

FULL PAPER

Models of Water-Assisted Hydrolyses of Methyl Formate, Formamide, and Urea from Combined DFT-SCRF Calculations

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Received: 1 April 1998 / Accepted: 15 May 1998 / Published: 5 June 1998

Abstract In this work we present theoretical studies of the hydrolytic reaction of methyl formate, formamide and urea with one water molecule. The studied systems contain two additional water molecules which can act as bifunctional acid-base catalysts. These water molecules catalyze proton transfers between the primary reacting species. Our models describe the concerted transfer of two protons in every reaction step. The calculations have been carried out with the Becke3LYP/6-31G* method. Unspecific solvation effects have been included by means of a polarizable continuum model. Substrate reactivity differences as well as preferences for different reaction pathways can be discussed with the aid of these molecular systems. The studied alternative mechanisms include the common addition-elimination mechanism via a tetrahedral intermediate, and a concerted S_N -like mechanism without a reaction intermediate. Our results suggest that the proved decreasing substrate reactivity in the order ester, amide, urea is caused by a rising resonance stabilization of the reaction centre, and not by a different positive partial charge of the carbonyl carbon. It is also concluded, that the probability of a concerted addition of a nucleophile and elimination of a leaving group without a tetrahedral intermediate rises in the order ester, amide, urea. The ordering of reactivity is not influenced by this behaviour.

Keywords Ester hydrolysis, Amide hydrolysis, Urea hydrolysis, Solvent effect, Molecular orbital calculation

Introduction

The reactions of acyl derivatives like esters and amides with nucleophiles received much attention through the years because of their fundamental importance in enzyme-catalyzed reactions. The collected experimental data for hydrolytic reactions in aqueous media and studies on their catalysis by acids and bases provided a deep insight into alternative re-

action mechanisms, sources of substrate reactivities and catalytic effects [1-3]. It is well established today that the majority of such reactions proceed via an addition-elimination mechanism, which involves rate limiting formation of a short-living intermediate with a tetrahedral carbon centre (see Fig. 1) [4]. This reaction scheme is one marginal case of an S_N -type reaction, which can in principle also proceed via a concerted attack and bond cleavage or an acid-catalyzed elimination-addition mechanism, where an acylium ion or a similar molecule is involved (see Fig. 1). In the case of ureas with at least one primary or secondary amino group an ad-

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ditional reaction mechanism was postulated [5,6]. It involves the elimination of an amine and formation of an isocyanate via a zwitterionic short-living tautomer, which may be formed by deprotonation of one NHR group and protonation of the other NR₂ group of an urea. A nucleophile is not required for this reaction step. However, the primary formed isocyanate can undergo subsequent hydrolysis after addition of a nucleophile. General or specific base catalysis of all these reactions is important for increasing the strength of a nucleophile or providing stronger nucleophiles. Catalysis by weak Brønsted acids or solvated protons yields activation of the substrate against nucleophilic attack and forcing of the addition step by energetic stabilization of the tetrahedral intermediate. The same source of catalysis is discussed for reactions promoted by Lewis acids like transition metal ions. Both general acid catalysis via stabilization of the addition intermediate, and general base catalysis via activation of nucleophiles, are also operated by various hydrolytic enzymes like serine, cysteine or aspartate amidases and esterases, zinc proteases and urease [7,8].

Although these general features of such reactions seem to be well known, there exist many uncertainties about the details of the primary reaction steps in condensed phases, and about the importance of alternative reaction pathways. From experiments in H₂O/D₂O-mixtures and evaluations of pH-profiles by means of acidity functions [2] it was stated that besides a nucleophile some solvent molecules are involved in the elementary reactions in aqueous solution, which act as bifunctional acid-base catalysts in proton transfer steps. Recently, this idea was realized in theoretical computations of the reaction of formaldehyde with up to four water molecules [9], and formamide with one nucleophilic water and one additional catalytic water molecule [10,11]. There it was shown that these reaction models provide a more realistic picture of energy profiles and details of the bond-forming and bond-breaking processes than reduced models (substrate + nucleophile only) [6,12-15] can do, although already these truncated systems enable one to study principal features of a reaction mechanism. In [9] it was proved that the transfer of a proton from a water molecule attacking the carbonyl carbon of formaldehyde onto the carbonyl oxygen of the same substrate molecule represents the essential step of the addition reaction. The free energy barrier of this proton transfer depends on the number of water molecules acting as bifunctional proton-accepting and proton-donating catalysts through a hydrogen-bonded chain, which connects the primary acid (the neutral nucleophile) with the terminating base (the acyl derivative). It was found that the subsequent inclusion of water molecules reduces the energy barrier of activation, until this positive effect is overruled by the entropic term of a free energy barrier.

The potential energy hypersurfaces of the models of neutral and H₃O⁺-catalyzed hydrolysis of formamide presented in [10,11] were screened for stationary points related to a nucleophilic substitution reaction at the neutral or O-protonated amide yielding formic acid and ammonia. These models contain one ancillary water molecule, which was placed in such a way that it transfers a proton from the nucleophilic

water onto the amide nitrogen. The stationary points found under these restrictions were interpreted in terms of a concerted reaction without addition intermediate in the neutral case and in terms of an addition-elimination mechanism in the O-protonated case. It was concluded that pyramidalization of the nitrogen atom by its protonation should be a key feature in these reactions.

However, the latter study lacks the possibility to deprotonate a neutral nucleophile by water-assisted protonation of the carbonyl oxygen in the neutral case. It also lacks the possibility to protonate the leaving group rather than the carbonyl oxygen in a pre-equilibrium of the acid catalyzed hydrolysis. These alternative mechanisms should be taken into account, because the carbonyl oxygen of many carboxylic acid derivatives is proved to be more basic than the leaving group even in water, but it is also concluded that O-protonation yields deactivation of the substrate against nucleophilic attack because of an increasing resonance stabilization [16]. In order to prove these estimations of substrate properties and catalytic effects, we decided to model the hydrolyses of the simplest ester, amide, and urea by theoretical computations and utilization of molecular systems, which make comparisons between alternative reaction pathways possible. Our work presents the first results from studies of the neutral water-assisted reaction.

Model construction

In distinction to simple systems of reacting species used for quantum mechanical studies in the gas phase, the construction and study of complex systems with many unknown stationary points is the critical step in this work. A given model has to incorporate all relevant features of the process of interest, otherwise an interpretation in the light of a given problem is impossible. In our case, the question to answer is related to a quantitative comparison of different possible reaction mechanisms on structurally related substrates. Therefore, three general presuppositions have to be given, which lead to prerequisites of the molecular systems and features of stationary points.

