The Alcoholysis Reaction of Isocyanates Giving Urethanes: Evidence for a Multimolecular Mechanism

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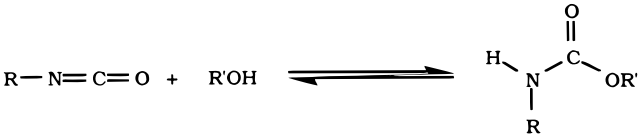
A kinetic and mechanistic investigation of the catalyzed alcoholysis of isocyanates was undertaken. Both experimental and theoretical results showed that the alcoholysis should be understood by a multimolecular intervention of the alcohols. The alcoholysis of isocyanate was examined experimentally for 2-propanol and cyclohexanol in low and high concentrations. It is suggested that either two or three molecules of the alcohol are implicated from the kinetic study, while the reaction with trimers becomes dominant at high alcohol concentrations. In accordance with these results, theoretical study suggests an active participation of at least three alcohol molecules in a reacting supersystem, giving rise to a genuine effect. The detailed reaction mechanism for the alcoholysis reaction by methanol and methanol clusters ($HN{=}C{=}O + n(CH_3OH)$, $n = 1-3$) was modeled by ab initio methods, both in the gas phase and in solution. The nucleophilic addition occurs in a concerted way across the N=C bond of the isocyanate rather than across the C=O, similar to the isocyanate hydrolysis. The bulk solvent effect, which is treated by a polarizable continuum model (PCM), does not affect the preference of the alcohol to attack across the N=C bond as pointed out by the gas-phase values.

Introduction

The reaction of alcohols with isocyanates giving carbamates (urethanes, Scheme 1) and its application to polyfunctional alcohols and isocyanates is the basis of the polyurethane industry.[1] The investigation of the mechanism and catalysis of these reactions is important for the control of industrial processes, on one hand, and for the development of a fundamental understanding of chemical kinetics and homogeneous catalysis in liquid phase, on the other hand.

Early experiments by Baker and Gaunt,[2] using approximately equimolar concentrations of alcohols and isocyanates, led them to the conclusion that the solvolysis reaction was first order in each reactant. However, under such conditions, as the reaction proceeds, there is a substantial decrease in alcohol concentration that gave an ostensible second-order rate constant. These early studies were carried out in aprotic solvents that promote self-association of the alcohols, catalysts, and reaction products via intermolecular hydrogen bonding. As a consequence, the availability of the reacting hydroxyl groups is reduced. The alcoholysis reaction has been shown to be greatly influenced by the medium in which it is conducted. Ephraim and co-workers[3] found that there is a deviation from the second-order reaction toward higher orders with increasing hydrogen-bonding capacity of the solvent. Lillford and Satchell[4] proposed that the reactive species, for the addition reaction, are actually the alcohol polymers. However, the factors controlling polymerization are not fully understood. This group[5] also studied the self-association of some aliphatic alcohols in different nonhydroxylic solvents such as ether,[5] isooctane, and carbon tetrachloride.[6] In ether, at low concentrations the principal polymer was the dimer. In isooctane, slow attack by both alcohol monomers and trimers has been identified, the latter being the more reactive. The behavior of the alcohol in the presence of covalent metal halides has also been studied.[7] While most alcohols had similar reactivities, bulkier alcohols appeared to be less reactive than the less hindered ones. Other authors[8,9] also appeared to accept the intervention of alcohol oligomers.

Scheme 1



A few theoretical studies[10,11] using semiempirical methods were also reported, in which only the addition of one

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and two methanol molecules across the isocyanide C═N bond has been considered. Nevertheless, as in the case of the hydrolysis of isocyanates,[12] the mechanism of alcoholysis is not completely elucidated yet. Overall, similar points of discussion concerning the detailed mechanism still need to be clarified: (i) If the alcohol oligomers are actively involved in the reaction process, then what is the number of alcohol molecules playing a key factor? (ii) Does the addition of alcohol occur in a concerted way across the N═C bond of isocyanate, or in a two-step process involving an initial attack across the C═O bond of the isocyanate? (iii) Does the solvent play an important role?

