotation,[12] is in fact best described as a stabilizing C_o-H_o...O interaction (a blue-shifting hydrogen bond, shown in Figure 7-1 by the dotted line),[110] characterized by the contraction of the C_o–H_o bond upon interaction.

7.3.1.b. N-Sulfinylhydrazines (R–NH–NSO)

Unlike the numerous works on N-sulfinylamines, there are only a few studies on the structural characterization and reactivity of aromatic N-sulfinylhydrazines. While in general N-sulfinylhydrazines, like other hydrazines, can bear two substituents R on the hydrazine nitrogen atom (N_R in Figure 7-1), here only mono-substituted N-sulfinylhydrazines are considered. Formation of hydrogen-bonded dimers in condensed phases is one of the remarkable features of these species. For N-phenyl-N'-sulfinylhydrazine (Ph–NH–NSO, **PhSHn**), two distinct networks of hydrogen bonds have been proposed, one based on experimental X-ray and neutron diffraction studies,[54,199] the other on quantum chemical calculations.[209,212] While the former work suggests N–H...O interactions only, the latter suggests the additional participation of C_o–H_o...O interactions (Figure 7-2), similar to that in **PhSAn** (Figure 7-1), which have since been confirmed through ^{1}H NMR studies.[213] Depending on the solvent, the dimers dissociate upon dilution to varying degrees,[212] and monomers would dominate in conditions suitable for hydrolysis studies, yet hydrolysis was not observed experimentally.[19]

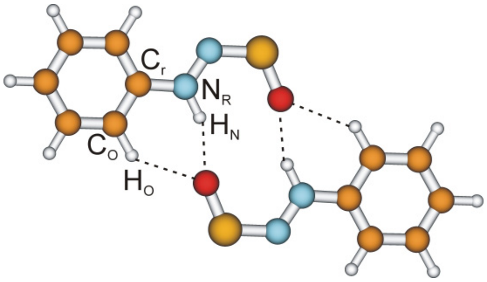


Figure 7-2. Network of weak interactions in the **PhSHn** dimer as suggested from references.[209,212]

Because of the lack of experimental results for aliphatic N-sulfinylhydrazines, selected geometric parameters for H–NH–NSO (**HSHn**), Me–NH–NSO (**MeSHn**) and Ph–NH–NSO (**PhSHn**) are summarized in Table 7-1, with the graphical representation of the optimized **PhSHn** given in Figure 7-1.

Table 7-1. Selected geometric parameters (bond lengths in pm, angles in degrees) of N-sulfinylhydrazines (R–NH–NSO) **RSHn**.

	HSHn	**MeSHn**	**PhSHn**
S=O	149.6	150.2	150.0
N=S	157.8	158.8	158.9
$N{-}N_R$	132.6	131.4	131.4
$N_R{-}H_r$ or $N_R{-}C_r$	100.7	144.9	140.0
$N_R{-}H_N$	101.7	101.9	102.1
NSO	112.2	111.5	111.5
SNN_R	117.6	117.5	117.0
NN_RH_N	118.4	116.9	117.1
NN_RC_r or NN_RH_r	115.3	119.3	122.8
$C_rN_RH_N$ or $H_rN_RH_N$	120.0	120.9	120.0

For the two aliphatic species, **HSHn** and **MeSHn**, the $OSNN_RH_N$ skeleton is not planar. The deviation from planarity, determined as the sum of the bond angles on N_R, decreases from 353.7° (**HSHn**) to 357.1° (**MeSHn**), and vanishes for **PhSHn** (359.9°). This suggests an increasing conjugation of the electron lone pair of N_R with the NSO moiety in the series. The $n(N_R)\rightarrow\pi^*(N=S)$ orbital interaction, determined from NBO analysis,[196] that defines the efficiency of conjugation consequently increases across the series and is largest for **PhSHn** with 76.6 kcal mol^{-1} (Table 7-2). Despite the higher value for this aromatic N-sulfinylhydrazine, Table 7-1 shows that the S=O, N=S and $N-N_R$ bond lengths do not differ much between the methyl- and phenyl-substituted molecules, suggesting similar inductive properties of these substituents. This is clearly in contrast to the unsubstituted **HSHn,** where the S=O and N=S bonds are shorter, while $N-N_R$ is longer, illustrating once again the well-known fact that conclusions drawn from such a minimalistic model cannot always be generalized. For the aromatic **PhSHn**, conjugation extends from the NSO group through N_R to the phenyl ring, with an $n(N_R)\rightarrow\pi^*(C=C)$ interaction of 33.2 kcal mol^{-1}, a value resembling that in the related aniline (25.5 kcal mol^{-1}). This interaction is reflected in the shortening of the N_R-C_r bond by almost 5 pm from **MeSHn**.

The most characteristic geometrical feature that distinguishes N-sulfinylhydrazines from N-sulfinylamines is the significantly smaller NSO angle of the former, about 112° compared to 120°, which hardly changes upon substitution (Table 7-1). Further down, this smaller angle will be addressed in more detail, its origin and effect on the hydrolytic behavior of N-sulfinylhydrazines. A consequence of the small angle for the geometry of these molecules is the resulting proximity of H_N and NSO oxygen atoms, determined to be 230.3 (**HSHn**), 224.1 (**MeSHn**) and 221.9 (**PhSHn**) pm. Yet, despite these small distances, intramolecular N–H...O interactions are not detected for the N-sulfinylhydrazines from QTAIM with the model chemistry used here. From hydrogen-bonding criteria, this could simply be attributed to the unfavorable, small

N_RH_NO angle (between 106.5 and 110º, depending on the substituent).[214] On the other hand, the presence or absence of the N–H...O interaction in the monomers of **PhSHn**, as indicated through a bond critical point in QTAIM, depends on minute geometry changes and therefore on the model chemistry: the proximity of bond and ring critical points in (substituted) N-phenyl-N'-sulfinylhydrazines as determined with B3LYP/6-31+G(d) demonstrates the structural instability of these molecules,[45,212] where a small increase in H...O distance leads to the annihilation of both critical points.[51] Considering the angle, any H...O bond critical point in these monomers should probably be attributed to the presence of favorable bond dipole interactions rather than to hydrogen bond formation.[47,209]

Table 7-2. Important orbital interactions (kcal mol^{-1}) within N-sulfinylhydrazines, ketones of -hydrazides and related compounds, from NBO.

	$n(N_R)\rightarrow\pi^*(N{=}S)$	$n(N)\rightarrow\pi^*(C{=}O)$	$\pi(N_RC)\rightarrow\pi^*(NS)$[a]	$\pi(NS)\rightarrow\pi^*(N_RC)$[a]
HSHn	45.5			
MeSHn	74.9			
PhSHn	76.7	33.2 (C=C)[b,c]		
HSHd-(Z)	60.4	46.5[b]	21.8	9.0
HSHd-(E)	63.7	45.5[b]	20.9	9.3
MeSHd-(Z)	68.3	44.2[b]	24.4	8.9
MeSHd-(E)	62.8	44.1[b]	22.5	9.2
PhSHd-(Z)	62.4	42.4[b]	26.8	8.4
PhSHd-(E)	62.4	41.4[b]	23.2	9.7
Formamide		62.7		
Acetamide		59.7		
Benzamide		44.5		
HSAd		6.2 (4.7)[d]		
MeSAd		14.0		
PhSAd		11.1		

[a] Orbital interactions in enol tautomers of N-sulfinylhydrazides. [b] Electron lone pair on N_R. [c] For the $n(N)\rightarrow\pi^*(C{=}C)$ interaction. [d] $n(N)\rightarrow\sigma^*(CO)$.

7.3.1.c. N-Sulfinylhydrazides (R–CO–NH–NSO)

Despite the fact that N-sulfinylhydrazides can be regarded as the amido derivatives of N-sulfinylhydrazines, with one exception they are known to react with water readily.[19,86] Benzyl-N-sulfinylhydrazide ($PhCH_2$–CO–NH-NSO) was found to be thermally and hydrolytically quite stable, which was attributed to the greater charge delocalization in its enol form compared to that of the enol form of phenyl-analog.[86]

Even disregarding syn-anti isomerization of the NSO group, N-sulfinylhydrazides are rich in isomers. The two enols (E_E and E_Z, where E or Z reflect the configuration of the C_r–O_r with respect to the N–N_R bond) and two ketones (K_E and K_Z) are shown in Figure 7-1 for phenyl-N-sulfinylhydrazide (Ph–CO–NH–NSO, **PhSHd**). Their relative stabilities, rotational barriers around the N_R–C_r bond and keto-enol tautomerization, along with those for the unsubstituted (H–CO–NH–NSO, **HSHd**) and the methyl- (Me–CO–NH–NSO, **MeSHd**) N-sulfinylhydrazide, were studied in detail and are presented separately.[210] Besides differences in S=O, N=S and N–N_R bond lengths for the various isomers of N-sulfinylhydrazides, which will be discussed below with respect to the NRT analysis of resonance structure weights, NSO angles of about 120° (resembling N-sulfinylamines) are found for the enols, whereas NSO angles of about 113° (resembling N-sulfinylhydrazines) are found for the keto tautomers.

The keto forms of N-sulfinylhydrazides are significantly lower in enthalpy than the enol forms, by about 6–10 (Z isomers) and 12.5 (E isomers) kcal mol^{-1}, in analogy to "regular" ketones or amides and their enol tautomers.[185-187] These differences can be rationalized in terms of the different orbital interactions within keto and enol tautomers of N-sulfinylhydrazides. The *p*-type electron lone pair of N_R in a keto form conjugates with both adjacent π systems, and in particular the size of the $n(N_R)\rightarrow\pi^*(C_r{=}O_r)$ interaction agrees well with that in "regular" amides (Table 7-2). In contrast, the corresponding sp^2-type lone pair in an enol form is restricted to interactions with the σ-framework, and the N=C/N=S interactions, whose mutual contributions are given in Table 7-2, cannot compensate. The electronic effects will be further discussed below in connection with the reactivity.

7.3.1.d. N-Sulfinylamides (R–CO–NSO)

The selected geometric parameters of N-sulfinylamides H–CO–NSO (**HSAd**), Me–CO–NSO (**MeSAd**) and Ph–CO–NSO (**PhSAd**) are summarized in Table 7-3 with the graphical representation of the optimized **PhSAd** given in Figure 7-1. The close-to-perpendicular orientation of C_ROR and NSO planes is the most characteristic geometrical feature of this class of N-sulfinyl compounds, distinguishing it from all others included in this study. The SNC_rO_r dihedral angles are given in Table 7-3. For **PhSAd**, the NSO group is twisted away from the electron cloud of the aromatic ring and towards the carbonyl oxygen atom with its smaller repulsive interaction. The stabilization of the perpendicular orientation of the carbonyl group with respect to the NSO moiety is aided by the favorable and sizeable $n(N)\rightarrow\pi^*(C{=}O)$ interaction (Table 7-2).

The barriers for rotation about the C_R–N bond are calculated to be 2.2 (**HSAd**), 2.9 (**MeSAd**) and 1.9 (**PhSAd**) kcal mol^{-1} for the antiperiplanar (with respect to the substituent), and, in the same order, 0.6, 3.0 and 7.9 kcal mol^{-1} for the synperiplanar transition states. The smaller repulsion between the carbonyl and NSO oxygen atoms is responsible for the lower barrier to rotation in the antiperiplanar transition states, while the increasing values for synperiplanar planarization are due to the tremendous changes in C_RNS angle in the transition states. Starting with a decrease of 5.4° in **HSAd** due to the favorable alignment of S=O and C_RH_r bond dipoles, C_RNS increases by 3.7° in **MeSAd** and 21.5° in **PhSAd**, resulting in $C_RH_r\ldots O$ and $C_oH_o\ldots O$ interactions in the substituted species.

Table 7-3. Selected geometric parameters (bond lengths in pm, angles in degrees) of N-sulfinylamides **RSAd**.

	HSAd	**MeSAd**	**PhSAd**
S=O	146.4	146.7	146.6
N=S	152.6	152.5	152.5
N−C_R	141.4	143.2	143.1
C_R=O_r	119.9	120.3	120.9
C_R−H_r or C_R−C_r	110.3	150.5	148.5
NSO	119.2	119.2	119.6
SNC_R	129.6	128.4	128.0
N$C_R$$O_r$	123.5	120.0	119.8
N$C_R$$H_r$ or N$C_R$$C_r$	112.5	114.3	115.6
$O_r$$C_R$$H_r$ or $O_r$$C_R$$C_r$	123.9	125.6	124.5
SN$C_R$$O_r$	89.9	91.1	71.1

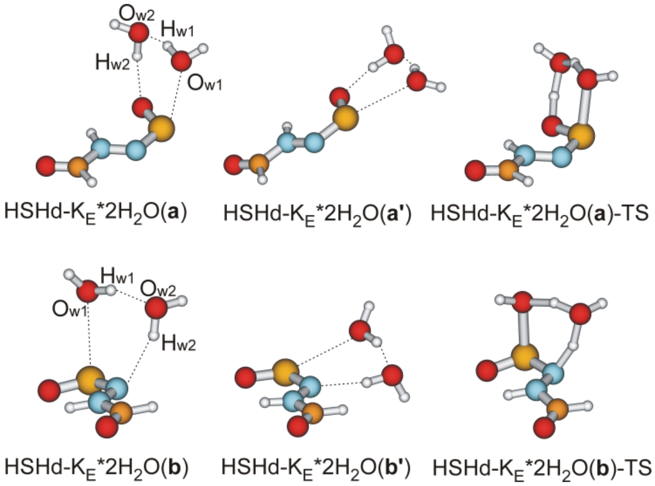
Despite the fundamental difference in orientation of substituent and NSO planes in N-sulfinylamides, the NSO angles of about 120° belong to the range characteristic for most N-sulfinyl species. In agreement with the twist between NSO and CO π-systems, a comparison of the selected geometric parameters within the series shows that the N=S and S=O bonds of N-sulfinylamides are much less affected by substitution than those in N-sulfinylamines or -hydrazines, but show a certain sensitivity to the electron-donation by methyl and phenyl groups (elongation of both the N−C_R and C_R=O_r bonds).