At first, we assume that the general mechanisms of the reactions under study are similar to those derived from experiment (see Fig. 1). That means in detail, that the reaction starts with a water molecule approaching the carbonyl carbon of an acyl derivative. During hydrolytic reactions in neutral or acidic aqueous solution, often addition products which are dihydroxylated at the carbonyl carbon are found by experiment. They are unstable molecules and can decompose into the reactant molecules or the products of the hydrolytic reaction. These intermediates T⁰ can be formed by deprotonating the neutral nucleophile before or during the addition step. Does the reaction mixture contain only water molecules except the substrate, then other water molecules can act as proton acceptors. Since water is a very weak base in water (pK_b about 16), deprotonation of the nucleophile probably leads to protonation of the acyl derivative, if it itself

or a structure occurring during the reaction is more basic than water, and if the reaction time scale allows multiple proton transfers. By neglecting reaction dynamics, a proton transfer from the approaching nucleophile onto the substrate on an adiabatic potential hypersurface can be constructed. This event is probably involved in the transition state **TS1⁰** which connects the reactant state and the addition intermediate **T⁰**. These statements lead to the construction of selected ensembles of nuclei, which represent starting structures for finding stationary points related to the assumed reaction mechanism. The finding of meaningful structures which are not postulated in this way is improbable. That means, that the reaction models to construct can be used to verify or to rule out a guessed reaction pathway. A screening of the whole potential energy hypersurface in order to look for unknown pathways is not done.

The substrates under study bear two basic groups, which can act as final acceptors of the proton donated from the neutral nucleophile. The finding that the carbonyl oxygen is the preferred site of protonation of common molecules of this type leads to the known addition-elimination mechanism, which has to be proved by searching for an addition intermediate **T⁰** formed after proton transfer from the nucleophile onto the carbonyl oxygen. The following elimination step includes breakdown of the C-X-bond (X=O for esters, X=N for amides and ureas) and proton transfer from the forming acid onto the leaving group. The construction of this second proton transfer is validated by the known high basicity of the primary formed anionic leaving groups (alcoholate or deprotonated amine) and from the known high acidity of diprotonated carboxylic acids. This estimation leads to the starting structures for the transition state of the elimination reaction **TS2⁰**, which involves the necessary proton transfer either from the former nucleophile or from the protonated carbonyl oxygen. The same assumptions can be made for direct protonation of the leaving group during approach of the nucleophile via a transition state **TS^X**. This alternative mechanism represents an abridgement for reaching the same products without protonating and deprotonating the acyl portion in subsequent steps. The occurrence of postulated intermediates and transition states, and the concertedness of bond-forming and bond-breaking processes and proton transfers has to be proved by the calculations. In addition, they have to show, which mechanism is preferred for which substrate and which elementary reaction step should be rate limiting.

At second, proton transfers are involved in the reactions under study. One could assume that the proton transfers postulated above occur directly between the substrate and the neutral nucleophile. This assumption leads to restricted models containing a substrate and one water molecule only. They were extensively described in the literature. We will present results from these models for our systems and will discuss their ability to answer the questions given above. By anticipating the results from these simple models, it is clear, that proton transfers as involved in the reactions under study always require the formation of hydrogen bonds between the proton donor and the acceptor [17]. From that follows, that additional water molecules have to be included in the mod-

els, because a water molecule which is H-bonded to a carbonyl oxygen or an ester or amide leaving group cannot act as a nucleophile at the same substrate molecule without a high strain for proton transfer. In this work we present models, which contain one additional water molecule for each postulated proton transfer. The proton transfer chains always form six-membered rings, for which the steric strain of proton transfers should be small.

The third prerequisite for our aim is the possibility to compare the constructed models for different reactions and substrates in a quantitative way. Therefore it is necessary to build similar models for each substrate, and a molecular system for one substrate, in which both possible mechanisms can occur without large rearrangements of the reacting species, especially without changes in hydrogen bond patterns. Otherwise the calculated energies would bear the potential of artefacts from model construction. The latter statement leads to models containing three water molecules, which are placed to carry out a desired function (see Fig. 2) either as nucleophile, as acid-base catalyst or as solvating spectator.

Computational details

All computations were carried out with the Becke3LYP density functional hybrid method [18] in combination with the 6-31G* basis set [19] as implemented in the Gaussian94 program package [20]. Preliminary studies were done with the HF/3-21G method. This choice was made because the systems described in this paper contain proton transfers in weak hydrogen bonds. It is known that a small basis set like 3-21G will yield unusual strong hydrogen bonds. This property leads to high basis set superposition errors of interaction energies, but it also enables one to obtain reliable guesses for starting

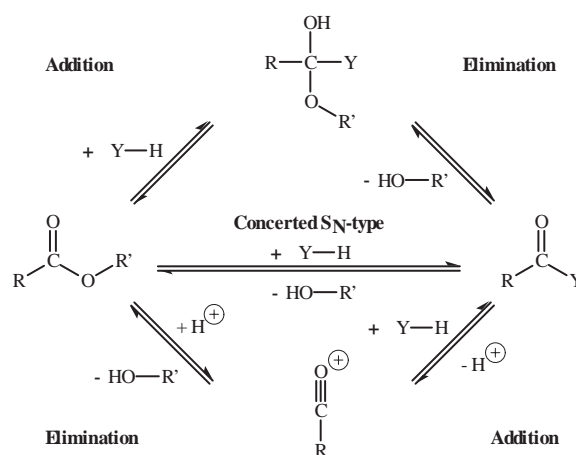


Figure 1 General possible reaction pathways of hydrolytic reactions of an ester with a neutral nucleophile

structures of weak interacting molecules within an appropriate time. Geometries of stationary points were optimized without any constraints. Local minima and first order saddle points on adiabatic potential energy hypersurfaces were identified by their number of imaginary vibrational frequencies, which were calculated from analytical second derivatives of the potential energy in the harmonic approximation. Free energy profiles were calculated after thermal correction of the potential energy using standard formulas of statistical thermodynamics at $T = 298$ K and $p = 1$ atm. Calculated vibrational frequencies were used unscaled.

Presented reaction pathways connecting a postulated reactant and product state over a transition state were verified by calculations of intrinsic reaction coordinates (IRC) in mass-weighted internal coordinates [21] with the HF/3-21G method.

Effects of the bulk solvent on energies and electron densities of found stationary points were estimated by single-point calculations with the Self-Consistent Isodensity Polarized Continuum Model (SCI-PCM) [22-24], using a cavity definition by a 0.0004 au isodensity cutoff and a dielectric constant of 78.54 for pure water.

Electron densities of the presented structures were analyzed in terms of possible valence structure representations by means of localized bond orbitals with the aid of the NBO 4.0 program [25].

The calculations were done on IBM RS/6000, Sun SuperSPARC, UltraSPARC and SGI Origin 2000 workstations at the Universität Potsdam, on a Cray J916 at the Konrad-Zuse-Zentrum für Informationstechnik Berlin (ZIB) and on a Cray J932 at the University of Kiel.

Results and discussion

General reaction pathways

The stationary points for a possible reaction pathway for the hydrolysis of formamide corresponding to an addition-elimination mechanism with only one water molecule involved are shown in Fig. 3. These structures are known in principle from many previous works. That's why we will discuss only their energetics in a subsequent section. The more complicated systems with three water molecules yield structures as shown in Fig. 4. The stationary points found for methyl formate and urea are the same in principle, except details for some hydrogen bonds. Before we go into the structural and energetic details, we should explain the character of this two-step mechanism and its variants for these models. During the first reaction step the oxygen atom O1 of water W1 attacks the carbonyl carbon C (for the atom labeling scheme see Fig. 2). Our models show an attack onto the si-site of the prochiral carbonyl carbon of formamide and methyl formate (the C of urea is not prochiral). The water molecules W2 and W3 form hydrogen bonds to W1 during this step. W1 acts as proton donor for both partners. W2 also forms a H-bond to the carbonyl oxygen O. This hydrogen bond is required for the suc-

cessful reaction shown in Fig. 4. Because of steric circumstances all models of this kind lack a interaction between W3 and O via a hydrogen bond. This circumstance is owed to the reduced representation of the complete hydrate shell of the substrates, which might show a different structure. During the addition step a transfer of the protons H1a and H2 occurs in the H-bonds O1-H1a-O2 and O2-H2-O. This transfer leads to deprotonation of W1 and protonation of O. The water molecule W2 acts as an acid-base-catalyst, whereas W3 is only a spectator. The formation of a bond C-O1 and the transfer of these two protons are the essential properties of the transition state TS1^o for all three substrates. They can also be found, when the models do not contain W3. We verified this possibility by studies with the HF/3-21G method. These models cannot be compared with similar models for alternative reaction pathways, so we do not present them here.