In the present work, an attempt is made to provide some answers to these questions by carrying out both kinetic and theoretical investigations. The Experimental Aspects concern the study of alcohol addition reactions in an aprotic solvent. A wide concentration range was considered, up to pure alcohol solutions. From a theoretical point of view, calculations were considered using high level ab initio methods. Besides an explicit treatment of the attack of multiple alcohol molecules on isocyanate, the solvent is also concerned as a dielectric continuum, simulating the influence of the bulk. For the sake of comparison with the hydrolysis of isocyanates, which has been reported in the preceding paper,[12] a similar approach has been employed.

Results and Discussion

A. Experimental Aspects. Let us first present results of a general kinetic study on the alcoholysis of isocyanate using 2-propanol and cyclohexanol. Since the half-life of this reaction at low alcohol concentration is very short, the reaction was rather difficult to monitor. Evaluation of the rate constants under such conditions has been done employing a technique that consists of adding a high concentration of the isocyanate to the low-concentration alcohol solution and analyzing the first straight lines portion of the UV plots. The reactions involving high concentrations of the alcohol were known to encompass a certain absorbance range on addition of a known low concentration of isocyanate. By relating the absorbance with the concentration of isocyanate added, a scale could be set up that was correlated to the slope obtained when a high concentration of isocyanate was added to solutions of low alcohol concentration. Good correlations between observed rates and calculated rates were obtained at higher alcohol concentrations, and so values for the low concentration alcohol solutions are expected to be accurate. The results obtained for the two alcohols, cyclohexanol and 2-propanol, are detailed in Tables 1 and 2, respectively. Previously, it has been found that alcoholysis of isocyanates generally shows a kinetic order greater than 1, at least at relatively high alcohol concentration, in almost all the solvents studied.[3] Plots of the above results indicate that the observed rate increases at a greater rate than unit dependence on the total alcohol concentration present. It appears from the plot of k_{obs} against [alcohol], shown in Figure 1, that at least three alcohol molecules are reacting since the graphs of the different alcohols show minimum third-order dependence on the alcohol concentration. The extent of the involvement of higher than the dimer species may be verified from the plots of k_{obs}/[alcohol] against [alcohol], Figure 2, and k_{obs}/[alcohol]$_2$ against [alcohol], Figure 3. An upward curvature is observed in Figure 2, which indicates at least a second-order rate dependence on the [alcohol]. Since a positive increase is observed in the plot of k_{obs}/[alcohol]^2 against [alcohol], it can be seen that the trimeric species may also be reactive. The extent to which the different polymers are present

Table 1. Observed Rate Constants for the Reaction of Cyclohexanol with Phenyl Isocyanate at 25 °C

[cyclohexanol] (M)	k_{obs} ($\times 10^4$) (s^{-1})	$k_{obs}/^c$[HexOH] ($\times 10^4$), (s^{-1} M^{-1})	$k_{obs}/^c$[HexOH]$_2$ ($\times 10^4$), (s^{-1} M^{-2})
0.50	0.191	0.382	0.765
0.60	0.280	0.467	0.777
0.80	0.500	0.625	0.782
1.00	0.793	0.793	0.793
1.25	1.277	1.022	0.817
2.00	3.355	1.678	0.839
2.50	5.434	2.136	0.869
5.00	23.562	4.712	0.942

Table 2. Observed Rate Constants for the Reaction of 2-Propanol with Phenyl Isocyanate in the Presence and Absence of Catalysts at 25 °C