7.3.2. Hydrolytic behavior of various N-sulfinyl species as a result of their electronic structures.

7.3.2.a. Reactivity

Earlier experimental works conclude that hydroxylation of sulfur is the rate-determining step of the hydrolysis.[17,89] Modeling of the reaction confirms this conclusion and suggests a concerted mechanism with simultaneous hydroxylation of either oxygen or nitrogen of the NSO group.[147,189]

For N-sulfinylamines, pre-reaction complexation occurs in close-to-perpendicular orientation of the water dimer with respect to the N=S=O plane, for both reaction across the S=O (path **a**) and the N=S (path **b**) bond, according to the mechanism in Scheme 7-2. In addition, in the case of N-sulfinylhydrazines and for the keto forms of N-sulfinylhydrazides, relaxed optimizations of their complexes with the water dimer result in the formation of planar (**a'** and **b'**) complexes. Both types of complexes are presented in Figure 7-3 for **HSHd-K$_E$**. The binding and activation enthalpies for the hydrolysis of all N-sulfinyl species studied here are summarized in Table 7-4; the geometrical parameters are presented in Table D-2 of the Appendix D. In Table 7-4, a reaction barrier is calculated based on the enthalpy of the respective perpendicular complex (**a**, **b**); binding energies for the in-plane complexes (**a'**, **b'**) are included for comparison.



HSHd-K_E*$2H_2O$(**a**) HSHd-K_E*$2H_2O$(**a'**) HSHd-K_E*$2H_2O$(**a**)-TS

HSHd-K_E*$2H_2O$(**b**) HSHd-K_E*$2H_2O$(**b'**) HSHd-K_E*$2H_2O$(**b**)-TS

Figure 7-3. Optimized complexes and transition states for reaction of N-sulfinylhydrazide **HSHd-K$_E$** with two water molecules across the S=O (**a, a'**) and the N=S (**b, b'**) bond. Weak bonding interactions in the complexes are shown as dotted lines.

Table 7-4. Complexation[a] (ΔH_{bind}, kcal mol^{-1}) and activation ($\Delta H^{\ddagger}$, kcal mol^{-1}) enthalpies for the reaction of various N-sulfinyl species with two water molecules across the S=O and N=S bonds, as well as atomic charges (q, au) for atoms of the NSO group in the non-interacting molecules.

		across S=O			across N=S			q(N)	q(S)	q(O)
		ΔH_{bind}		$\Delta H^{\ddagger}$	ΔH_{bind}		$\Delta H^{\ddagger}$			
		a	**a'**		**b**	**b'**				
HSAn		-7.9		20.8	-7.2		18.3	-1.240	1.942	-1.115
MeSAn		-7.9		22.9	-6.8		21.1	-1.191	1.878	-1.127
PhSAn		-7.6		24.3	-6.0		24.8	-1.249	1.828	-1.121
HSHn		-8.7[b]	-8.5	30.0	-4.6	-5.7	28.8	-0.700	1.613	-1.136
MeSHn		-8.8	-8.7	30.7	-4.4	-5.1	30.0	-0.687	1.552	-1.139
PhSHn		-8.6[b]	-8.5	30.9	-4.5[b]	-5.2	32.0	-0.683	1.569	-1.134
HSHd	**E_E**	-8.1		22.5	-4.3		23.0	-0.810	1.777	-1.103
	E_Z	-7.5		22.9	-5.3		23.8	-0.856	1.798	-1.092
	K_Z	-6.8	-7.8	25.7	-6.5	-8.3	26.8	-0.707	1.721	-1.123
	K_E	-7.4	-8.1	26.3	-4.6	-5.2	28.9			
		(-11.1)[b,c]	(-10.4)[c]		(-11.7)[c]	(-12.3)[b,c]		-0.733	1.711	-1.121
MeSHd	**E_E**	-8.1	-7.9	23.5	-3.9		24.2	-0.807	1.757	-1.106
	E_Z	-8.0		23.9	-4.6		24.1	-0.855	1.777	-1.097
	K_Z	-6.7	-7.9	26.3	-6.5		27.5	-0.702	1.699	-1.128
	K_E	-7.5	-8.1	27.1	-4.2	-4.7	29.4	-0.728	1.684	-1.123
PhSHd	**E_E**	-8.0		24.0	-3.6		25.0	-0.790	1.735	-1.106
	E_Z	-7.9[b]		23.6	-5.4		24.7	-0.835	1.744	-1.099
	K_Z	-7.2	-7.9	27.0	-5.9		28.1	-0.695	1.688	-1.129
	K_E	-7.7	-8.2	27.4	-4.2		29.1	-0.720	1.677	-1.123
BzSHd[d]	**E_Z**	-8.7		24.1	-4.0		23.8	-0.853	1.776	-1.098
	K_E	-8.5[c]	-7.5	28.0	-4.3	-3.9	29.4	-0.727	1.686	-1.123
HSAd		-8.9		19.8	-7.9		14.2	-1.222	1.963	-1.098
MeSAd		-9.0		22.2	-7.4		17.6	-1.213	1.943	-1.107
PhSAd		-9.3		22.6	-6.0		19.8	-1.217	1.946	-1.100

[a] Perpendicular (**a** and **b**) and planar (**a'** and **b'**) complexes. [b] Possesses one imaginary frequency in the range 4*i* to 30*i*. [c] Values in parentheses are from MP2(fc)/6-311+G(d,p).[d] Ph–CH_2–CO–NH–NSO.

The energetic difference between perpendicular and in-plane complexes is not pronounced and, with a few exceptions, the perpendicular mode of binding is energetically favored by on average 0.7 kcal mol^{-1}, with the largest deviation of 1.8 kcal mol^{-1} found for interaction across the N=S bond for **HSHd-K$_E$** (data given in Table D-2 of Appendix D). For N-sulfinylhydrazines and -hydrazides, complexation across the N=S bond is in general less favorable, in agreement with the smaller negative charge on nitrogen compared to oxygen (Table 7-4). The interaction between the NSO sulfur atom and the water molecule in both perpendicular and planar complexes is mostly of electrostatic nature, as can be deduced from the small degree of charge transfer in the $n(O_{w1}) \rightarrow \pi^*$ interactions (1.3 kcal mol^{-1} for π^*(S=O) and 1.2 kcal mol^{-1} for π^*(N=S)) of the perpendicular complexes, and the $n(O_{w1}) \rightarrow \sigma^*$ interactions (0.3 kcal mol^{-1} for σ^*(SO) and 1.0 kcal mol^{-1} for σ^*(NS)) of the planar complexes. For comparison, the charge transfer in the $n(O) \rightarrow \sigma^*(OH)$ interaction in the water dimer of about 12 kcal mol^{-1} is an order of magnitude larger for this model chemistry. The change in the NSO…O$_w$ dihedral angle for reaction across the S=O bond in going from a perpendicular (**a**) to a planar (**a'**) complex results in a change in binding energy ranging from 7.4 to 8.4 kcal mol^{-1}, which implies a flat potential energy surface for the S…O$_w$ weak electrostatic intermolecular interaction.

To validate the notion of planar complexes, we employed MP2(fc)/6-311+G(d,p) calculations for the complexation of **HSHd-K$_E$**, with the results summarized in parentheses in Table 7-4; the geometric parameters are summarized in Table D-2 of Appendix D. Both modes of binding are confirmed from the MP2 calculations, and differences in geometries between the two model chemistries are not pronounced.

In previous work on the comparison of the hydrolytic behavior of N-sulfinylamines and isocyanates, strong correlations were established between the activation enthalpies and the charge, q, on the electrophilic atom (q(S) in R–NSO, q(C) in R–NCO) for R = H, Me, Ph and CF_3.[189] Even for this small N-sulfinylamine series, q(S) was shown to vary over a wide range, leading to a decrease in activation enthalpy with increasing electron-withdrawing ability of the substituent.[189] Figure 7-4 illustrates the correlation of activation enthalpy with q(S) for a much larger variety of reactants, for reaction across S=O and N=S bonds. Included are all species discussed above, with activation enthalpies and charges from Table 7-4, as well as a further eight N-sulfinylamines with substituents of varying electron-donating/withdrawing ability and electronegativity (R = Cl, CCl_3, t-Bu, CN, CF_3, SiH_3, OH, OCH_3). Activation enthalpies and charges are given in Table D-3 of the Appendix D. The inclusion of this last set of N-sulfinylamines slightly changes the correlations from R^2 of 0.8596 (across S=O, smaller slope in Table 7-4) and 0.8997 (across N=S, larger slope), to 0.8709 and 0.8960, respectively. The correlation of the reactivity of N-sulfinyl species with their varying electrophilicity of sulfur, as expressed through its charge, is thus in excellent agreement with the above findings on the electrostatic nature of the $S...O_w$ interaction in the complexes. With increasing positive charge on sulfur, the order of reactivity for the various N-sulfinyl classes, i.e., hydrazines, hydrazides (keto forms), hydrazides (enol forms), amines and amides, established computationally reflects the one suggested qualitatively from the various independent experiments.

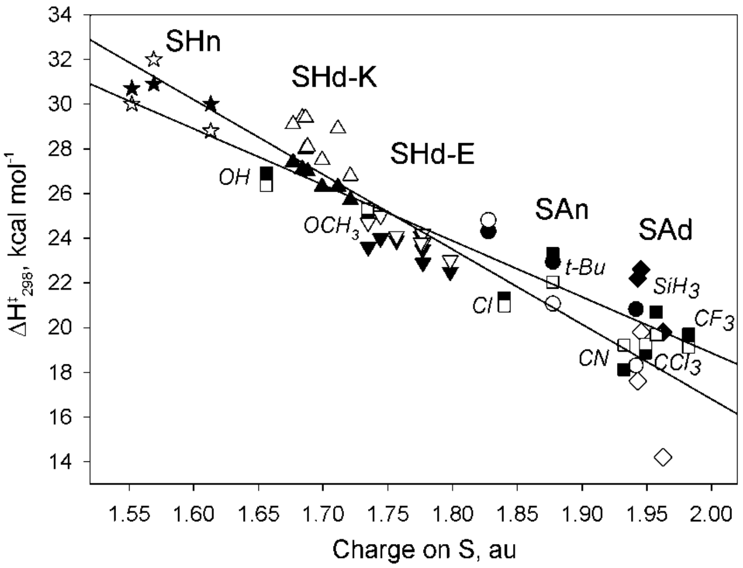
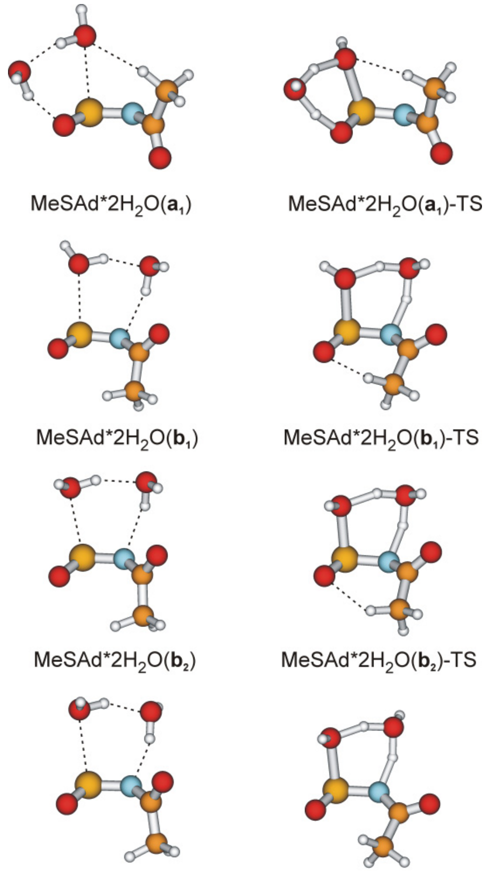


Figure 7-4. Dependence of the activation enthalpy on the charge on sulfur for the reaction with two water molecules across the S=O (filled symbols) and N=S (open symbols) bonds for N-sulfinyl ★ hydrazines, ▲ hydrazides (keto form), ▼ hydrazides (enol form), ◆ amides, ● amines and ■ extended N-sulfinylamine series (see text). Activation enthalpies are based on the enthalpies of the perpendicular pre-reaction complexes.

From the linear correlations in Figure 7-4, some general conclusions can be drawn. The N=S bond, which is directly attached to the substituent, exhibits a higher sensitivity to substitution compared to the terminal S=O bond and exhibits the stronger correlation. The aromatic N-sulfinylamine and -hydrazine and all -hydrazides favor the reaction across the N=S bond, whereas their aliphatic analogs and all N-sulfinylamides prefer reaction across the S=O bond. Within each N-sulfinyl class, the aliphatic members are generally more reactive, which agrees well with the available experimental data.[24] The Z-enol and E-keto forms of phenyl-N-sulfinylhydrazide, who require 0.3 kcal mol^{-1} less activation enthalpy than the corresponding methyl species, are exceptions, but the small difference in energies should not be overinterpreted. More reactive than hydrazines, N-sulfinylhydrazides react with water through the enol rather than the keto tautomer, while N-sulfinylamides are very sensitive to moisture and undergo fast hydrolysis.

The latter compounds are particularly interesting, because the carbonyl group is not co-planar with the NSO moiety, and the charges on nitrogen, sulfur and oxygen atoms of the NSO group exhibit the least sensitivity to substitution. This class of compounds also demonstrates a much larger range of activation enthalpies, both with respect to the reacting bond (S=O or N=S) and to the substituent. Binding and activation enthalpies depend on the orientation of the water dimer with respect to the NSO reactive centre(s), and the distinctly different binding motifs for reaction across S=O and N=S bonds are presented in Figure 7-5 for methyl-N-sulfinylamide (**MeSAm**). Firstly, reaction across the N=S bond favors the face containing the carbonyl $C_R=O_r$ group, whereas reaction across the S=O bond is more likely to occur from the face containing the $C_R–H_r$ bond (Figure 7-5). Secondly, $\mathbf{a_1}$ and $\mathbf{b_1}$ are the lowest-enthalpy structures, with exception of **PhSAm**, which favors $\mathbf{b_3}$; the data are included in Table 7-4. Enthalpies for additional types of binding, where found, are presented in Table D-3 of the Appendix D.