If W3 is present and if it connects W1 and O via two hydrogen bonds like W2 does in Fig. 4, then the roles of W2 and W3 might be changed. A transition state TS1^o which involves transfer of the protons H1b and H3 instead of H1a and H2 can be found (see structure a) in Fig. 5), but the energies of the variants of TS1^o are the same in all systems (results not shown). Here a direct interaction between W3 and X is not observed.

After passing the transition state TS1^o all systems studied reach an intermediate T^o which is solvated with two water molecules. It is proved to be a local minimum on the potential hypersurfaces. It can decompose via three pathways. Did a transfer of protons involve W2 and does W3 connect W1 and O in the state T^o as shown in Fig. 4, then H1b can be transferred from O1 via W3 onto the carbonyl oxygen in a subsequent step (see structure d) in Fig. 5). This process yields decomposition of T^o back into the substrate and three water molecules, where the carbonyl oxygen of the substrate is now

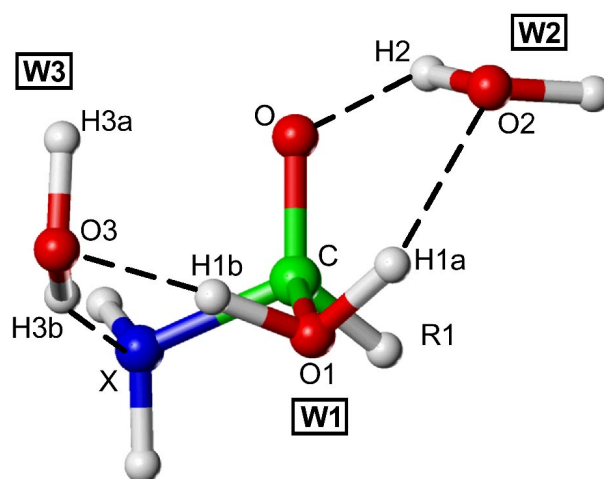


Figure 2 Principal scheme of composition of the used reaction models containing three water molecules

formed by O1 of the former W1. This non-productive reaction pathway might be used as a model for ^{18}O -exchange experiments. These measurements serve as indication to the existence of tetrahedral intermediates in hydrolytic reactions [26] of the described type. However, we will not discuss this reaction any further, because the energies of these transition states were essentially the same like those of the described variants of TS1^{O} for all three substrates and all variants of T^{O} .

Does W3 form H-bonds to H1b at O1 and to X, then the intermediate can decompose into products via fission of the bond C-X and transfer of the protons H1b and H3b (see Fig. 4). Here the former nucleophile W1 will become fully deprotonated and forms the carbonyl oxygen of the acid product. W2 is a spectator in this reaction step. These events are the essential elements of the transition states TS2^{O} of all three substrates. A similar pathway can begin from intermediates, which were formed by proton transfer from W1 to O via W3 (see structure b) in Fig. 5). Does W3 connect X with H1b at O, then simultaneous transfer of H1b and H3 yield another transition state TS2^{O} and products (see structure c) in Fig. 5). During this reaction, the carbonyl oxygen of the acid product is the same atom as the carbonyl oxygen of the substrate. Again modeling of this variant is without problems in these systems, and the energies of the two TS2^{O} are near the same again (results not shown).

There exist other possibilities to place W2 and W3 leading to further variants of these systems. For instance, W3 can connect the atoms X and O1 via H-bonds, and it can form an additional H-bond to W2, which is connected to O. In such a system, a transition state TS1^{O} could involve simultaneous transfer of three protons. This might be possible in principle, but our aim was not to find the best number of bifunctional water molecules in these reactions.

The presented systems also make the study of an alternative reaction pathway possible. The transition state TS^{X} for a concerted nucleophilic attack and breakdown of formamide reacting with only one water molecule is shown in Fig. 3. By searching for saddle points in the refined models, transition states TS^{X} were also found for all three substrates. They involve transfer of the protons H1b and H3 via W3 between W1 and X, leaving H1a at O1 (see Fig. 6). W2 does not act as a proton-transferring molecule here, it connects W1 and O via a hydrogen bond during the whole reaction. The transition state TS^{X} involves the transfer of the protons H1b and H3b in the H-bonds O1-H1a-O3 and O3-H3b-X, formation of the bond C-O1, and fission of the bond C-X. A local minimum representing an intermediate is not part of this reaction coordinate, as verified by IRC calculations. If the spectator W2 is omitted in these models, the systems are the same as presented in [10,11] for formamide. They can be used for a successful modeling of such a reaction on formamide and methyl formate. In the case of urea, W1 will interact with the second amino group, when W2 is not present. Then W1 cannot act as a nucleophile. But other reaction pathways as mentioned in the introduction might be studied on this system. We do not describe these studies here, because the transfer of a proton from one N to the other leading to elimination of

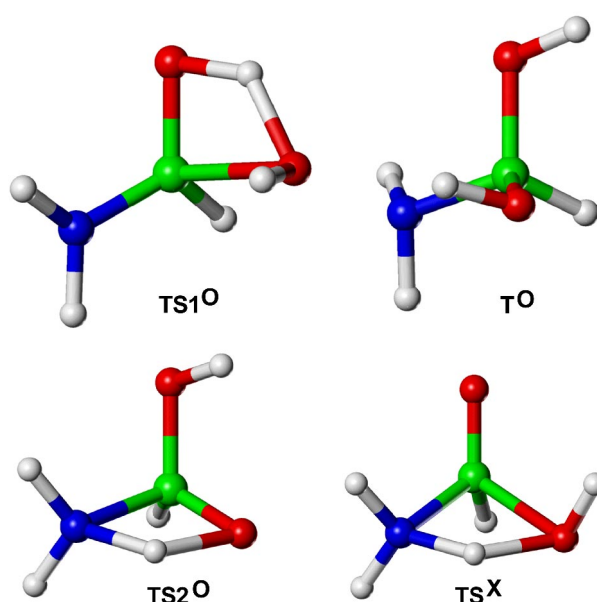


Figure 3 Stationary points for the non-catalyzed reaction of formamide with one water molecule via an addition-elimination (TS1^{O} , T^{O} , TS2^{O}) and a concerted (TS^{X}) mechanism

ammonia and formation of HNC(O) is unique for urea in this restricted system. So no comparisons can be made regarding to the meaning of this mechanism with respect to the others.

Structures of stationary points

The following discussion focuses on structural properties of transition states and intermediates in order to derive explanations for the calculated behaviour during the studied reactions. Table 1 lists essential geometry parameters of stationary points. In order to discuss the strength of particular bonds, bond indices are also listed. The discussion of each type of a stationary point first describes its general features, then we focus on differences between these structures for the three substrates. This is done because each type of a stationary point has the same principal properties for all substrates.