[2-propanol] (M)	k_{obs} ($\times 10^4$) (s^{-1}) (uncatalyzed reaction)	k_{obs}/[Pr^{i}OH] ($\times 10^4$) (s^{-1} M^{-1})	k_{obs}/[Pr^{i}OH]^2 ($\times 10^4$) (s^{-1} M^{-2})
0.40	0.181	0.4525	1.131
0.50	0.285	0.570	1.140
0.60	0.414	0.690	1.150
0.80	0.760	0.950	1.187
1.00	1.202	1.202	1.202
1.25	1.920	1.536	1.229
2.00	5.170	2.585	1.293
2.50	8.370	3.348	1.329
5.00	37.750	7.550	1.512
6.00	56.840	9.470	1.583
7.00	79.920	11.420	1.629
8.00	108.530	13.566	1.711
9.00	144.460	16.050	1.794
10.00	189.760	18.976	1.906

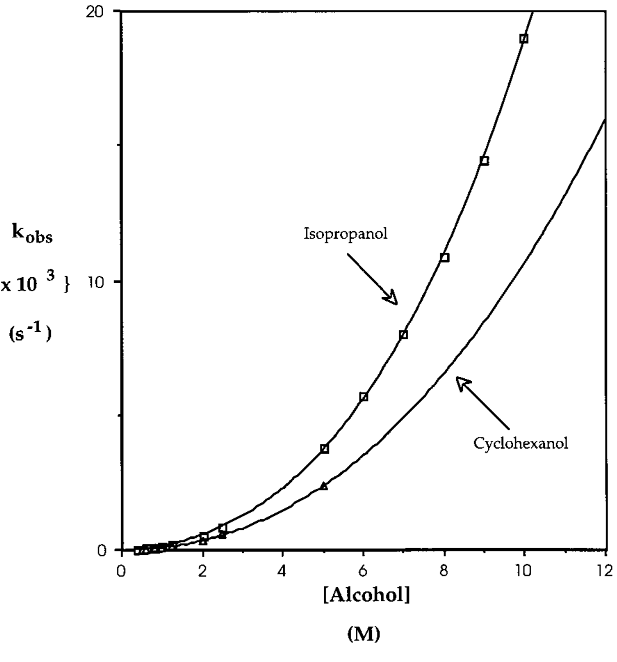

Figure 1. Plot of observed rate against alcohol concentration at 25 °C for (i) 2-propanol and (ii) cyclohexanol with phenyl isocyanate.

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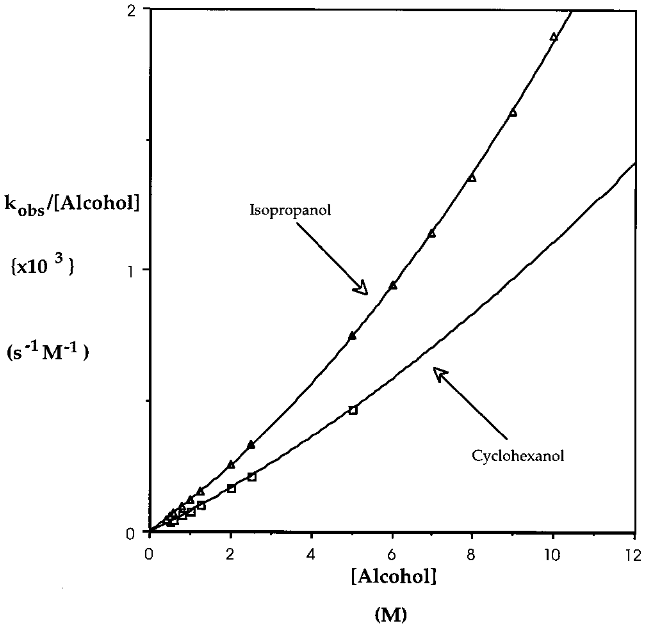

Figure 2. Plot of the k_{obs}/[alcohol] against alcohol concentration for the reactions of (i) 2-propanol and (ii) cyclohexanol with phenyl isocyanate at 25 °C.