The small study illustrated in Figure 7-5 has large impact on the results given in Figure 7-4: while the different constellations in Figure 7-5 result in the formation of various weak bonding interactions within complexes and transition states for **MeSAd** and **PhSAd**, which affects their barriers to hydrolysis, the isolation or quantification of each particular effect seems hardly possible. Finally, the maximum difference in enthalpy between most and least favorable complexes and transition states is found to be about 2 kcal mol^{-1}, which is considered the maximum error in situations where not all possible binding modes are probed.



MeSAd*2H_2O($\mathbf{a_1}$) MeSAd*2H_2O($\mathbf{a_1}$)-TS

MeSAd*2H_2O($\mathbf{b_1}$) MeSAd*2H_2O($\mathbf{b_1}$)-TS

MeSAd*2H_2O($\mathbf{b_2}$) MeSAd*2H_2O($\mathbf{b_2}$)-TS

MeSAd*2H_2O($\mathbf{b_3}$) MeSAd*2H_2O($\mathbf{b_3}$)-TS

Figure 7-5. Illustration of the attack onto the two NSO faces of **MeSAd** for S=O (**a**) and N=S interactions ($\mathbf{b_1}$, $\mathbf{b_2}$ and $\mathbf{b_3}$ represent different orientations of the water dimer). Weak bonding interactions in the complexes are shown as dotted lines.

Benzyl-N-sulfinylhydrazide ($PhCH_2$–CO–NH–NSO), which was suggested to have an exceptional hydrolytic stability amongst N-sulfinylhydrazides,[86] was included for comparison. Specifically, reaction of its E-keto (**BzSHd-** $\mathbf{K_E}$) and Z-enol (**BzSHd-**$\mathbf{E_Z}$) forms as the two lower-energy isomers with the water dimer was modeled across N=S and S=O bonds. The calculated charges and complexation and activation enthalpies (Table 7-4) are, not surprisingly, almost identical to those of the related **MeSHd,** suggesting that **BzSHd** should also react with water. The source of this discrepancy with experiment is unclear.

7.3.2.b. Electronic effects

Figure 7-4 positions each N-sulfinyl class on its distinct part of the reactivity scale, with the charge on sulfur as a measure of the electrophilicity. With respect to the rather large spread of charges, exceeding 0.4 au, it now remains to ask for the origin of this spread.

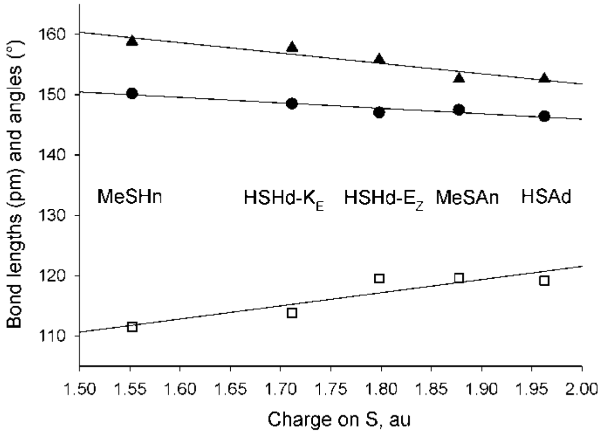
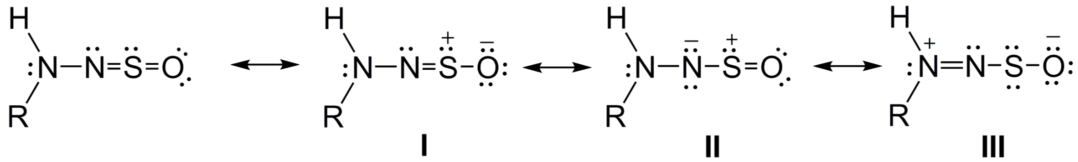


Figure 7-6. Selected geometric parameters as a function of the charge on sulfur: S=O (●) and N=S (▲) bond lengths and NSO (▫) angle.

For a better understanding of the impact of changes in geometry and electronic structure on the hydrolytic reactivity, **MeSAn**, **MeSHn**, **HSHd-E$_Z$**, **HSHd-K$_E$**, **HSAd** as typical representatives of each class were chosen for further analysis. This choice of substituent might seem random, but the collection consists of the smallest representatives with a non-hydrogen atom directly attached to the NSO group, except for hydrazines, where **MeSHn** exhibits a larger similarity to the keto and enol forms of the hydrazides due to the presence of the N_R–C_r bond. The dependence of selected geometric parameters of the NSO group on q(S) is presented graphically in Figure 7-6.



Scheme 7-3. Resonance representation of various N-sulfinyl compounds.

Figure 7-6 illustrates that the aforementioned changes in NSO bond angle correlate with q(S) over the full range of N-sulfinyl classes. And while the contraction of S=O and N=S bonds can be easily understood in view of an increasing positive charge on sulfur, Figure 7-6 seems to suggest that, instead of changes in q(S), subtle changes in the hybridization of sulfur should lead to the same correlations. These hybridization changes should be described through changes in the relative weights of the various resonance contributors. General resonance structures are presented in Scheme 7-3, and their relative weights from NRT analyses are listed in Table 7-5 for the small test set of five species given in Figure 7-6.

Resonance structures **I** and **II** represent the charge separation in S=O and N=S bonds and constitute the basis of Scheme 7-2 with its description of the two different concerted mechanisms. These two resonance structures are found in all N-sulfinyl species (Table 7-5). Not unexpectedly, **I** is the major resonance contributor with about 60%, and its contribution to the overall electronic structure varies only slightly. This is in accord with earlier descriptions of the S=O bond in **MeSAn**, **MeSHn** and SO_2[49] and with the conclusions from NMR studies,[40] and it is a further illustration of the similarity between this type of SO bond and the C=O bond in carbonyls.[16,18,40,41,51,215] On the other hand, the presence of the additional sulfide-like resonance structure **III** in N-sulfinylhydrazines and in the keto forms of N-sulfinylhydrazides is substantially more important for the understanding of their reduced hydrolytic reactivity.

Table 7-5. Normalized[a] weights (%) of resonance structures for representatives of the different N-sulfinyl classes.

	MeSHn	**HSHd-K$_E$**	**HSHd-E$_Z$**	**MeSAn**	**HSAd**
I	58.2	63.0	59.3	62.7	59.0
II	19.2	23.8	40.7	37.3	41.0
III	22.6	13.2			

[a] Based on the two or three most important resonance contributors determined in the NRT analyses.

The presence of resonance structure **III** in **MeSHn** and **HSHd-K$_E$** agrees well with the longest N=S and S=O bonds determined for these species as well as with their small NSO angles of about 112° (Table 7-1 and Figure 7-6), a value close to that of the CSC angle of 113° in sulfides.[216] It also agrees with the smallest polarization of both N=S and S=O bonds in **MeSHn** and **HSHd-K$_E$**. While the charge separation in the N=S bond varies in the wide range of 3.184 to 2.240 au in the series from Figure 7-6, the polarization of the S=O bond is much smaller, varying from 3.061 (**HSAd**) to 2.691 (**MeSHn**) au.

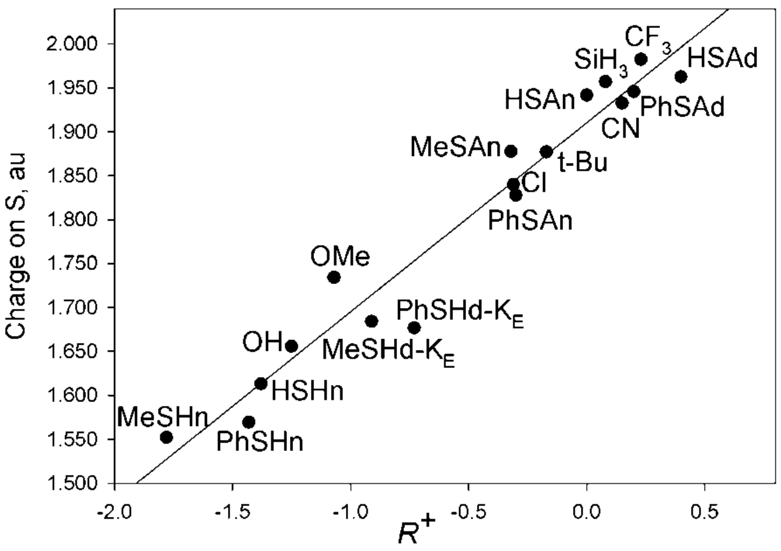


Figure 7-7. Dependence of the charge on sulfur on the Hammett substituent resonance constant R^+ for various N-sulfinyl species ($R^2 = 0.9529$).

Finally, and presenting a real practical value for the non-computational chemist, the charge on sulfur as a measure of the electrophilicity of N-sulfinyl species (R–NSO) is proportional to modified Hammett substituent constants. The correlation with Hansch's resonance substituent constants R^+ is shown in Figure 7-7, and it is superior to that with the more frequently used σ_p^+ constants (Figure D-3 of the Appendix D). R^+ constants were derived based on σ_p^+ constants,[217-221] and both scales were designed for substituents that delocalize a positive charge of an adjacent conjugated reaction center. In Hansch's scale, the R^+ values are enhanced for π-electron donating substituents. Large negative values of R^+ correspond to strongly electron-donating substituents. For example, Me–NH–NSO possesses the NHMe substituent, and it holds the largest negative R^+ of all substituents in this study. Accordingly, Figure 7-7 shows that its strong π-conjugation with the NSO electron deficient reactive centre leads to the smallest q(S). In fact, all N-sulfinylhydrazines and -hydrazides for which R^+ substituent constants are reported are featured in the lower left of Figure 7-7 due to the conjugation of the NSO group with electron donating substituents that decrease the positive charge on their sulfur atoms. This conjugation is illustrated through resonance structure **III** (Scheme 7-3), and the presence of **III** with the resulting introduction of sulfide-like properties hinders the reaction with water for these classes of N-sulfinyl compounds.

7.4. Conclusions

Substituent effects were studied in the concerted hydrolysis of various N-sulfinyl classes (R–NSO). While small substituent effects on reactivity are apparent within each class (N-sulfinylamines, -hydrazines, -hydrazides and -amides with H-, Me- and Ph-substituents), substituent effect across all classes results in the complete range of reactivities, from inert to explosive. Results of the calculations show a remarkable agreement with available experimental data. It was established that the decrease in the enthalpy of activation for hydrolysis, which follows the qualitatively determined order of reactivity from experiment, correlates with an increasing charge on sulfur as the measure of electrophilicity of the R–NSO species. N-sulfinylhydrazines (R–NH–NSO) possess the lowest positive charge on sulfur and, thus, exhibit the largest reaction barriers, responsible for their hydrolytic inertness. At the other end of the spectrum, N-sulfinylamides (R–CO–NSO), known to react with water very readily, have activation enthalpies half as small and charges that are 0.45 au more positive. The hydrolytic reactivity of N-sulfinylhydrazides is governed by their keto-enol tautomerization, and the enols are found to be the reactive species, whereas the electronic structure of the keto tautomers resembles that of the inert N-sulfinylhydrazines.

The π-electron delocalization, which influences the NSO geometry, its charge distribution and its resonance representation, determines the electrophilicity of the sulfur atom. In addition to resonance structures describing charge separation on S=O and N=S bonds, a sulfide-like resonance structure is determined for the keto tautomers of N-sulfinylhydrazides and for N-sulfinylhydrazines and assumed responsible for their hindered hydrolytic reactivity.

Particular value is ascribed to the use of tabulated R^+ substituent constants in the estimation of charges and activation enthalpies across all R–NSO compounds. This can be of tremendous use, for experimentalists, in the prediction of the hydrolytic reactivity of N-sulfinyl species not considered previously.

Chapter 8.

Conclusions and outlook

In this thesis, the reaction of various classes of N-sulfinyl species with water was investigated form computational point of view. This work was motivated by the vastly different hydrolytic behaviour of N-sulfinylhydrazines (inert to water), N-sulfinylhydrazides (react slowly) and N-sulfinylamines and -amides (depending on the substituent can hydrolyse explosively), as determined qualitatively in experimental studies.

The validation of several model chemistries revealed that gas phase calculations with the B3LYP method and the 6-31+G(2d,2p) basis set are the best choice, showing a good accuracy in the reproduction of experimental geometries and providing reliable results on the reactivity of N-sulfinylaniline (PhNSO) with water. In comparison with results from a counterpoise correction study, this model chemistry gave the smallest basis set superposition error.

The binding mode consisting of the nucleophilic interaction of the oxygen atom of water towards the NSO sulfur atom was modeled for complexes of PhNSO with one to three and five water molecules. An increase in the number of water molecule leads to strengthening of the S…O interaction, which occurs close to perpendicular to the NSO plane, and thus decreases the activation barrier for hydrolysis. This effect is significant in going from one to three and becomes less pronounced for five water molecules.

The two-water-molecule model was found adequate and sufficient for the proper description of the hydrolysis reaction, which is consistent with the first order dependence in both water and base that was determined experimentally for the base catalyzed reaction of PhNSO, if one water molecule is considered to take the role of the base. The relative orientation of the two water molecules within the dimer with respect to the plane of the NSO group was found to be of minor importance for complexation and following reaction, as long as hydroxylation of sulfur and protonation of either nitrogen or oxygen of the NSO group are considered in a concerted fashion. The full reaction profile was probed for this model and S…O interaction with proton transfer from water was found to be the rate-determining step in both mechanisms, i.e., for reaction across S=O and N=S bonds. While for two water molecules, both mechanisms are equally probable, the calculated enthalpies of activation for the neutral hydrolysis reaction are larger than the experimentally determined barriers for the neutral hydrolysis reaction.