Transition states TS1^{O}

These transition states are determined by the attack of the nucleophile onto the carbonyl carbon, leading to a partial bond between C and O1. NBO-calculations on these structures show, that this bond is formed by the p_z hybrid orbital of C, which participated in the $p(\text{C}=\text{O})$ bond of the former substrate. The carbonyl carbon changes its hybridization state from sp^2 to sp^3 , which leads to a tetrahedral structure in this region. This event implies elongation of the C-O distance, leading to a single C-O bond. The conjugation of p-electrons

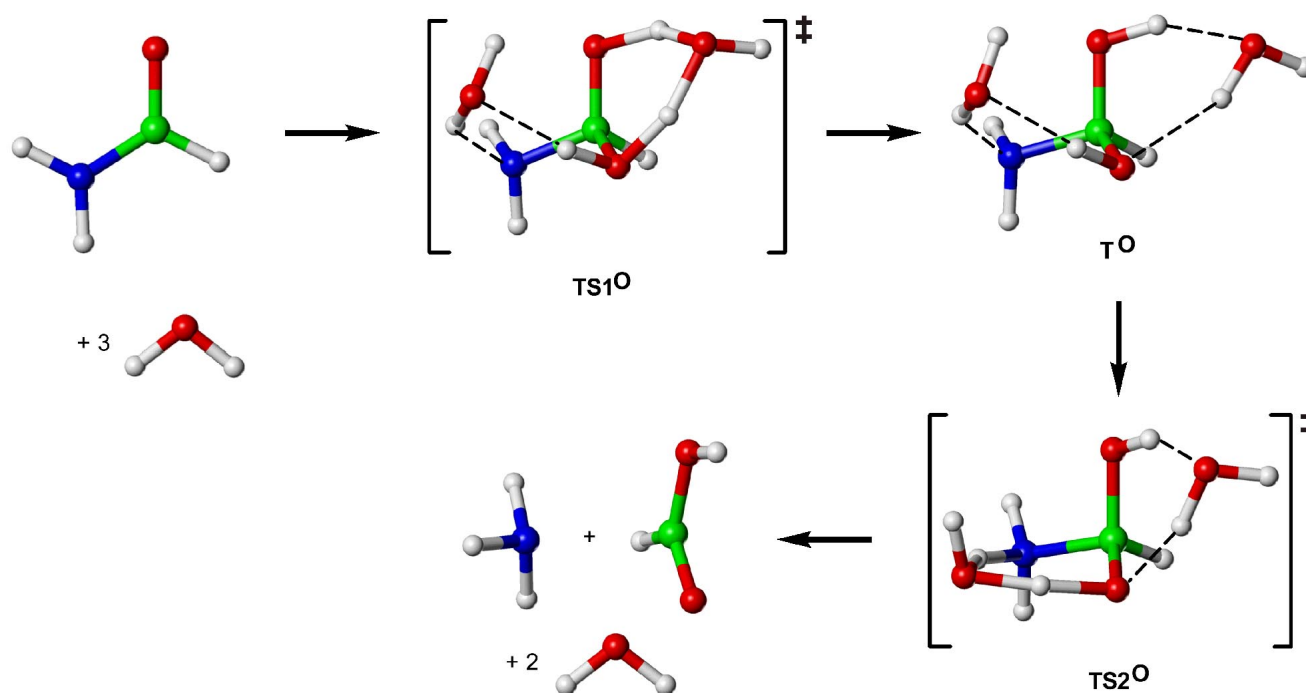


Figure 4 Stationary points for the water-assisted reaction of formamide with one water molecule via an addition-elimination mechanism

from X into the C=O-bond decreases, which implies elongation of the C-X-bond and pyramidal amino groups for formamide and urea. However, the transition state structures we calculated are dominated by the more or less concerted transfer of the two protons H1a and H2. This movement forms the major part of the eigenvector of the Hessian matrices, which corresponds to the reaction coordinate (see Fig. 9).

The found transition states show a more or less concerted formation and breakdown of several covalent bonds, but there exist asymmetries especially in the proton transfer events. If the formation of the C-O1 bond is concerted with the proton transfer or not, can be illustrated by means of intrinsic reaction coordinates (see Fig. 8). It is proved that the approach of the nucleophile onto the reaction centre proceeds nearly continuously on the reaction coordinate, followed by several structural changes of the substrate. In the transition state the formation of the tetrahedral geometry around the carbonyl carbon is almost complete. Shortly before reaching the transition state the proton transfers occur. But the approach of H2 onto the carbonyl carbon can already be seen much earlier on the reaction coordinate. The developing negative charge at O implied by changing the hybridization of the reaction centre should be the reason for that, yielding a rising strength of the H-bond O-W2. The transfer of H2 from O2 to O begins earlier than the deprotonation of the nucleophile. The latter is also completed much later on the reaction coordinate.

The hypotheses which can be derived from these results are as follows: a) the interaction between the attacking oxygen of neutral W1 and the reaction centre C is repulsive in the gas phase at distances shorter than about 3 Å. An attack yields a rising potential energy, which is the main part of the energy barrier during the first section of the reaction. b) A nucleophilic attack becomes easier, when the developing electron density at the carbonyl oxygen can be compensated. In our models, this occurs via the H-bond O-H2. c) The nucleophilic attack becomes successful in terms of a reaction, when the carbonyl oxygen becomes protonated. In our systems, this event (transfer of H2 onto O by deprotonation of W2) implies deprotonation of the nucleophile. The deprotonation of the neutral nucleophile seems to be of minor importance here. In continuation of this statement the question arises, if one can construct a stable molecule, which is formed by an O-protonated acyl derivative and a neutral nucleophile. This leads to models of proton catalyzed hydrolytic reactions, which are the subject of further studies.

Looking at features of the transition state of the studied substrates (see Table 1), some specialities become clear. The distance C-O1 is much shorter for the ester than for the other two substrates. The strength of this bond is higher. The transfer of the protons H1a from O1 to O2 and of H2 from O2 to O becomes more asymmetric in the order ester, amide, urea. In the TS1⁰ of urea, the breaking bond O1-H1a is the shortest, and the forming bond O-H2 the longest. With the aid of the interpretation of the essentials of this reaction step given above

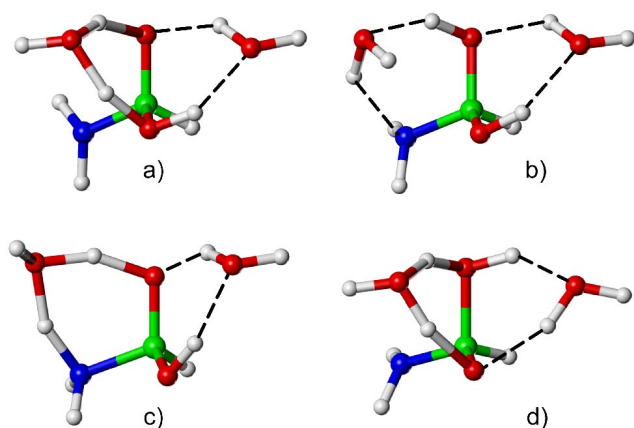


Figure 5 Additional stationary points for the water-assisted reaction of formamide with one water molecule via an addition-elimination mechanism (see text for description)

it can be concluded, that the repulsive interaction between C and O1 is lower for methyl formate than for the other two substrates. The reason for that should be the low electron density at C of esters, which forces its electrophilicity. But also in ureas the carbonyl carbon should be activated in this manner [28] because of the presence of two electronegative nitrogen atoms. But nevertheless, in the transition state TS1^O of urea a C-O1-distance is reached corresponding to that of formamide. A simple interpretation can base on the fact, that the partial charge at a carbonyl carbon is dominated by shifts of the s-electron density. But during nucleophilic reactions at a carbonyl carbon a reordering of the p-electron density takes place, which requires breakdown of resonance, using