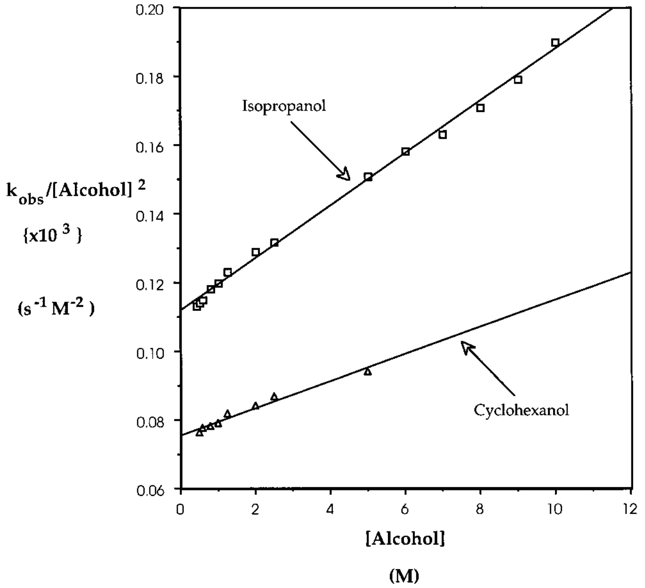

Figure 3. Plot of the k_{obs}/[alcohol]^2 against alcohol concentration for the reactions of (i) 2-propanol and (ii) cyclohexanol with phenyl isocyanate at 25 °C.

during the reaction can be deduced from the intercepts of Figures 2 and 3 for the alcohols studied. The intercepts of the plots for k_{obs}/[alcohol] against [alcohol] indicate whether the monomer is a reactive species. Generally, the reactivity of alcohol polymers is greater than that of monomers toward isocyanates. Hence, with increasing alcohol concentration, the relative concentration of the former is augmented, and consequently the overall reaction process is enhanced. In both of the above cases, the graphs pass very close to the origin, indicating that little reactive monomer is present and what is present does not contribute substantially to the observed rate. The upward slope observed for the graph of k_{obs}/[alcohol]^2 against [alcohol] indicates that trimers or higher polymers are involved in the reaction of these alcohols with isocyanates. It would appear more likely that these secondary alcohols, by virtue of their size, react as trimers rather higher polymers. The intercept in the case of these plots may be taken as an indication of the contribution of the dimers to the overall rate. The dimers of bulky alcohols have been shown to be less reactive than their less hindered counterparts.[5] In the present investigation, a slower rate is observed for the cyclohexanol compared with the 2-propanol when the reactions are carried out under the same conditions. This suggests that the polymers of the bulky cyclohexanol are less reactive toward isocyanates than are the less hindered polymers of the 2-propanol. This result may be classically interpreted in terms of steric factors. The bulky cyclohexanol polymers are not as effective as their less hindered counterparts. Also due to the bulkiness of this alcohol, larger polymer formation would not be very likely; thus, its reactivity will be curtailed as it would appear that the larger the polymer the more reactive it is. The relative retardation in the reaction rate of cyclohexanol compared with the 2-propanol rate toward the isocyanate may be due, in part, to the fact that it is more likely that tetramers of the 2-propanol exist rather than those of the cyclohexanol by virtue of their size.

Kinetic and mechanistic investigations of catalyzed reactions show that the reactivity of an alcohol toward isocyanates is independent of the chain length and the number of polyol functional groups in the alcoholic molecule. Investigations also indicate that primary alcohol groups are more reactive than secondary alcohols.[13] Observations made in this work would appear to be in agreement with this when compared with previous work done on some primary alcohols.

In conclusion, it is confirmed that in the alcoholysis reaction of isocyanate either two or three molecules of the alcohol are implicated from the kinetic study, while the reaction with trimers becomes dominant at high alcohol concentrations.