The effect of the substituent on the hydrolysis of the small series of N-sulfinylamines R–N=S=O with R = H, CH_3, Ph and CF_3 was investigated in comparison that on hydrolysis of substituted isocyanates (R–N=C=O). It revealed that despite the overall similar reactivity of these two classes of compounds, while the reaction across the N=C bond is strongly favoured for isocyanates, N-sulfinylamines can react across both N=S and S=O bonds with almost equal probability. The different proton affinities of the nitrogen and oxygen atoms in the NSO and NCO groups were found to be responsible for their different reactivity. Similar to what had been reported for substituted N-sulfinylanilines, namely that the rate of reaction decreases with increasing electron-donating ability of the substituent on the aromatic ring, smaller reaction barriers are determined with the more electron-withdrawing substituent directly attached to the NSO moiety of these N-sulfinylamines. Unlike N-sulfinylamines, the isocyanates exhibit a much smaller sensitivity to substitution, which becomes notable only in the presence of the strong electron-withdrawing CF_3 group, while Ph, CH_3 and H isocyanates exhibit a similar reactivity due to the close-to-zero conjugation energy between the substituent and the NCO group in aliphatic and phenyl isocyanates.

This part of the project revealed that the atomic charges on sulfur and carbon atoms as the reactive centers of N-sulfinylamines and isocyanates, respectively, are proportional to the activation barriers for hydrolysis and can be used as a measure of electrophilicity of these compounds with respect to water. This conclusion was successfully applied in the further study of the larger series of N-sulfinyl species, subdivided into classes based on their constitution and different reactivity towards water reported experimentally. Hydrogen, methyl and phenyl substituents R were included for N-sulfinylhydrazines (R–NH–NSO), -hydrazides (R–CO–NH–NSO) and -amides (R–CO–NSO), in comparison to the corresponding N-sulfinylamines (R–NSO). The electronic structures of the N-sulfinylhydrazides and -amides were investigated and reported for the first time.

N-sulfinylhydrazides presented a particular interest due to the presence of the amide moiety, which itself is a subject of extensive studies because of its biochemical importance. The presence of this functional group in N-sulfinylhydrazides gives rise to the possibility of keto-enol tautomerization, which had been proposed to have an influence on the reactivity of these species with water. Moreover, rotation around the CN bond, reported for amides, results in the existence of four configurational syn isomers whose relative stabilities and isomerizations needed to be determined.

The keto tautomers were found to be significantly more energetically favourable than the corresponding enols, with the E ketone (oxygen and (N)H on the same side) being the lowest energy species for the series of substituted N-sulfinylhydrazides. The effects of conjugation and hydrogen bonding were discussed in relation to the stability and isomerization barriers of N-sulfinylhydrazides and with respect to the substituent. The barrier for keto-enol tautomerization is found to decrease in going from hydrogen to phenyl N-sulfinylhydrazides. The barrier also decreases upon addition of water into the reaction coordinate, but more importantly also increases the population of the enol tautomers, increasing their importance in the reaction with water.

In the final stage of the project, the concerted hydrolysis of various classes of N-sulfinyl species was investigated. The results show a remarkable agreement between the experimentally reported and computationally determined reactivities of N-sulfinyl compounds, varying from inert to explosive. The decrease in the enthalpy of activation for hydrolysis correlates with an increasing charge of sulfur as the measure of electrophilicity of the R–NSO species. Interestingly, with decreasing charge on sulfur (for N-sulfinylhydrazines and -hydrazides) not only perpendicular complexes with the water dimer, but also in-plane complexes of electrostatic nature and of similar strength were located.

The lowest charge on sulfur in N-sulfinylhydrazines (R–NH–NSO) is responsible for their largest reaction barriers (30 kcal mol^{-1}), experimentally seen in their insensitivity towards moisture. The hydrolytic reactivity of N-sulfinylhydrazides is affected by their keto-enol tautomerization, and the less populated enols are found to be the reactive species, whereas the electronic structure of the keto tautomers resembles that of the inert N-sulfinylhydrazines. N-sulfinylamides (R–CO–NSO), at the other end of reactivity spectrum, known to react with water very readily, have charges on sulfur that are 0.45 au more positive, as compared to those of N-sulfinylhydrazines, and demonstrate significantly smaller activation enthalpies (15-20 kcal mol^{-1}).

The π-electron delocalization within the NSO moiety, which can be extended to a directly attached suitable π-system, has a significant impact on its geometry, charge distribution and resonance representation, and it determines the electrophilicity of the sulfur atom. In addition to resonance structures describing charge separation on S=O and N=S bonds, a sulfide-like resonance structure is determined for the keto tautomers of N-sulfinylhydrazides and for N-sulfinylhydrazines and is assumed responsible for their hindered hydrolytic reactivity.

The facts that the charge on sulfur is found to correlate with the hydrolytic reactivity of N-sulfinyl species and that these charges can be obtained at relatively low computational expenses, provide a valuable aid for the experimentalist evaluating the stability of R–NSO compounds in experiments. Hydrolysis in the present case serves as an example, but this approach is expected to be applicable for the prediction of reactivity in many more reactions of N-sulfinyl compounds involving nucleophilic attack on sulfur.

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Appendix A.

Bonding and charge distribution analysis methods

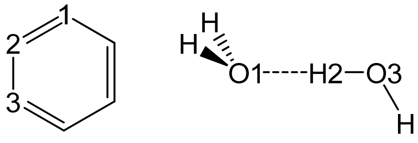
A.1. Introduction

Quantum chemistry methods allow calculate the wavefunction, which contains all the information about the system and many observable molecular properties can be derived from it. However, many concepts used by chemists, such as the atomic charge or the chemical bond, are not physical observables and cannot be obtained from the wavefunction directly. To make this possible, various ways to extract chemical information from the results of quantum chemistry calculations have been proposed. Thus, population analysis methods for the calculation of atom-centered charges, such as the Mulliken method[222], Natural Population Analysis (NPA)[223] as well as charge integration over atomic basins employed in the Quantum Theory of Atoms in Molecules (QTAIM)[224] were used in the current study. Also, to address the nature of bonding between atoms, including covalent bonds and weak bonding interactions, we used two different, yet complementary, approaches: the Natural Bond Orbital[225] (NBO) method and QTAIM.[51,226]

A.1. Natural Bond Orbitals and related methods

The NBO method represents the molecular wavefunction composed from highly delocalized MOs, which are hard to interpret chemically, as a set of valence-bond-like ‘natural bond orbitals’ (NBOs) by using a series of special unitary transformations of the initial wavefunction.[139,196,223,225] Unlike canonical MOs, NBOs are either centered on a single atom (lone pairs *n* and core orbitals *c*) or shared between two atoms (bonding orbitals of σ or π-type); in rare cases three-center bonding orbitals are also encountered. NBOs are constructed from natural hybrid sp^xd^y orbitals, which are formed from the combination of natural atomic orbitals (NAOs). This is a generalization of the classical *sp*, sp^2 and sp^3 hybrid orbitals from valence-bond theory. The atomic charges in Natural Population Analysis (NPA)[223] are obtained through the summation of the electronic occupancies of the NAOs belonging to a particular atom.

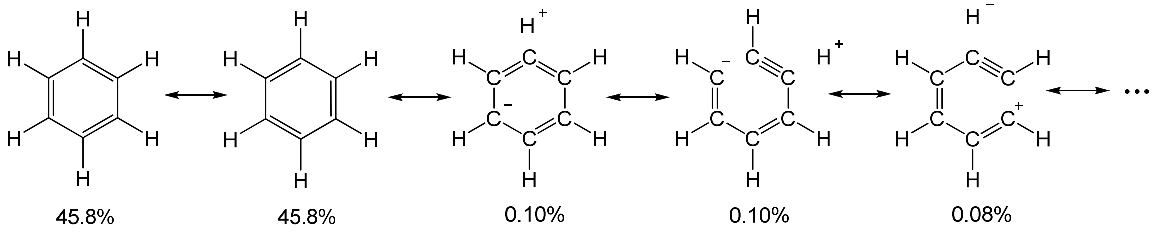
The NBO method provides a chemically intuitive description of the electronic structure, representing it by a Lewis structure with single, double and triple bonds between pairs of atoms and single-atom centered lone pairs. Since many molecules have complex electronic structures, deviations from a single Lewis structure picture is expressed through the charge-transfer (CT) orbital interactions between the combination of bonding or lone-pair NBOs and sets of anti-bonding σ* and π*, and Rydberg *r* orbitals. These interactions stabilize the molecule and lead to non-zero occupations of the anti-bonding and Rydberg NBOs, and to less than 2.0 electron occupations of bonding and lone-pair NBOs. Conjugative, hyperconjugative and intermolecular interactions in donor-acceptor and hydrogen-bonded complexes can thus be examined in terms of these CT interactions, whose strength is calculated with second-order perturbation theory.[139] The benzene molecule, for example, represented in NBO as a single Kekulé structure (Scheme A-1, **1**), and its aromatic nature is described by a significant π(C1–C2)→π*(C2–C3) charge transfer of about 60-80 kcal/mol. On the other hand, the hydrogen bonding in the water dimer, represented in terms of donor-acceptor interaction *n*(O1)→σ*(H2–O3), is characterized by a much smaller (about 6 kcal/mol) charge transfer among the interacting orbitals (Scheme A-1, **2**).[139]



1 **2**

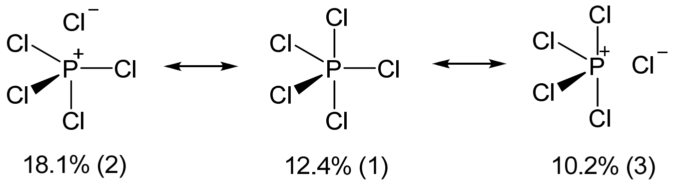
Scheme A-1

Natural Resonance Theory[211] (NRT) as an extension of the NBO method, represents the molecular electronic structure as a combination of several Lewis structures – resonance structures. The NRT procedure generates possible resonance structures based on the existing CT orbital interactions obtained from the NBO analysis and then fits the relative weights of each resonance structure to completely describe the electron density distribution in the molecule. For example, in the case of benzene, two major resonance structures obtained from NRT analysis are the classical Kekulé structures of equal contribution (45.8%), whereas a multitude of somewhat unlikely resonance structures with very small contributions (<< 1%) are generated in addition (Scheme A-2).[211]



Scheme A-2

Compounds that possess atoms of normal valency are well described by the Lewis octet rule within the NRT analysis. However, hyper- and hypo-valent structures can also be treated upon invoking the multireference weighting through charge separation. For example, each one of the PCl bonds in the five leading resonance structures of pentavalent PCl_5, for about 67% of the NRT expansion, have a significant ionic character (Scheme A-3). The remaining 20% were not specified.[211]



Scheme A-3

In many cases the minor resonance structures are necessary to describe the fine features of the electron density distribution, while in other cases they can be safely neglected. The NRT procedure in its standard implementation automatically generates only octet resonance structures, and if there is a suspicion that non-octet resonance structures may play a major role they must be entered manually.[227] However, for the molecules studied in this thesis, non-octet structures with significant contributions were not found.

A.2. Quantum Theory of Atoms in Molecules

NBO and similar methods are based on manipulations of the multi-dimensional molecular wavefinction $\Psi(r_1, r_2, \ldots, r_N)$, which depends on the coordinates $r_1, r_2, \ldots, r_N$ of all N electrons in the molecule. In contrast, the Quantum Theory of Atoms In Molecules (QTAIM),[51] often referred to as AIM theory, is based on the analysis of the electron density $\rho(r)$ distribution and its derivatives.

The total electron density $\rho(r)$ is the probability of finding an electron at a point r in 3-dimentional space. It is not only a much simpler mathematical object than the wavefunction, but is also a physical observable, and as such can be measured experimentally. AIM theory provides a solid interpretation of ρ(r) distributions in terms of classical chemical concepts and allows their quantitative study.

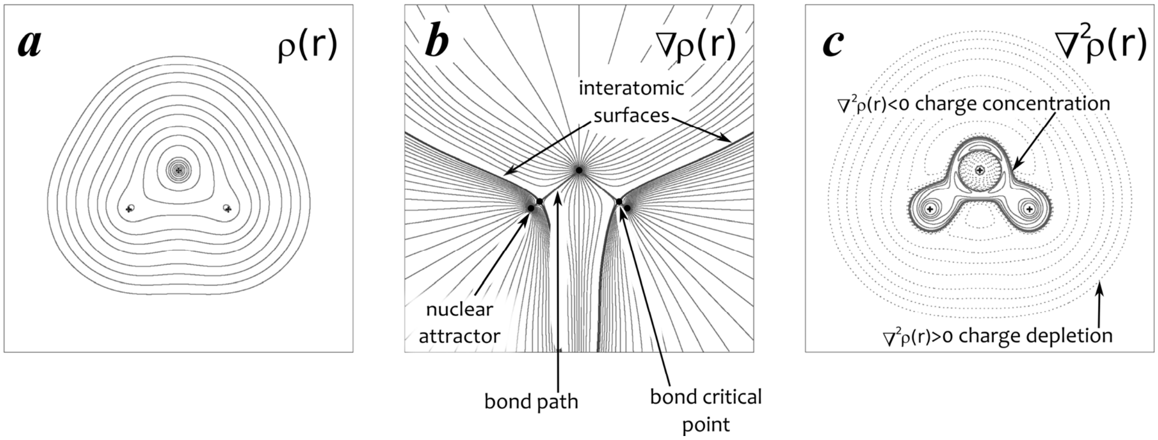


Figure A-1. AIM theory-based analysis of the chemical boding in a water molecule.

a) electron density (the outermost contour value is 0.001 au), b) vector field of the electron density, c) Laplacian of the electron density.