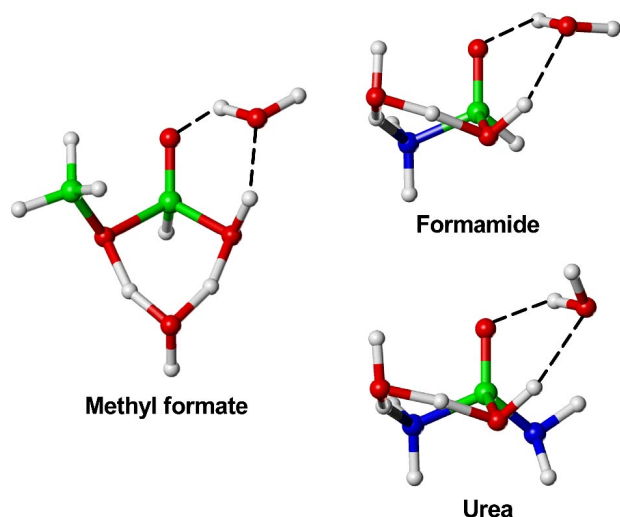


Figure 6 Transition states TS^X for the water-assisted reaction of methyl formate, formamide, and urea with one water molecule via a concerted S_N-type mechanism

the language common for chemists. The delocalization of the p-electron density at the reaction centre of ureas is the highest in this series [27]. The relation between overall electron density and delocalized p-electron density at C should be a reason for the observed differences. Regarding to the position of H2 in the transition state, a direct connection to the basicity at O can be constructed. Ureas are much stronger bases at this site than esters or amides [16]. This leads to short O-H2-distances and long O2-H2-distances in the transition state of urea. The transfer of this proton is the more complete in the transition state, the more basic the acceptor atom is. The position of H1a cannot be explained by the basicity of W2 alone, which itself is determined by the basicity of the substrate at O. Therefore the acidity of W1 has to be included, which is determined by the strength of the forming bond to the substrate.

Intermediates T^O

The geometries of these states (see Table 1) show, that the geometry changes discussed in the preceding section are completed. The structures of intermediates of the studied substrates are similar in principle. All covalent bonds have single bond character, as proved by NBO calculations. The hydrogen bond lengths between the intermediates and the surrounding water molecules are in a region which is expected for interactions between neutral dipolar molecules. The NBO analysis of not hydrated intermediates yields preferred Lewis structures with s-bonds and lone pairs only. These valence bond formulas explain more than 99 % of the overall electron density, indicating a very low amount of resonance. From this point of view the character of the formation of these intermediates can be paraphrased by breakdown of resonance

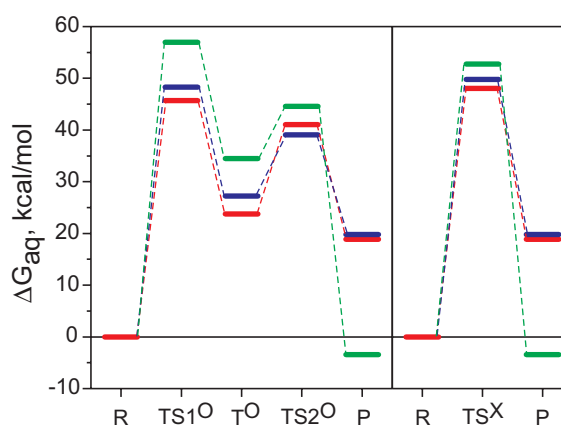


Figure 7 Free energy profiles for water assisted hydrolyses with inclusion of unspecific solvation effects for an addition-elimination (left) and a concerted (right) mechanism (red: methyl formate, blue: formamide, green: urea)

stabilization of the substrates. This statement can also be derived from energy profiles (see next section).

Transition states $TS2^0$

The structure of these states is determined by fission of the C-X bond and rehybridization of the carbonyl carbon towards sp^2 . The bond C-O1 becomes shorter due to an increasing double bond character yielding the carbonyl group of the acid product. The bond C-O lengthens. The group O-H2 will become the hydroxyl group of the forming acid product. Isolated carboxylic acids mostly show trans conformation of the hydroxyl proton with respect to the acid substituent. This position is already present in the transition states we calculated. But in comparison with these structural conversions, the transfer of the protons H1b and H3b is the essential event in these transition states. The transfer is asymmetric again (see Table 2). The structure around O3 of the ester model

resembles nearly that of an H_3O^+ ion (H1b is near completely transferred onto O3, which is still strongly bonded to H3b).

These observations may be compared with structural and energetic changes after full protonation of the atom X in isolated carboxylic acid derivatives [16]. With respect to the energy profiles discussed below the following conclusions can be derived: a) The breakdown of the tetrahedral addition intermediate is coupled with the basicity of the leaving group and with the acidity of a hydroxyl group of the intermediate. Because the intermediates show near no delocalization of the lone pair electrons at X into other structure parts, their basicity with respect to an OH proton donor should be similar to that of a saturated ether or a secondary amine. This yields a higher activation energy for the breakdown of the ester intermediate, which is coupled with the extent of protonation of its ether oxygen. b) The possibility of resonance stabilization of the acid product of the urea substrate forces the breakdown of its intermediate. The similar statement may be valid for the leaving group in the case of phenoles or anilines.