B. Theoretical Aspects. In this section, a theoretical study on the simplest alcohol addition reactions $HN{=}C{=}O + n(CH_3OH)$, $n = 1-3$, has been undertaken. The results obtained by ab initio MO calculations were carried out using the Gaussian 94 set of programs.[14] The initial exploration of the energy surface as well as a vibrational analysis of stationary points was performed with the dp-polarized 6-31G(d,p) basis set in the Hartree–Fock framework. Geometrical parameters of the relevant equilibrium structures and transition structures were subsequently refined using second-order perturbation theory. Needless to say, the effort has been put up to the limit of our computational resources. Single-point calculations at the MP2/6-311++G(d,p) (++ indicates a set of sp-diffuse functions on C, N, and O and s-diffuse functions on H) level were performed on the MP2/6-31G(d,p) geometries. Inclusion of electrostatic solvent effects was examined by means of the polarizable continuum

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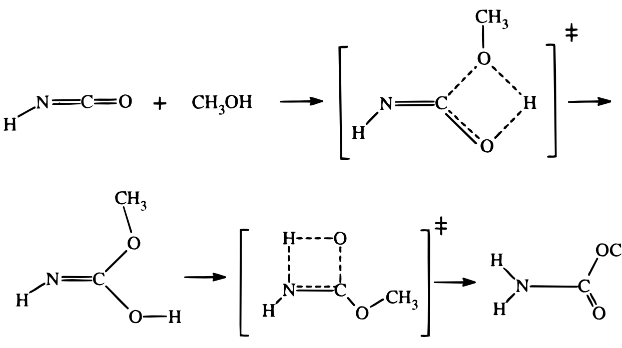
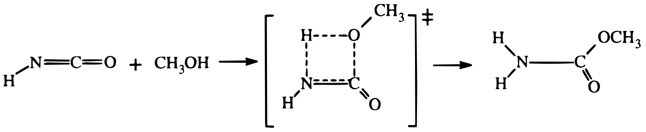
Scheme 2



Scheme 3



method (PCM).[15] The solvent is thereby presented as a continuum characterized by its dielectric constant ϵ (ϵ = 32.6 for methanol), and the solute is embedded in a cavity, made by a superposition of spheres to probe the molecular shape of the solute. As summarized in the Experimental Aspects, the number of alcohol molecules effectively involved in the alcoholysis, as derived from measurements of the apparent kinetic orders with respect to alcohol, amounts to either two or three. This result will now be scrutinized by theoretical results that contain calculated total and relative energies for the alcoholysis of isocyanate including progressively the actively participating methanol molecules ($HN{=}C{=}O + n(CH_3OH)$) ($H_2NCOOCH_3 + (n - 1)\ CH_3OH$, $n = 1-3$). Moreover, theoretical findings in this section concern two possibilities of alcohol attack, either across the C=O or the N=C bond of isocyanic acid. The C=O addition has not been considered in earlier MO studies.[10-11] Throughout this paper, calculated bond lengths are given in angstroms, calculated bond angles in degrees, total energies in hartrees, and calculated zero point energies and relative energies, unless otherwise stated, in kilojoules per mol.

Reaction between HN=C=O and CH_3OH. As mentioned above, the alcoholysis of isocyanate could conceivably occur in two possible ways: (i) either in a stepwise fashion, with an addition of the alcohol across the C=O bond to yield an enol intermediate, followed by a 1,3-H-shift giving the urethane product (Scheme 2), or in a concerted fashion, in which the alcohol addition is carried out across the N=C bond and immediately results in the product (Scheme 3).