Whereas an analysis of the electron density ρ(r) itself can show the shape of the molecule through the positions of the nuclei as bumps in the electron density (Figure A-1a), an examination of its first derivative (Figure A-1b), the gradient vector field ∇ρ(r), allows finding the gradient paths and critical points (minima, maxima, saddle points) of ρ(r), which are related to the classical concepts of chemical bonding. Local maxima of ρ(r) correspond to the positions of atomic nuclei. Two nuclear critical points can be connected by a gradient path (atomic interaction line or bond path), corresponding to the line of maximum ρ(r) between them and indicating the chemical bonding between the two atoms. Various numerical properties of the point of minimum ρ(r) along a bond path, the bond critical point (BCP), characterize the nature of bonding between two atoms.

A surface perpendicular to a bond path ("zero-flux" surface) at a BCP separates the atoms in molecules from each other (interatomic surface, Figure A-1b). Numerical integration of the electron density over an atomic basin (i.e., the space containing the nucleus, or nuclear attractor, and separated from other nuclei by interatomic surfaces), yields the electron population of the atom and can be used to calculate the atomic charge by subtracting the nuclear charge.

The Laplacian $\nabla^2\rho(r)$ (Figure A-1c), the second derivative of the electron density, allows the identification of regions of charge concentration ($\nabla^2\rho < 0$) and depletion ($\nabla^2\rho > 0$). Strong covalent bonds are usually characterized by a region of charge concentration shared between two atoms and negative values at the BCP (e.g, O–H bonds in Figure A-1c), in contrast to ionic bonds or weak bonding interactions.

Appendix B.

Supporting information for Chapter 5

Table B-1. Electronic and zero-point vibrational (ZPVE) corrected energies, enthalpies and Gibbs free energies[a] (au) of water, the N-sulfinylamines (**I-IV**) and isocyanates (**V-VIII**), their complexes and transition states, and their protonated species.

	E_{el}	E_{el} + ZPVE	H_{298}	G_{298}
H_2O	-76.441069	-76.419706	-76.415926	-76.438004
I	-528.736427	-528.718250	-528.714036	-528.743288
I-1a	-605.181537	-605.140344	-605.131937	
I-1a-TS	-605.127478	-605.088155	-605.082522	
I-1a-P[b]	-605.156259	-605.113062	-605.106645	
I-1a-TS2	-605.116751	-605.077379	-605.071711	
I-1a-P2[c]	-605.183249	-605.138843	-605.132715	
I-1b-TS	-605.126483	-605.087527	-605.081665	
I-2a	-681.636177	-681.569132	-681.558534	
I-2a-TS	-681.596520	-681.532699	-681.525366	-681.563011
I-2b	-681.635124	-681.568027	-681.557420	
I-2b-TS	-681.598765	-681.535553	-681.528253	-681.565581
I-3a	-758.091505	-757.999056	-757.985874	
I-3a-TS	-758.052996	-757.964966	-757.955333	
I-3b	-758.091192	-757.998522	-757.985486	
I-3b-TS	-758.056526	-758.056526	-757.960428	
II	-865.793112	-865.769902	-865.762547	-865.801921
II-1a	-942.239185	-942.192876	-942.181398	
II-1a-TS	-942.185992	-942.141787	-942.132897	
II-1b-TS	-942.185379	-942.141556	-942.132464	
II-2a	-1018.694443	-1018.622393	-1018.608647	
II-2a-TS	-1018.657120	-1018.588042	-1018.577232	-1018.624962

	E_{el}	E_{el} + ZPVE	H_{298}	G_{298}
II-2b	-1018.692519	-1018.620705	-1018.606801	
II-2b-TS	-1018.655543	-1018.587098	-1018.576355	-1018.62316
II-3a	-1095.149534	-1095.052258	-1095.035802	
II-3a-TS	-1095.123269	-1095.027905	-1095.015155	
II-3b	-1095.149699	-1095.052147	-1095.035947	
II-3b-TS	-1095.118708	-1095.025395	-1095.012345	
III	-568.052008	-568.005655	-567.999876	-568.033824
III-1a	-644.496569	-644.427162	-644.417210	
III-1a-TS	-644.441819	-644.374477	-644.367146	
III-1b-TS	-644.438835	-644.371590	-644.363992	
III-2a	-720.951736	-720.856762	-720.844372	
III-2a-TS	-720.908438	-720.816949	-720.807827	-720.85003
III-2b	-720.950055	-720.855089	-720.842619	
III-2b-TS	-720.909008	-720.818207	-720.809039	-720.850969
III-3a	-797.407102	-797.286805	-797.271771	
III-3a-TS	-797.363862	-797.248374	-797.236853	
III-3b	-797.404877	-797.284544	-797.269537	
III-3b-TS	-797.368286	-797.255006	-797.243561	
IV	-759.811591	-759.711892	-759.703552	-759.744859
IV-1a	-836.255744	-836.133042	-836.120484	
IV-1a-TS	-836.199402	-836.079012	-836.068877	
IV-1b-TS	-836.193196	-836.073030	-836.062605	
IV-2a	-912.710720	-912.562579	-912.547481	
IV-2a-TS	-912.665029	-912.520710	-912.508745	-912.559205
IV-2b	-912.708424	-912.560220	-912.545030	
IV-2b-TS	-912.661079	-912.517559	-912.505502	-912.55564
IV-3a	-989.164674	-988.991597	-988.973598	
IV-3a-TS	-989.120910	-988.952285	-988.937976	
IV-3b	-989.162650	-988.989247	-988.971435	
IV-3b-TS	-989.120013	-988.954007	-988.939706	
V	-168.701469	-168.680168	-168.675991	-168.703070
V-1a-TS	-245.068524	-245.023852	-245.018965	
V-1a-P[d]	-245.142994	-245.091900	-245.086912	
V-1a-TS2	-245.090350	-245.044432	-245.039563	
V-1a-P2[e]	-245.174539	-245.123404	-245.118088	
V-1b-TS	-245.084790	-245.040495	-245.035340	
V-2a-TS	-321.553983	-321.483184	-321.476877	-321.511709
V-2b-TS	-321.563726	-321.493744	-321.487267	-321.522418
V-3a-TS	-398.016414	-397.920434	-397.911859	

	E_{el}	E_{el} + ZPVE	H_{298}	G_{298}
V-3b-TS	-398.022787	-397.927752	-397.919013	
VI	-505.760844	-505.733285	-505.726383	-505.764968
VI-1a-TS	-582.133128	-582.083432	-582.075269	
VI-1b-TS	-582.147715	-582.098352	-582.090005	
VI-2a-TS	-658.624330	-658.548614	-658.538823	-658.583649
VI-2b-TS	-658.630742	-658.555435	-658.545550	-658.590415
VI-3a-TS	-735.090093	-734.989134	-734.976803	
VI-3b-TS	-735.092499	-734.991755	-734.979405	
VII	-208.011542	-207.961003	-207.955342	-207.988618
VII-1a-TS	-284.378082	-284.305475	-284.298799	
VII-1b-TS	-284.396662	-284.324333	-284.317452	
VII-2a-TS	-360.862876	-360.764593	-360.756469	-360.79612
VII-2b-TS	-360.872537	-360.775094	-360.766664	-360.80777
VII-3a-TS	-437.325143	-437.202020	-437.191647	
VII-3b-TS	-437.330435	-437.208186	-437.197680	
VIII	-399.769703	-399.666061	-399.658031	-399.698499
VIII-1a-TS	-476.136290	-476.010614	-476.001287	
VIII-1b-TS	-476.154770	-476.029328	-476.019871	
VIII-2a-TS	-552.622016	-552.470558	-552.459711	-552.507056
VIII-2b-TS	-552.630598	-552.479872	-552.468878	-552.516304
VIII-3a-TS	-629.085474	-628.908769	-628.895623	
VIII-3b-TS	-629.088902	-628.912719	-628.899553	
	Protonated N-sulfinylamines and isocyanates			
I-NH+	-529.038009	-529.007500	-529.003019	
I-OH+(1)[f]	-529.017174	-528.988252	-528.983613	
I-OH+(2)[f]	-529.019543	-528.990451	-528.985836	
II-NH+	-866.076672	-866.041379	-866.033719	
II-OH+(1)[f]	-866.064229	-866.029920	-866.022153	
II-OH+(2)[f]	-866.062354	-866.028143	-866.020252	
III-NH+	-568.368955	-568.309923	-568.304001	
III-OH+(1)[f]	-568.352231	-568.295409	-568.289056	
III-OH+(2)[f]	-568.355625	-568.298663	-568.292373	
IV-NH+	-760.139969	-760.027704	-760.019124	
IV-OH+(2)	-760.140834	-760.030380	-760.021300	
V-NH+	-168.985263	-168.951410	-168.946933	
V-OH+	-168.949007	-168.916662	-168.912180	
VI-NH+	-506.025034	-505.985775	-505.978479	
VI-OH+	-505.993195	-505.954794	-505.947370	

	E_{el}	E_{el} + ZPVE	H_{298}	G_{298}
VII-NH+	-208.311991	-208.249008	-208.243299	
VII-OH+	-208.285105	-208.223372	-208.217341	
VIII-NH+	-400.072101	-399.956810	-399.948396	
VIII-OH+	-400.047826	-399.933129	-399.924656	

[a] Gibbs free energies are only given for structures used in determination of the reaction rates. [b] Sulfurimidic acid. [c] Sulfinamic acid. [d] Carbonimidic acid. [e] Carbamic acid. [f] Two protonation sites for oxygen in the N-sulfinylamines **I-III**. The average value is taken for the calculation of the proton affinity.

Table B-2. Selected geometrical parameters (bond length in pm, angles in degrees) and binding enthalpies (kcal mol^{-1}) of complexes of N-sulfinylamines **I–IV** with one water molecule.

	I-1a	**II-1a**	**III-1a**	**IV-1a**
S=O	147.3	146.3	148.0	148.7
N=S	152.3	153.0	152.3	153.0
N–H or N–C	102.4	142.0	145.4	139.3
NSO	119.4	119.3	119.4	120.3
CNS or HNS	115.7	126.3	124.8	132.8
$S\ldots O_w$	308.7	294.7	311.4	319.0
O_w–H_w	96.5	96.4	96.5	96.5
$H_w\ldots O$	246.3	260.5	251.9	240.4
$NSOO_w$	114.4	105.3	101.9	101.9
OSNC	-1.7	-8.5	4.2	6.9
$\Delta H^{298}{}_{bind}$	1.2	1.8	0.9	1.2

Table B-3. Selected geometrical parameters (bond lengths in pm, angles in degrees) of complexes and transition states in the reaction of N-sulfinylamines **I–IV** with three water molecules across the S=O (**a**) and N=S (**b**) bonds.

	I-3				**II-3**				**III-3**				**IV-3**			
	a	**a-TS**	**b**	**b-TS**	**a**	**a-TS**	**b**	**b-TS**	**a**	**a-TS**	**b**	**b-TS**	**a**	**a-TS**	**b**	**b-TS**
S=O	148.1	153.8	146.5	147.2	147.1	151.1	145.8	146.4	148.7	154.7	147.0	146.6	149.2	154.7	147.4	146.7
N=S	151.9	152.2	153.5	158.0	152.6	155.8	154.7	160.0	151.9	151.5	153.5	157.4	152.7	151.9	154.3	159.1
H–N or C–N	102.4	102.2	102.4	102.1	142.0	137.5	141.8	140.5	145.4	145.7	145.9	146.3	139.3	140.1	140.0	141.9
NSO	118.1	113.0	117.3	111.6	118.3	116.3	117.7	114.7	118.1	113.0	117.6	113.2	119.0	114.8	119.1	113.9
HNS or CNS	115.6	114.3	114.2	111.9	126.3	127.7	124.9	123.7	125.0	124.9	123.2	122.6	133.1	133.1	131.6	128.5
$S\ldots O_w$	277.5	204.1	275.0	204.3	262.7	188.8	257.5	195.4	290.1	210.0	290.4	214.9	298.9	208.7	296.2	210.7
$NSOO_w$	104.1	109.3	107.6	108.3	104.1	109.0	107.2	103.9	99.8	109.7	105.3	103.1	105.0	109.0	107.1	109.6
C–H[a]													108.0	108.0	108.0	108.0
H…O[a]													235.4	238.1	230.2	236.9
CHO[a]													125.3	122.6	126.0	116.4

[a] For the C–H bond involved in the C–H…O interaction.

Table B-4. Selected geometrical parameters (bond lengths in pm, angles in degrees) of transition states in the reaction of isocyanates **V–VIII** with three water molecules across the C=O (**a**) and N=C (**b**) bonds.

	V-3		**VI-3**		**VII-3**		**VIII-3**	
	a-TS	**b-TS**	**a-TS**	**b-TS**	**a-TS**	**b-TS**	**a-TS**	**b-TS**
C=O	124.8	120.8	122.4	119.9	125.3	121.0	124.6	121.0
N=C	127.8	129.9	129.0	130.8	127.2	129.3	128.1	130.1
H–N or C–N	101.6	101.5	139.0	139.6	145.5	146.5	140.4	141.6
NCO	138.3	139.8	139.0	139.7	137.7	139.2	138.6	140.3
HNC or CNC	109.8	108.6	118.3	116.3	117.3	114.1	123.0	120.2
C…O_w	139.8	155.9	150.2	154.4	150.0	156.7	150.0	155.3
NCOO_w	179.7	178.9	179.8	179.4	178.9	178.7	179.5	179.7
C–H[a]							108.1	108.0
H…O[a]							232.0	226.7
CHO[a]							118.3	118.5

[a] For the C–H bond involved in the C–H…O interaction.

Table B-5. Proton affinities[a] (PA, kcal mol^{-1}) of nitrogen and oxygen atoms of N-sulfinylamines **I–IV** and isocyanates **V–VIII**.