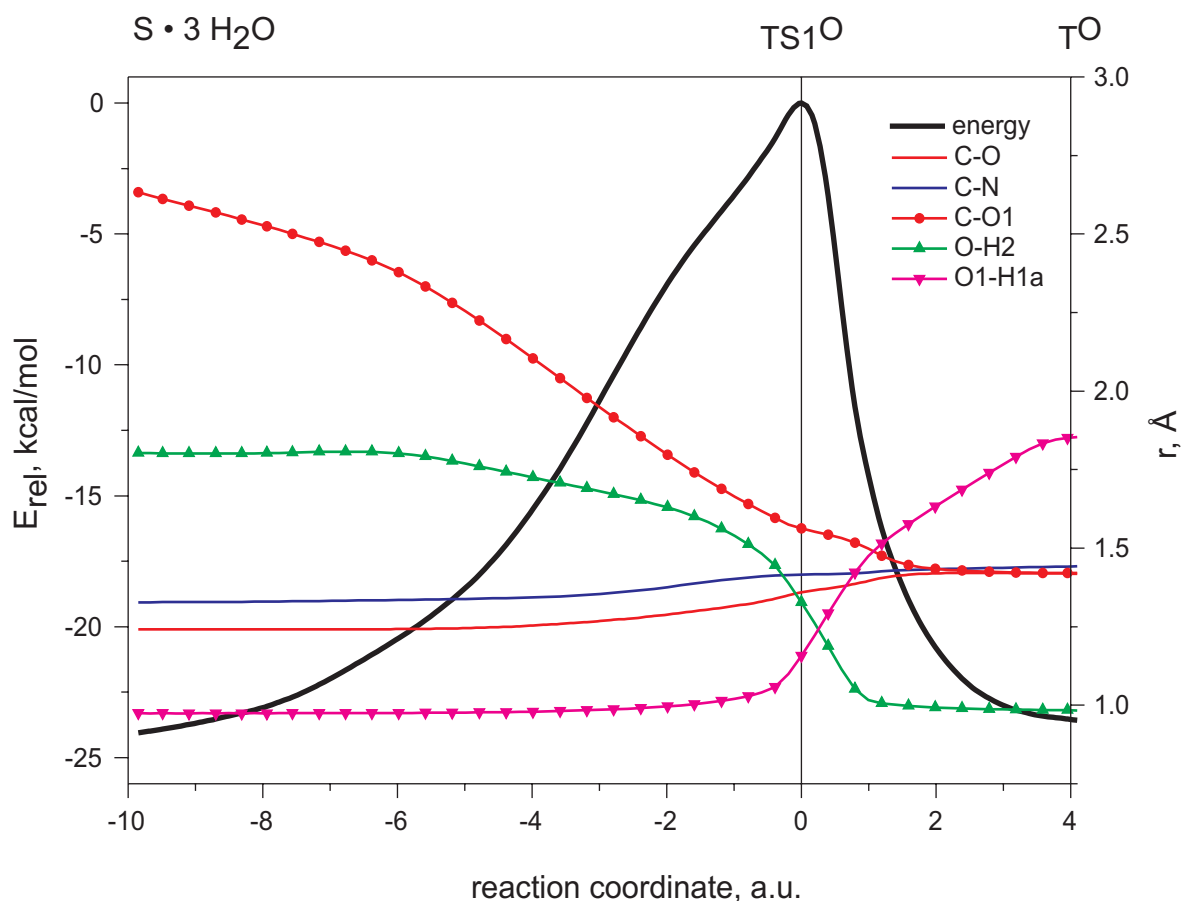


Figure 8 Changes of selected bond lengths and the total energy along the intrinsic reaction coordinate for the water-assisted addition of a water molecule onto formamide (HF/3-21G)

Table 1 Relative energies and enthalpies of stationary states of neutral hydrolysis [a].

	Methyl formate		Formamide		Urea	
	+ 3 H ₂ O	+ H ₂ O	+ 3 H ₂ O	+ H ₂ O	+ 3 H ₂ O	+ H ₂ O
ΔE_{gas}						
TS1 ⁰	-1.20	38.00	-2.64	36.14	6.36	39.78
T ⁰	-25.79	0.09	-26.93	1.55	-18.35	10.28
TS2 ⁰	-4.77	35.95	-9.07	33.01	-3.37	41.96
TS ^X	3.65	38.43	0.58	37.43	6.18	39.88
P [b]	1.32	1.32	-3.52	-3.52	-6.17	-6.17
ΔE_{aq} [c]						
TS1 ⁰	10.49	41.27	12.36	39.72	22.51	42.57
T ⁰	-13.64	3.63	-11.97	7.78	-2.46	17.64
TS2 ⁰	7.06	39.45	3.00	23.76	10.58	48.14
TS ^X	14.49	42.09	13.92	40.31	19.31	43.86
P [b]	1.53	1.53	0.42	0.42	-3.29	-3.29
ΔH_{gas}						
TS1 ⁰	1.17	36.75	0.16	35.22	7.84	38.50
T ⁰	-18.95	2.61	-19.43	4.69	-11.75	12.47
TS2 ⁰	2.82	34.21	-6.13	35.61	-1.32	40.68
TS ^X	5.16	37.02	3.20	36.60	7.99	39.10
P [b]	1.83	1.83	-2.75	-2.75	-5.76	-5.76
ΔH_{aq} [c]						
TS1 ⁰	12.87	40.01	15.16	38.81	23.99	41.30
T ⁰	-6.80	6.14	-4.47	10.92	4.14	19.83
TS2 ⁰	9.01	37.70	5.95	38.82	12.90	46.86
TS ^X	15.99	40.69	16.54	39.48	21.11	43.08
P [b]	2.04	2.04	1.19	1.19	-2.89	-2.89
ΔG_{aq} [c]						
TS1 ⁰	45.66	51.33	48.30	50.71	56.98	51.92
T ⁰	23.76	17.18	27.21	22.73	34.47	30.28
TS2 ⁰	41.03	49.67	39.05	51.04	44.60	57.60
TS ^X	48.05	51.84	49.78	51.50	52.76	53.89
P [b]	18.88	18.88	19.80	19.80	-3.46	-3.46

[a] Values in kcal/mol, related to the sum of energies or enthalpies of the isolated reacting molecules $S + n \text{H}_2\text{O}$, $n = 3$ or 1 .

[b] Products are given by $\text{RXH} + \text{R1COOH} + (n-1) \text{H}_2\text{O}$, $n = 3$ or 1 .

[c] Relative energy or enthalpy with inclusion of solvent effects via SCI-PCM.

Transition states TS^X

The structures of these states show selected properties of both transition states TS1⁰ and TS2⁰. The bond C-O1 is formed, and the bond C-X becomes broken. Again the transition state is determined by the transfer of two protons (H1b and H3b, see Fig. 10).

In order to discuss the main features of these states with respect to a more or less concerted reaction mechanism, we

again monitored changes of several internal coordinates on intrinsic reaction coordinates (see Fig. 11). Like already shown for the first step of an addition-elimination reaction, the concerted reaction also begins with the approach of the nucleophile onto the carbonyl carbon, along with lengthening of the C-X- and C-O bonds. These processes are coupled with breakdown of delocalization of lone pair electrons from substituents at the carbonyl group into the reaction centre. This change of electronic structure also yields an increasing ac-

Table 2 Structural parameters of stationary points of neutral hydrolyses [a].

	TS1 ^o			T ^o		
	E	A	U	E	A	U
Distances in Å						
C-O1	1.544	1.600	1.594	1.393	1.410	1.410
C-O	1.321	1.313	1.339	1.410	1.398	1.416
C-X	1.401	1.449	1.433	1.396	1.458	1.462
O1-H1a	1.206	1.184	1.175	1.967	1.924	1.897
O2-H1a	1.251	1.272	1.288	0.981	0.982	0.983
O2-H2a	1.112	1.149	1.162	1.847	1.862	1.910
O-H2a	1.365	1.311	1.300	0.988	0.986	0.984
O1-H1b	1.009	1.006	1.003	0.994	0.996	0.994
O3-H1b	1.739	1.742	1.765	1.826	1.811	1.800
O3-H3a	0.987	0.975	0.988	0.979	0.972	0.972
O-H3a	1.956	2.437	1.910	2.086	2.631	2.630
O3-H3b	0.972	0.983	0.972	0.972	0.986	0.988
X-H3b	2.542	2.049	2.595	2.449	1.992	1.964
Bond orders						
C-O1	0.722	0.661	0.695	0.962	0.935	0.926
C-O	1.174	1.200	1.136	0.922	0.952	0.924
C-X	0.902	1.000	1.034	0.911	0.980	0.974
	TS2 ^o			TS ^x		
	E	A	U	E	A	U
Distances in Å						
C-O1	1.315	1.348	1.355	1.547	1.600	1.740
C-O	1.344	1.405	1.412	1.238	1.268	1.245
C-X	1.700	1.546	1.548	1.652	1.532	1.563
O1-H1a	1.843	1.806	1.825	1.004	0.997	0.989
O2-H1a	0.986	0.990	0.989	1.719	1.780	1.827
O2-H2a	1.795	1.823	1.841	0.992	0.997	0.991
O-H2a	0.995	0.988	0.988	1.783	1.743	1.763
O1-H1b	1.276	1.268	1.219	1.244	1.294	1.214
O3-H1b	1.172	1.186	1.224	1.190	1.166	1.222
O3-H3a	0.971	0.972	0.971	0.971	0.975	0.970
O-H3a	4.626	3.266	3.426	4.679	2.806	4.686
O3-H3b	1.213	1.297	1.305	1.142	1.162	1.289
X-H3b	1.222	1.232	1.222	1.303	1.381	1.231
Bond orders						
C-O1	1.173	1.096	1.072	0.703	0.656	0.509
C-O	1.085	0.934	0.928	1.527	1.387	1.492
C-X	0.527	0.833	0.820	0.577	0.843	0.791

[a] E: methyl formate, A: formamide, U: urea. For atom numbers see Fig. 2.

cessibility of the atom X for hydrogen bonding (see distance X-H3b). The net energy change is positive. All these processes are more or less concerted for all models studied. So it can not be decided, if either the H-bond X-W3 activates the

substrate for nucleophilic attack or if the attack of the nucleophile forces the protonation of X.

When the state TS^x is reached, the protons H1b and H3b are turning over. Again the deprotonation of the nucleophile occurs later on the reaction coordinate than the protonation

of the substrate. After transfer of the protons, the C-X bond lengthens further. The surrounding of C shows rehybridization towards sp^2 , which is coupled with the new formation of a delocalized p-electron system of the acid product. The remaining reaction coordinate in the studied systems is determined by formation of new hydrogen bonds between the products and the water molecules. They are without meaning for the character of the reaction, but make the complete following of intrinsic reaction coordinates complicated.

Looking at the position of proton transfer onto X on the reaction coordinates for the nitrogen containing substrates (see Table 2), relations to the localization of electron pairs at the acceptor atom in the reactant state can be made. The protonation of the leaving group is more complete for the urea substrate and less complete for formamide. The length of the forming bond between C and O1 again mirrors the order of resonance at the carbonyl group of the substrate. It is longer for urea. The calculated bond orders also show this tendency.

Energetics of the reactions

Fig. 7 shows the free energy changes calculated for the reaction of methyl formate, formamide, and urea with three water molecules with inclusion of electrostatic solvation effects of the bulk solvent. The complete set of results and additional data for the reduced models (without W2 and W3, see Fig. 3) are presented in Table 1. The reactant state is defined as the sum of the four reacting molecules (substrate and three water molecules) in infinite separation. We define the product site by the primary neutral products (formic acid / carbamic acid + methanol / ammonia + two water molecules). In aqueous solution they can become further protonated / deprotonated, thus yielding other overall reaction energies than presented in the scheme.

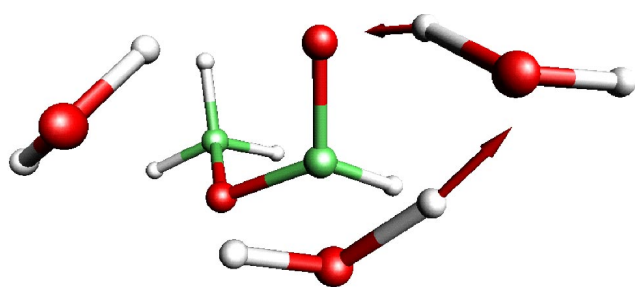


Figure 9 Components of the eigenvector with negative eigenvalue of the hessian matrix of $TS1^0$ of methyl formate (uncorrected amount of the wavenumber of the imaginary vibration: methyl formate: 1282.5 cm^{-1} , formamide: 1349.7 cm^{-1} , urea: 1334.1 cm^{-1} , Becke3LYP/6-31G*)

Addition-elimination mechanism

The profiles for the addition-elimination mechanism show the same general characteristics for all three substrates. After passing the transition state $TS1^0$ a local minimum corresponding to T^0 is reached. This intermediate decomposes via $TS2^0$ into primary products. The not hydrated intermediates T^0 show a decreasing stability in the order ester > amide > urea (see Table 1) in relation to the isolated reactants. The calculated activation parameters for the water-assisted addition step follow this ordering. That means, that the probability for formation of an addition product decreases in the order ester > amide > urea, and that the source of this ordering is an intrinsic feature of the substrates and the intermediates. In a preceding section it was mentioned, that this feature can be accessed as resonance stabilization. Enthalpy profiles indicate the same behaviour. It is modified by inclusion of unspecific solvent effects and entropy effects only in a quantitative manner. The activation parameters for the elimination of the leaving group from T^0 show that the tendency of decomposition of the intermediate into products decreases in the ordering urea > amide > ester, which can be explained by the basicity of the leaving group in the intermediate state and by resonance stabilization of the reaction products.

An estimation of the character of the rate limiting step of this complex reaction can only be given after the discussion of the reactant state. By defining it as four molecules in infinite separation, the free activation energy of the addition step is dominated by its entropic term ($-T \Delta S$ about 33 kcal/mol , see difference between ΔG_{aq} and ΔH_{aq} in Table 1) because of the necessary aggregation of the reacting species. It also includes the free energy needed for partial desolvation of them, when a solvent model is used to estimate unspecific effect of the bulk solvent. These effects are absent for the free activation energy of the elimination step in the described models ($-T \Delta S$ about 1.5 kcal/mol). From this point of view, the rate limiting step in these models is clearly the addition step, but this finding bases mainly on its activation entropy. However,

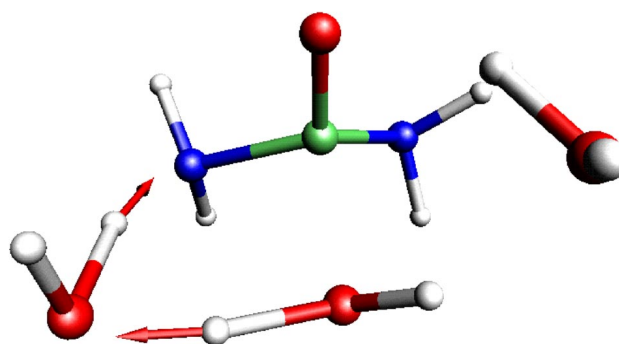


Figure 10 Components of the eigenvector with negative eigenvalue of the hessian matrix of TS^X of urea (uncorrected amount of the wavenumber of the imaginary vibration: methyl formate: 1264.6 cm^{-1} , formamide: 1258.3 cm^{-1} , urea: 1390.0 cm^{-1} , Becke3LYP/6-31G*)