	RNSO			RNCO		
R	N	O	ΔPA	N	O	ΔPA
H	183.0	171.6	11.4	171.7	149.9	21.8
CF_3	171.9	164.1	7.8	159.9	140.5	19.6
CH_3	192.4	184.3	8.1	182.2	166.1	16.1
Ph	199.7	201.4	-1.7	183.9	169.1	14.8

[a] Determined as PA = $-\Delta H_{prot}^{298} = -\Delta E^{0}_{el} - \Delta ZPVE + \Delta E_{vib} + 5/2RT$.[157] The term accounting for the change in the population of the vibrational levels, ΔE_{vib}, was set to be zero; 5/2RT = 1.5 kcal mol^{-1}; ΔPA = PA(N) – PA(O).

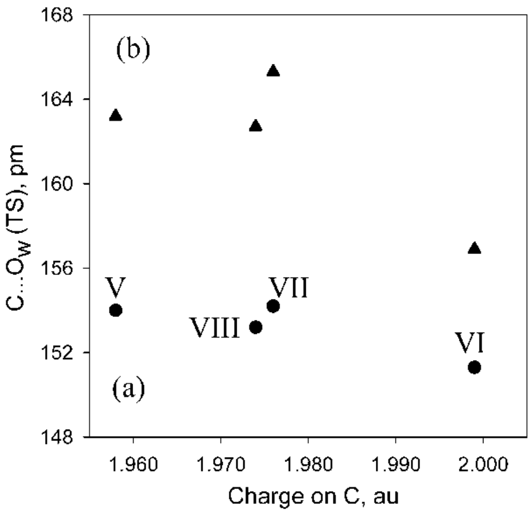


Figure B-1. Dependence of the C…O$_w$ intermolecular distance in the transition state of the reaction of **V–VIII** with two water molecules on the charge on carbon. Reaction across (**a**) the C=O (●) and (**b**) the N=C bond (▲).

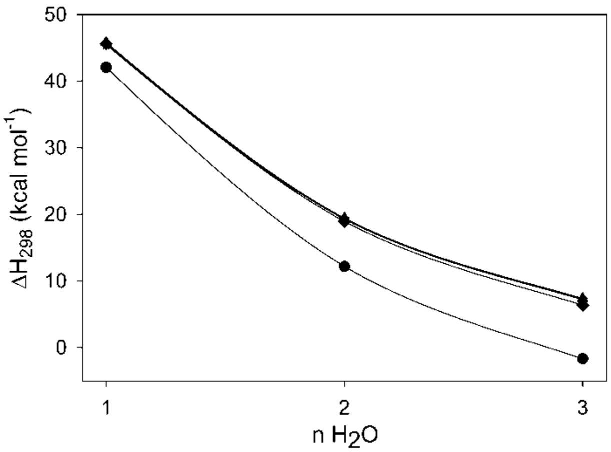


Figure B-2. Dependence of the activation barrier for hydrolysis of isocyanates **V–VIII** on the number of water molecules for attack across the C=O bond (path **a**). Data points have been traced for easier comparison of the trends. (H ▲, CF_3 ●, CH_3 ▼, Ph ◆).

Appendix C.

Supporting information for Chapter 6

Table C-1. Electronic, zero-point vibrational corrected (ZPVE) energies and enthalpies (au) of N-sulfinylhydrazides **1–3** and the isomerization transition states calculated with B3LYP/6-31+G(2d,2p).

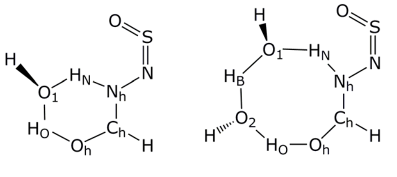
	$E_{el,}$ au	E_{el} + ZPVE, au	$H_{298,}$ au
1-K_E	-697.422136	-697.377011	-697.370086
1-K_Z	-697.417714	-697.372553	-697.365640
1-E_E	-697.349341	-697.356384	-697.349341
1-E_Z	-697.402080	-697.356673	-697.349805
1-TS_{KK}	-697.391811	-697.348173	-697.341607
1-TS_{EE}	-697.368782	-697.325295	-697.318521
1-TS_{KE}	-697.348254	-697.308360	-697.301587
H_2O	-76.441069	-76.419706	-76.415926
1-K_E*1H_2O	-773.874948	-773.805220	-773.795224
1-E_E*1H_2O	-773.861671	-773.791565	-773.781951
$TS_{K\text{-}E}$*1H_2O	-773.845300	-773.780238	-773.772069
1-K_E*2H_2O	-850.333362	-850.238235	-850.225805
1-E_E*2H_2O	-850.322243	-850.227127	-850.215041
$TS_{K\text{-}E}$*2H_2O	-850.310463	-850.220393	-850.210106
2-K_E	-736.752191	-736.679233	-736.670768
2-K_Z	-736.747260	-736.674559	-736.665887
2-E_E	-736.731737	-736.659018	-736.650450

	$E_{el,}$ au	E_{el} + ZPVE, au	$H_{298,}$ au
2-E_Z	-736.734530	-736.661647	-736.653242
2-TS_{KK}	-736.726065	-736.654397	-736.646508
2-TS_{EE}	-736.698750	-736.627629	-736.619224
2-TS_{KE}	-736.684270	-736.698750	-736.608193
3-K_E	-928.498632	-928.372211	-928.360850
3-K_Z	-928.498435	-928.372065	-928.360681
3-E_E	-928.479007	-928.352829	-928.341462
3-E_Z	-928.488715	-928.362292	-928.351055
3-TS_{KK}	-928.481042	-928.355563	-928.344850
3-TS_{EE}	-928.451965	-928.327522	-928.316217
3-TS_{KE}	-928.436500	-928.315113	-928.303926
Formamide (FM)	-169.918061	-169.872790	-169.868059
Formic acid (FA)	-169.897989	-169.851926	-169.847669
FM (TS-Z)	-169.887055	-169.842982	-169.838870
FM (TS-E)	-169.889419	-169.845053	-169.840946
TS (FM→FA)	-169.841951	-169.801560	-169.797363
FM*H_2O	-246.373175	-246.302374	-246.295112
FA*H_2O	-246.356020	-246.284223	-246.277670
TS (FM→FA) *H_2O	-246.338900	-246.273207	-246.267933
FM*2H_2O	-322.831884	-322.735358	-322.725741
FA*2H_2O	-322.815387	-322.718264	-322.709317
TS (FM→FA) *2H_2O	-322.799651467	-322.710925	-322.703665

Table C-2. Selected geometric parameters (bond lengths in pm, angles in degrees) for keto-enol tautomerization of N-sulfinylhydrazide **1**.

				$1H_2O$			**$2H_2O$**		
	K_E	**E_E**	**TS_{KE}**	**K_E* $1H_2O$**	**TS_{KE}* $1H_2O$**	**E_E* $1H_2O$**	**K_E* $2H_2O$**	**TS_{KE}* $2H_2O$**	**E_E* $2H_2O$**
S=O	148.5	147.3	147.7	148.1	148.3	147.8	148.2	149.3	148.3
N=S	157.0	155.9	156.8	156.6	156.7	156.2	156.3	156.6	155.9
$N{-}N_h$	133.5	137.2	133.8	133.9	134.8	136.6	134.2	135.0	136.8
N_hC_h	138.8	128.5	132.7	137.7	133.5	129.7	137.1	133.8	130.3
N_hH_N[a]	102.1		135.2	103.2	142.6	210.3	105.1	157.5	201.3
C_hO_h	120.6	132.7	127.0	121.5	126.4	131.0	121.8	125.5	129.7
$C_hH_h(C_R)$	110.0	97.1	108.6	110.0	109.4	108.9	110.0	109.7	109.0
O_hH_O[a]		108.3	133.3	205.0	132.5	100.0	187.0	138.2	102.0
NSO	113.8	119.7	117.6	115.3	116.7	118.4	116.7	116.7	118.2
SNN_h	118.6	120.0	120.6	120.1	118.9	118.8	121.9	119.5	119.9
NN_hH_h	119.9		160.9	122.3	138.4	140.6	122.2	123.2	117.8
NN_hC_h	120.3	111.7	124.5	118.7	115.6	112.2	117.5	112.6	110.6
$C_hN_hH_R$	119.8		74.6	119.0	106.0	107.2	120.2	123.6	130.8
$N_hC_hO_h$	122.3	120.9	106.6	123.0	120.6	121.8	123.6	123.4	123.8
$N_hC_hH_R$	112.1	125.1	128.0	103.2	142.6	210.3	105.1	157.5	201.3
$O_hC_hH_R$	125.5	113.9	125.4	205.0	132.5	100.0	187.0	138.2	102.0
H_NO_1[a]				195.0	112.3	97.6	171.7	104.5	97.8
O_1H_O[a]				97.1	113.9	170.5			
O_1H_B[a]							98.1	123.4	169.2
H_BO_2[a]							181.0	118.1	99.1
O_2H_O[a]							97.7	108.8	157.7

[a] The effect of explicit inclusion of water molecules on the changes in the geometric parameters of keto-enol tautomerization of N-sulfinylhydrazide **1** we will notation N for the hydrogen atom coordinated to hydrazide nitrogen, notation O for hydrogen atom coordinated to carbonyl carbon of the amide bond and B for the hydrogen bridging two oxygen atoms of water in the case of the dihydrated complexes, according to the Scheme (isolated TS is included for comparison).



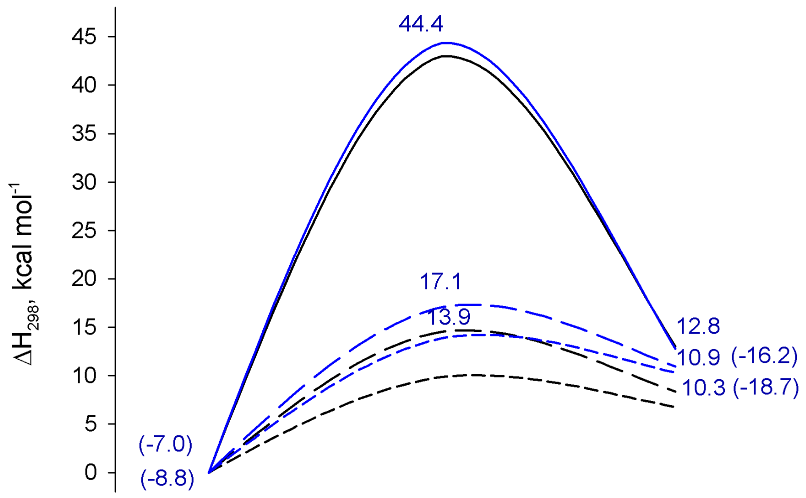


Figure C-1. Relative stabilities of complexes and keto-enol tautomerization barriers of formamide/formamidic acid (blue): isolated (solid line), hydrated (short-dashed line) and dihydrated (dotted line). N-sulfinylhydrazide **1** (black) is included for comparison. Values in brackets with negative sign represent the binding energies in complexes with one (upper) and two (lower) water molecules.

Appendix D.

Supporting information for Chapter 7

Table D-1. Electronic, zero-point vibrational corrected (ZPVE) energies, enthalpies (au) of water, N-sulfinyl species, their complexes and transition states.[a]

Compound	**E_{elec}**	**E_{elec}+ZPVE**	**H^{298}**	**G^{298}**
H_2O	-76.441069	-76.419706	-76.415926	-76.438004
HSHn	-584.078190	-584.042829	-584.037462	-584.069973
HSHn*2H_2O(a)	-736.978047	-736.894377	-736.883103	-736.931294
HSHn*2H_2O(a')	-736.978791	-736.894984	-736.882848	-736.933776
HSHn*2H_2O(a)-TS	-736.925287	-736.844125	-736.835242	-736.876724
HSHn*2H_2O(b)	-736.972612	-736.889068	-736.876705	-736.928700
HSHn*2H_2O(b')	-736.974418	-736.890545	-736.878396	-736.929962
HSHn*2H_2O(b)-TS	-736.919916	-736.839591	-736.830872	-736.871409
MeSHn	-623.393152	-623.329855	-623.322963	-623.359767
MeSHn*2H_2O(a)	-776.293383	-776.181667	-776.168883	-776.221656
MeSHn*2H_2O(a')	-776.294170	-776.182189	-776.168671	-776.223510
MeSHn*2H_2O(a)-TS	-776.239654	-776.130410	-776.119901	-776.165723
MeSHn*2H_2O(b)	-776.287194	-776.17596	-776.161895	-776.219155
MeSHn*2H_2O(b')	-776.288419	-776.176590	-776.162935	-776.217895
MeSHn*2H_2O(b)-TS	-776.232639	-776.124264	-776.114129	-776.158566
PhSHn	-815.153168	-815.036778	-815.027253	-815.071580
PhSHn*2H_2O(a)	-968.053121	-967.888249	-967.872883	-967.932386
PhSHn*2H_2O(a')	-968.053899	-967.888847	-967.872671	-967.934763
PhSHn*2H_2O(a)-TS	-967.999371	-967.837061	-967.823582	-967.878159
PhSHn*2H_2O(b)	-968.046287	-967.882279	-967.866327	-967.927578
PhSHn*2H_2O(b')	-968.048606	-967.883831	-967.86737	-967.930442
PhSHn*2H_2O(b)-TS	-967.989239	-967.828492	-967.815289	-967.868446
HSHd-E_E	-697.401364	-697.356384	-697.349341	-697.387128
HSHd-E_E*2H_2O(a)	-850.300332	-850.206901	-850.193119	-850.249332
HSHd-E_E*2H_2O(a)-TS	-850.257256	-850.167161	-850.156652	-850.202837
HSHd-E_E*2H_2O(b)	-850.296806	-850.203403	-850.189587	-850.246134
HSHd-E_E*2H_2O(b)-TS	-850.251305	-850.162277	-850.151646	-850.197955
HSHd-E_Z	-697.402080	-697.356673	-697.349805	-697.387556