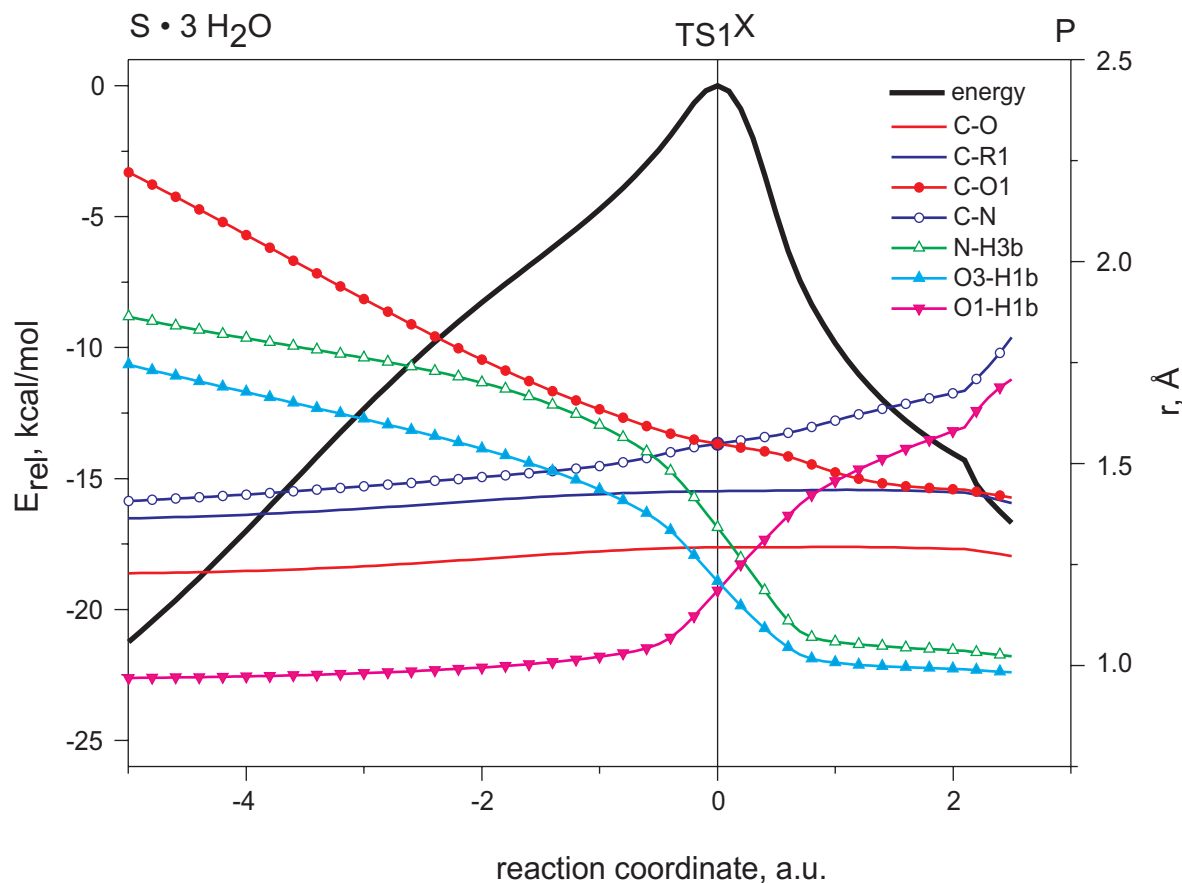


Figure 11 Changes of selected bond lengths and the total energy along the intrinsic reaction coordinate for the water-assisted concerted reaction of a water molecule with urea (HF/3-21G)

differences in the free activation energy of the addition of a water molecule to the three substrates are caused by intrinsic substrate properties, because the activation entropy is almost the same in these cases (see Table 1).

Concerted mechanism

The free energy profiles for the concerted one-step mechanism (see Fig. 7) show, that urea is still less reactive than the other two substrates. Besides this result, the comparison with the two-step mechanism for one substrate provides detailed insight into substrate behaviour. The energy profiles are comparable under the conditions noted in the introduction. We find that the difference between free activation energies of the rate limiting steps of the two alternative mechanisms decreases in the order ester > amide > urea. The entropy contributions to the important steps of both mechanisms are the same within 1 kcal/mol, that's why one can state reactivity differences because of intrinsic substrate properties again.

The data for the gas phase reaction (see Table 1) show, that the two-step mechanism should be the intrinsically preferred way for the reaction of methyl formate and formamide. Urea seems to prefer the one-step mechanism over the common addition-elimination pathway. After inclusion of effects from the bulk solvent this behavior is retained. This sentence can only be derived by studying complex systems. Models without additional water molecules do not provide such an interpretation. Here one cannot derive any conclusions about different substrate reactivity or a preferred reaction mechanism, because the calculated activation energies are near the same for all cases (see Table 1)! The reasons for this observation are clearly the highly strained proton transfer chains, which yield unrealistic activation energies.

From these results, the following conclusions can be derived: a) The rate of the neutral hydrolysis is proved to decrease in the order ester > amide > urea, when we restrict ourselves to the studied two mechanisms. This result is in qualitative agreement with experimental experience from extrapolations of pH-profiles of acid or base catalyzed hy-

drolyses of esters, amides and ureas with a similar substitution pattern. However, there exist no direct measurements of uncatalyzed hydrolyses of these compounds in neutral aqueous solution. So we cannot make a quantitative comparison with experiment. b) The relative stability of non-hydrated intermediates T^0 decreases in the same order as the resonance at the carbonyl group of the substrates increases [27]. The activation barrier for their formation follows this tendency. A relationship between the resonance stabilization of a substrate and its affinity against a neutral nucleophile can be derived. The electrophilicity of the carbonyl carbon expressed by its partial charge is proved to yield no reliable estimation of the reactivity of the substrates studied. Substrates with high electron delocalization like ureas are more inert both for the two-step and the concerted one-step mechanism. c) The studied ester clearly prefers the common addition-elimination mechanism, which involves a tetrahedral intermediate. Looking at formamide, the same result is obtained, but a concerted mechanism becomes more probable. Urea could hydrolyse probably via a concerted one-step reaction without formation of an intermediate. Here relations to basicities of the substrates at their alternatively proton accepting groups and structural effects of protonation [16] can be derived. An increasing basicity at X with respect to the basicity of the carbonyl oxygen yields a rising probability for the concerted reaction.

Summary

The presented results had shown, that models with explicit consideration of solvent molecules acting as acid-base catalysts are able to yield energy profiles for the studied reactions, which are in agreement with experimental experience. They can be used to derive conclusions about the general reaction pathway as well as about preferred reaction pathways. The combination with studies of properties of isolated substrates, reaction intermediates and products is helpful and yields hypotheses about sources of observed substrate reactivities and substrate activation by utilization of common chemical rules.

The used modelling of solvent effects via an electrostatic continuum yields mainly more realistic energy profiles. This approach is useful in our case, because no ionic species are present.

Nevertheless, these models are still restricted regarding to the number of protons transferred simultaneously, to the position and orientation of catalytic water molecules, and to the defined search for wanted stationary points. They can serve as example for quantum mechanical experiments in order to answer specific questions related to the behaviour of the models, but they are still arbitrary with regard to all details of such reactions in solution. Therefore, the structure and dynamics of the solvent shell in the vicinity of the substrate have to be considered.

Acknowledgement This work was granted by the Deutsche Forschungsgemeinschaft, Innovationskolleg "Biomolecular recognition elements for biochemical analytics", DFG-Gz. INK 16/A1-1.

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