Compound	**E$_{elec}$**	**E$_{elec}$+ZPVE**	**H^{298}**	**G^{298}**
HSHd-E$_{Z}$*2H$_{2}$O(a)	-850.302039	-850.208115	-850.19455	-850.25019
HSHd-E$_{Z}$*2H$_{2}$O(a)-TS	-850.259988	-850.168991	-850.158721	-850.204667
HSHd-E$_{Z}$*2H$_{2}$O(b)	-850.295815	-850.202218	-850.188477	-850.243671
HSHd-E$_{Z}$*2H$_{2}$O(b)-TS	-850.252237	-850.162023	-850.151756	-850.197703
HSHd-K$_{Z}$	-697.417715	-697.372553	-697.365640	-697.403019
HSHd-K$_{Z}$*2H$_{2}$O(a)	-850.315519	-850.222059	-850.208316	-850.264007
HSHd-K$_{Z}$*2H$_{2}$O(a')	-850.317276	-850.223667	-850.209993	-850.265748
HSHd-K$_{Z}$*2H$_{2}$O(a)-TS	-850.268253	-850.178018	-850.167425	-850.213801
HSHd-K$_{Z}$*2H$_{2}$O(b)	-850.315065	-850.221821	-850.207843	-850.264069
HSHd-K$_{Z}$*2H$_{2}$O(b')	-850.318081	-850.224448	-850.210749	-850.265871
HSHd-K$_{Z}$*2H$_{2}$O(b)-TS	-850.265845	-850.175676	-850.165139	-850.210827
HSHd-K$_{E}$	-697.422136	-697.377011	-697.370086	-697.407452
HSHd-K$_{E}$*2H$_{2}$O(a)	-850.3209112	-850.22742	-850.213711	-850.269477
HSHd-K$_{E}$*2H$_{2}$O(a')	-850.3221306	-850.228456	-850.214831	-850.270246
HSHd-K$_{E}$*2H$_{2}$O(a)-TS	-850.2727521	-850.182324	-850.171732	-850.218049
HSHd-K$_{E}$*2H$_{2}$O(b)	-850.316402	-850.223262	-850.209274	-850.265351
HSHd-K$_{E}$*2H$_{2}$O(b')	-850.317508	-850.22414	-850.210271	-850.266235
HSHd-K$_{E}$*2H$_{2}$O(b)-TS	-850.263511	-850.173885	-850.163288	-850.209458
MeSHd-E$_{E}$	-736.731737	-736.659018	-736.65045	-736.692465
MeSHd-E$_{E}$*2H$_{2}$O(a)	-889.6314804	-889.510313	-889.495011	-889.556937
MeSHd-E$_{E}$*2H$_{2}$O(a)-TS	-889.5867961	-889.469017	-889.456958	-889.50721
MeSHd-E$_{E}$*2H$_{2}$O(b)	-889.626237	-889.504896	-889.489699	-889.548345
MeSHd-E$_{E}$*2H$_{2}$O(b)-TS	-889.580326	-889.463469	-889.451345	-889.501444
MeSHd-E$_{Z}$	-736.73453	-736.661647	-736.653242	-736.694513
MeSHd-E$_{Z}$*2H$_{2}$O(a)	-889.6345584	-889.513251	-889.498041	-889.557745
MeSHd-E$_{Z}$*2H$_{2}$O(a')	-889.634198	-889.512921	-889.497672	-889.558902
MeSHd-E$_{Z}$*2H$_{2}$O(a)-TS	-889.5907848	-889.472463	-889.46062	-889.510074
MeSHd-E$_{Z}$*2H$_{2}$O(b)	-889.627666	-889.506626	-889.49128	-889.550209
MeSHd-E$_{Z}$*2H$_{2}$O(b)-TS	-889.582063	-889.464528	-889.45268	-889.501737
MeSHd-K$_{Z}$	-736.747261	-736.674559	-736.665887	-736.708332
MeSHd-K$_{Z}$*2H$_{2}$O(a)	-889.6449295	-889.523971	-889.508443	-889.569345
MeSHd-K$_{Z}$*2H$_{2}$O(a')	-889.6469355	-889.52571	-889.510334	-889.570649
MeSHd-K$_{Z}$*2H$_{2}$O(a)-TS	-889.596708	-889.4789	-889.466558	-889.517621
MeSHd-K$_{Z}$*2H$_{2}$O(b)	-889.644572	-889.523859	-889.50808	-889.570269
MeSHd-K$_{Z}$*2H$_{2}$O(b)-TS	-889.594278	-889.476511	-889.46428	-889.514144
MeSHd-K$_{E}$	-736.752192	-736.679233	-736.670768	-736.711987
MeSHd-K$_{E}$*2H$_{2}$O(a)	-889.6512596	-889.529928	-889.514649	-889.57468
MeSHd-K$_{E}$*2H$_{2}$O(a')	-889.6522728	-889.530814	-889.515603	-889.575153
MeSHd-K$_{E}$*2H$_{2}$O(a)-TS	-889.6018866	-889.483738	-889.471531	-889.521894
MeSHd-K$_{E}$*2H$_{2}$O(b)	-889.645899	-889.524812	-889.50933	-889.569066
MeSHd-K$_{E}$*2H$_{2}$O(b')	-889.646698	-889.52552	-889.510069	-889.570339
MeSHd-K$_{E}$*2H$_{2}$O(b)-TS	-889.592005	-889.474604	-889.462556	-889.512083
PhSHd-E$_{E}$	-928.479007	-928.352829	-928.341462	-928.391111
PhSHd-E$_{E}$*2H$_{2}$O(a)	-1081.377585	-1081.203149	-1081.185831	-1081.250701
PhSHd-E$_{E}$*2H$_{2}$O(a)-TS	-1081.334199	-1081.163046	-1081.148145	-1081.206242
PhSHd-E$_{E}$*2H$_{2}$O(b)	-1081.374508	-1081.200221	-1081.181883	-1081.250382
PhSHd-E$_{E}$*2H$_{2}$O(b)-TS	-1081.327732	-1081.157518	-1081.142537	-1081.200177
PhSHd-E$_{Z}$	-928.488715	-928.362292	-928.351055	-928.400015
PhSHd-E$_{Z}$*2H$_{2}$O(a)	-1081.388583	-1081.213725	-1081.195714	-1081.265199
PhSHd-E$_{Z}$*2H$_{2}$O(a)-TS	-1081.343884	-1081.172309	-1081.157516	-1081.215057

Compound	**E_{elec}**	**E_{elec}+ZPVE**	**H^{298}**	**G^{298}**
PhSHd-E_Z*2H_2O(b)	-1081.381197	-1081.206995	-1081.188570	-1081.256238
PhSHd-E_Z*2H_2O(b)-TS	-1081.334408	-1081.163490	-1081.148671	-1081.206447
PhSHd-K_Z	-928.498435	-928.372065	-928.360681	-928.410125
PhSHd-K_Z*2H_2O(a)	-1081.396979	-1081.222186	-1081.204055	-1081.272546
PhSHd-K_Z*2H_2O(a')	-1081.398136	-1081.223185	-1081.205104	-1081.272163
PhSHd-K_Z*2H_2O(a)-TS	-1081.347527	-1081.176109	-1081.160995	-1081.219270
PhSHd-K_Z*2H_2O(b)	-1081.394803	-1081.220388	-1081.201908	-1081.270417
PhSHd-K_Z*2H_2O(b)-TS	-1081.343330	-1081.172237	-1081.157162	-1081.215340
PhSHd-K_E	-928.498632	-928.372211	-928.36085	-928.410143
PhSHd-K_E*2H_2O(a)	-1081.397899	-1081.223074	-1081.204951	-1081.273241
PhSHd-K_E*2H_2O(a')	-1081.398874	-1081.223907	-1081.205827	-1081.272973
PhSHd-K_E*2H_2O(a)-TS	-1081.348037	-1081.176479	-1081.161365	-1081.219696
PhSHd-K_E*2H_2O(b)	-1081.392208	-1081.218126	-1081.199466	-1081.268435
PhSHd-K_E*2H_2O(b)-TS	-1081.338921	-1081.168172	-1081.153064	-1081.210767
BzSHd-E_Z	-967.801607	-967.647039	-967.634342	-967.688351
BzSHd-E_Z*2H_2O(a)	-1120.701594	-1120.498675	-1120.480078	-1120.548550
BzSHd-E_Z*2H_2O(a)-TS	-1120.657840	-1120.457928	-1120.441729	-1120.504458
BzSHd-E_Z*2H_2O(b)	-1120.694887	-1120.492267	-1120.472581	-1120.544498
BzSHd-E_Z*2H_2O(b)-TS	-1120.650114	-1120.450878	-1120.434707	-1120.496421
BzSHd-K_E	-967.818844	-967.664056	-967.651370	-967.704721
BzSHd-K_E*2H_2O(a)	-1120.718575	-1120.515353	-1120.496827	-1120.564778
BzSHd-K_E*2H_2O(a')	-1120.719034	-1120.515723	-1120.496289	-1120.567837
BzSHd-K_E*2H_2O(a)-TS	-1120.668525	-1120.468627	-1120.452153	-1120.514911
BzSHd-K_E*2H_2O(b)	-1120.712011	-1120.509281	-1120.489445	-1120.561895
BzSHd-K_E*2H_2O(b')	-1120.712828	-1120.509770	-1120.490152	-1120.561326
BzSHd-K_E*2H_2O(b)-TS	-1120.658078	-1120.458897	-1120.442617	-1120.504098
HSAd	-642.063514	-642.035901	-642.029716	-642.065515
HSAd*2H_2O(a)	-794.964872	-794.888473	-794.875802	-794.928562
HSAd*2H_2O(a)-TS	-794.927316	-794.853779	-794.844289	-794.888225
HSAd*2H_2O(b)	-794.963478	-794.886311	-794.874213	-794.924186
HSAd*2H_2O(b)-TS	-794.934767	-794.860821	-794.851593	-794.894291
MeSAd	-681.396352	-681.340778	-681.33316	-681.372639
MeSAd*2H_2O(a)	-834.297897	-834.193580	-834.179432	-834.235533
MeSAd*2H_2O(a)-TS	-834.256301	-834.155142	-834.144106	-834.191813
MeSAd*2H_2O(b)	-834.29536	-834.190639	-834.176752	-834.231167
MeSAd*2H_2O(b)-TS	-834.261513	-834.159602	-834.148773	-834.195537
PhSAd	-873.149132	-873.039828	-873.029450	-873.076778
PhSAd*2H_2O(a)	-1026.051067	-1025.892891	-1025.876070	-1025.938767
PhSAd*2H_2O(a)-TS	-1026.008729	-1025.853898	-1025.840046	-1025.895742
PhSAd*2H_2O(b)	-1026.045951	-1025.887561	-1025.870879	-1025.934819
PhSAd*2H_2O(b)-TS	-1026.007760	-1025.852871	-1025.839374	-1025.893218
ClSAn	-988.290464	-988.281501	-988.276391	-988.309514
ClSAn *2H_2O(a)	-1141.190416	-1141.132769	-1141.121129	-1141.171043
ClSAn *2H_2O(a)-TS	-1141.150563	-1141.095594	-1141.087149	-1141.128365
ClSAn *2H_2O(b)	-1141.188111	-1141.130698	-1141.118878	-1141.168932
ClSAn *2H_2O(b)-TS	-1141.148145	-1141.093879	-1141.085463	-1141.126284
Cl_3CSAn	-1946.804841	-1946.787146	-1946.778442	-1946.821601
Cl_3CSAn *2H_2O(a)	-2099.70572	-2099.639248	-2099.624085	-2099.682988
Cl_3CSAn *2H_2O(a)-TS	-2099.670128	-2099.606111	-2099.594024	-2099.645616
Cl_3CSAn *2H_2O(b)	-2099.703474	-2099.637536	-2099.621991	-2099.682058

Compound	E_{elec}	E_{elec}+ZPVE	H^{298}	G^{298}
Cl_3CSAn *$2H_2O$(b)-TS	-2099.666581	-2099.603411	-2099.591326	-2099.641491
t-BuSAn	-686.011050	-685.880439	-685.870949	-685.913492
t-BuSAn *$2H_2O$(a)	-838.910928	-838.731625	-838.715543	-838.774995
t-BuSAn *$2H_2O$(a)-TS	-838.866842	-838.691386	-838.678379	-838.729302
t-BuSAn *$2H_2O$(b)	-838.908629	-838.729356	-838.713190	-838.773297
t-BuSAn *$2H_2O$(b)-TS	-838.865782	-838.691076	-838.678070	-838.728192
CNSAn	-620.963327	-620.946138	-620.940492	-620.974549
CNSAn *$2H_2O$(a)	-773.865142	-773.799095	-773.787041	-773.837149
CNSAn *$2H_2O$(a)-TS	-773.831367	-773.767058	-773.758170	-773.800174
CNSAn *$2H_2O$(b)	-773.862627	-773.796995	-773.784621	-773.835674
CNSAn *$2H_2O$(b)-TS	-773.826185	-773.762954	-773.754021	-773.795921
F_3CSAn	-865.793112	-865.769902	-865.762547	-865.801921
F_3CSAn *$2H_2O$(a)	-1018.694443	-1018.622393	-1018.608647	-1018.663842
F_3CSAn *$2H_2O$(a)-TS	-1018.657120	-1018.588042	-1018.577232	-1018.624962
F_3CSAn *$2H_2O$(b)	-1018.692519	-1018.620705	-1018.606801	-1018.661943
F_3CSAn *$2H_2O$(b)-TS	-1018.655543	-1018.587098	-1018.576355	-1018.623159
OHSAn	-603.916224	-603.893353	-603.888462	-603.920200
OHSAn *$2H_2O$(a)	-756.816148	-756.744692	-756.733144	-756.782667
OHSAn *$2H_2O$(a)-TS	-756.766930	-756.698751	-756.690248	-756.730974
OHSAn *$2H_2O$(b)	-756.814954	-756.743510	-756.732002	-756.780824
OHSAn *$2H_2O$(b)-TS	-756.765842	-756.698370	-756.689967	-756.729870
OMeSAn	-643.221046	-643.170571	-643.163876	-643.200260
OMeSAn *$2H_2O$(a)	-796.120707	-796.021760	-796.008335	-796.064554
OMeSAn *$2H_2O$(a)-TS	-796.074121	-795.978445	-795.968289	-796.013245
OMeSAn *$2H_2O$(b)	-796.116899	-796.018109	-796.004479	-796.060204
OMeSAn *$2H_2O$(b)-TS	-796.069250	-795.974173	-795.964149	-796.008515
H_3SiSAn	-819.457350	-819.423422	-819.416832	-819.453699
H_3SiSAn *$2H_2O$(a)	-972.357045	-972.274486	-972.261328	-972.315437
H_3SiSAn *$2H_2O$(a)-TS	-972.317506	-972.238235	-972.228334	-972.273328
H_3SiSAn *$2H_2O$(b)	-972.354665	-972.272139	-972.258954	-972.312501
H_3SiSAn *$2H_2O$(b)-TS	-972.315923	-972.237331	-972.227593	-972.271168

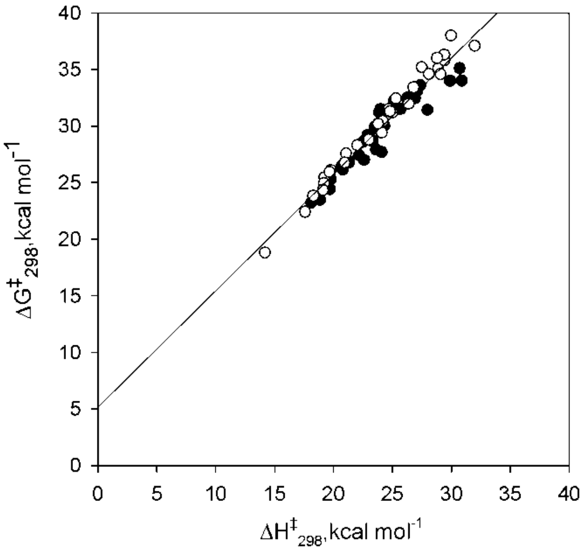


Figure D-1. The correlation between the Gibbs free energy ($\Delta G^{\ddagger}_{298}$) and enthalpy ($\Delta H^{\ddagger}_{298}$) of activation for reaction of various N-sulfinyl species with two water molecules for attack across the S=O (●, R^2=0.8958, slope=0.94, intercept=6.77) and the N=S (○, R^2=0.9806, slope=1.09, intercept=4.04) bonds. The averaged values for both mechanisms resulting from the linear regression for all data on the plot are: R^2=0.9410, slope=1.03, intercept=4.97. The intercept of 4.97 kcal mol^{-1} depicts the averaged entropy -TΔS contribution to the Gibb's free energy.

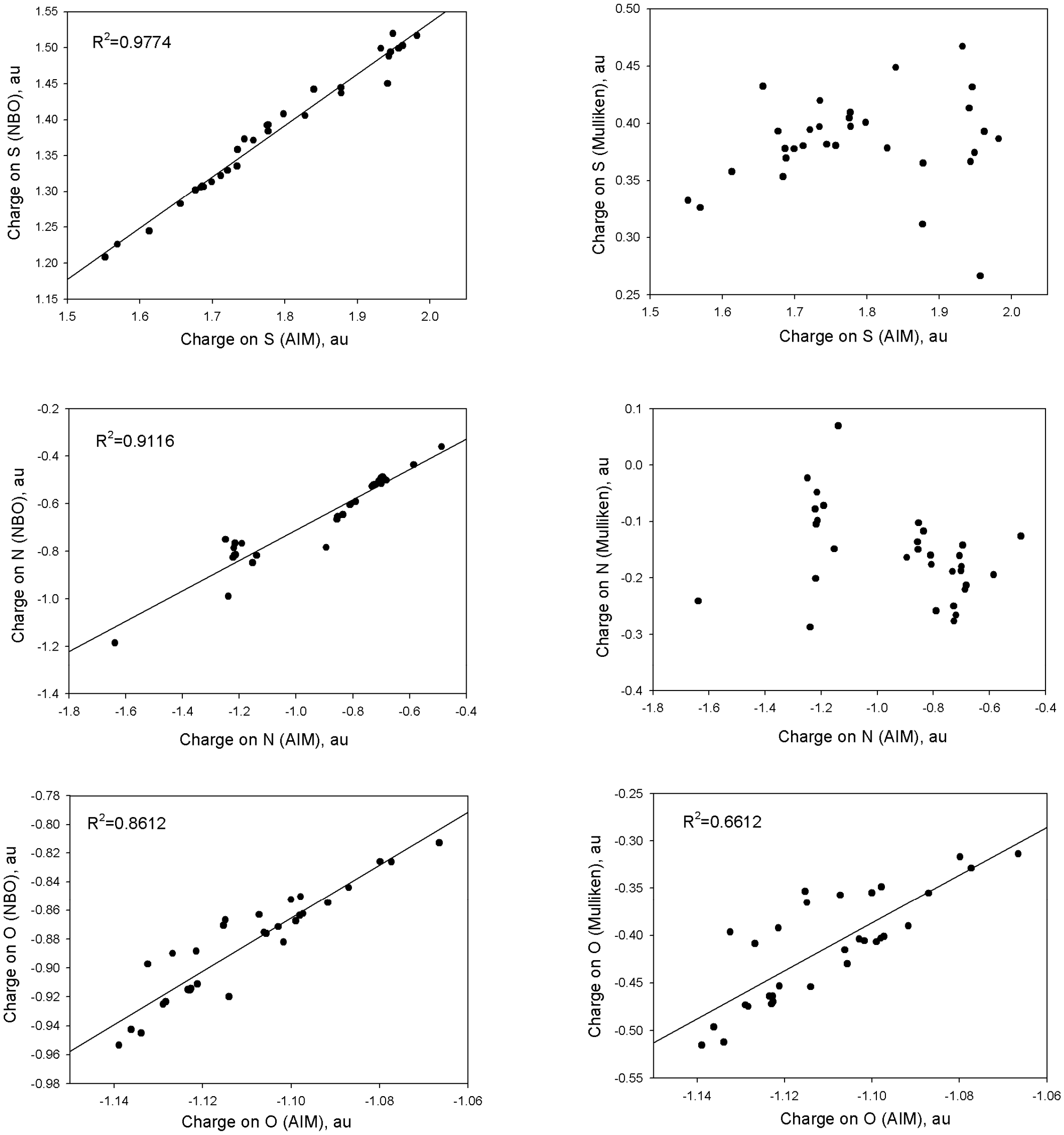


Figure D-2. The correlation between the charges on atoms of the NSO group calculated with Quantum Theory of Atoms in Molecules, Natural Bond Resonance Theory and Mulliken analysis.

Table D-2. Selected geometric parameters (bond lengths in pm, angles in degrees) perpendicular (**a, b**) and planar (**a', b'**) complexes and transition states (TS) of **HSHd-$\mathrm{K_E}$**[a] in reaction with two water molecules across the S=O (**a**) and N=S (**b**) bonds calculated with the B3LYP/6-31+G(2d, 2p) and MP2/6-311+G(p,d)[b] model chemistries.

			Across the S=O bond					Across the N=S bond				
	SHd1-$\mathrm{K_E}$[a]		Complex				TS	Complex				TS
			a		**a'**			**b**		**b'**		
S=O	148.5	*148.7*	149.7	*149.5*	149.8	*149.5*	157.5	148.1	*148.7*	148.5	*149.0*	147.2
N=S	157.0	*159.2*	156.4	*158.8*	157.1	*159.1*	154.2	157.3	*160.6*	157.8	*161.2*	161.1
$N-N_R$	133.5	*135.2*	133.5	*135.0*	133.2	*134.9*	135.5	134.4	*135.6*	133.9	*135.4*	140.0
N_R-R	138.8	*102.3*	138.7	*138.9*	138.9	*139.0*	137.5	138.4	*138.9*	138.7	*139.0*	137.0
N_R-H_N	102.1	*139.0*	102.0	*102.2*	102.1	*102.3*	101.6	102.0	*102.4*	102.1	*102.4*	101.6
NSO	113.8	*113.5*	113.0	*112.3*	111.4	*111.1*	107.7	113.0	*112.2*	112.0	*110.9*	110.0
SNN_R	118.6	*115.2*	119.3	*115.7*	118.9	*115.5*	121.5	117.8	*114.7*	117.7	*114.0*	115.7
NN_RH_N	119.9	*120.5*	120.0	*120.3*	119.8	*120.1*	119.8	119.2	*119.6*	119.1	*119.6*	116.9
NN_RC_r	120.3	*119.3*	120.4	*119.5*	120.3	*119.4*	120.3	120.7	*119.7*	121.0	*119.8*	120.1
C_rN_RH	119.8	*120.1*	119.6	*120.1*	119.9	*120.4*	119.8	119.8	*119.8*	119.9	*120.1*	119.4
$S\cdots O_{w1}$			310.7	*293.7*	309.5	*298.8*	212.8	308.3	*298.0*	333.1	*308.4*	208.2
$O_{w1}H_{w1}$			97.5	*96.9*	97.5	*97.0*	140.9	97.3	*96.8*	97.3	*96.9*	134.2
$O_{w2}\cdots H_{w1}$			188.8	*192.1*	187.9	*189.6*	106.9	192.8	*192.3*	192.8	*191.5*	111.2
$O_{w2}H_{w2}$			97.2	*96.7*	97.3	*96.7*	126.1	96.8	*96.8*	97.1	*96.9*	122.4
$H_{w2}\cdots O$ or $H_{w2}\cdots N$			197.3	*194.1*	193.9	*193.4*	116.3	225.1	*206.3*	207.5	*200.5*	129.0
C_rN_RNS	0	0	1.1	*2.5*	0	*1.6*	9.2	5.0	*8.1*	1.9	*7.0*	8.9
$O_rC_rN_RN$	0	0	0	*1.0*	0	*1.0*	2.7	3.4	*5.5*	0	*3.2*	9.0
$SNOO_{w1}$			108.6	*117.9*	1.0	*11.1*	115.0	104.9	*104.9*	33.3	*20.7*	104.9
$OSNO_{w1}$			99.5	*98.2*	3.3	*42.1*	97.3	106.7	*111.9*	13.0	*5.6*	107.8

[a] HSHd-$\mathrm{K_E}$ included for comparison. [b] Shown as a second column for each structure.

Table D-3. Complexation (ΔH_{bind}, kcal mol^{-1}) and activation enthalpies ($\Delta H^{\ddagger}$, kcal mol^{-1}) for the reaction of various N-sulfinylamines with two water molecules across the S=O (**a**) and N=S (**b**) bonds.

	Across S=O bond (**a**)		Across N=S bond (**b**)		Charges		
	ΔH_{bind}	$\Delta H^{\ddagger}$	ΔH_{bind}	$\Delta H^{\ddagger}$	q(N)	q(S)	q(O)
OHSAn	-8.1	26.9	-7.3	26.4	-0.488	1.656	-1.114
OMeSAn	-7.9	25.1	-5.5	25.3	-0.585	1.734	-1.102
ClSAn	-8.1	21.3	-6.7	21.0	-0.894	1.840	-1.087
t-BuSAn	-8.0	23.3	-6.5	22.0	-1.215	1.877	-1.132
CNSAn	-9.2	18.1	-7.7	19.2	-1.220	1.932	-1.067
Cl_3C	-8.7	18.9	-7.3	19.2	-1.139	1.949	-1.080
H_3SiSAn	-7.9	20.7	-6.4	19.7	-1.638	1.957	-1.115
F_3CSAn	-8.9	19.7	-7.8	19.1	-1.153	1.982	-1.077
HSAd	-8.5[a]		-7.0[a]	14.0[a]			
			-7.6[b]	14.9[b]			
MeSAd			-5.7[a]	16.8[a]			
			-7.4[b]	19.8[b]			
PhSAd	-8.4[a]						
	-8.8[c]	23.1[c]					

The mode of binding is shown on Figure 7-5 ($\mathbf{b_1}$)[a] ($\mathbf{b_2}$)[b] and ($\mathbf{b_3}$)[c]

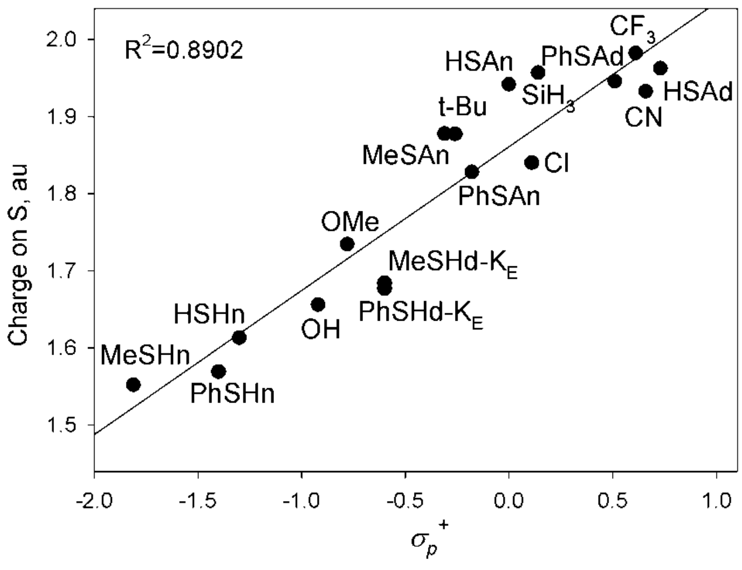


Figure D-3. Dependence of the charge on sulfur on the Hammett substituent resonance σ_p^+ constant for various N-sulfinyl species