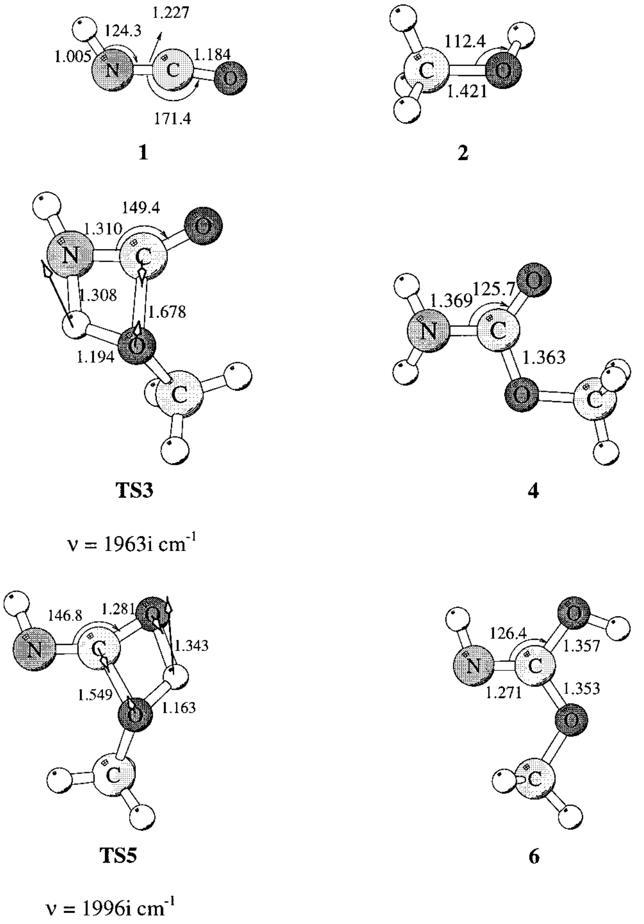


Figure 4. Optimized structures of the stationary points along the alcoholysis path of isocyanic acid with one CH_3OH molecule across both C=O and N=C bonds.

Table 3. Calculated Total (Hartree) and Zero-Point Vibrational (ZPE, kJ·mol^{-1}) Energies for the Alcoholysis of Isocyanic Acid (HN=C=O)

	MP2[a] 6-31G**	MP2[a] 6-311++G**	ZPE[b]
HN=C=O (**1**)	−168.230 73	−168.311 61	54
CH_3OH (**2**)	−115.382 01	−115.445 17	130
HN=C=O + CH_3OH	−283.612 74	−283.756 78	184
TS N=C (**TS3**)	−283.567 47	−283.706 52	187
NH_2COOCH_3 (**4**)	−283.653 83	−283.792 04	202
TS C=O (**TS5**)	−283.552 87	−283.692 82	189
$HN{=}COHOCH_3$ (**6**)	−283.621 84	−283.761 73	203
HN=C=O + 2CH_3OH	−398.994 75	−399.200 85	314
HN=C=O·2CH_3OH (N=C) (**7**)	−399.018 37	−399.221 16	325
TS N=C (**TS8**)	−398.995 90	−399.194 66	325
NH_2COOCH_3·CH_3OH (**9**)	−399.052 47	−399.249 39	338
HN=C=O·2CH_3OH (C=O) (**10**)	−399.016 19	−399.218 61	328
TS C=O (**TS11**)	−398.985 39	−399.182 46	326
$HN{=}COHOCH_3$·CH_3OH (**12**)	−399.024 00	−399.221 97	339
HN=C=O + 3CH_3OH	−514.37676		444
HN=C=O·3CH_3OH (N=C) (**13**)	−514.41958		461
TS N=C (**TS14**)	−514.40243		461
NH_2COOCH_3·2CH_3OH (**15**)	−514.45416		520
HN=C=O·3CH_3OH (C=O) (**16**)	−514.41949		465
TS C=O (**TS17**)	−514.39587		465
$HN{=}COHOCH_3$·2CH_3OH (**18**)	−514.42801		522

[a] Based on MP2/6-31G(d,p) geometries given in Figures 4−6.
[b] Zero-point energies from HF/6-31G(d,p) and scaled by 0.9.

Figure 4 shows MP2-optimized geometries of the reactants, transition structures (TS), and reaction products for the neutral uncatalyzed addition of methanol across both C=O and N=C bonds of isocyanic acid. Corresponding total and relative energies are reported in Tables 3 and 4. The energies are given relative to a noninteracting system of HN=C=O with one free methanol molecule. Along the reaction path through **TS3**, a methanol molecule interacts nucleophilically along the N=C bond of isocyanate. Table 4 indicates a substantial energy barrier for formation of urethane **4**, formed via **TS3**, which lies 135 kJ·mol^{-1} above the energy of the separated reactants. This reaction is clearly preferred over the C=O addition, having a barrier of 173 kJ·mol^{-1}. The latter reaction occurs via **TS5** giving rise to an enol intermediate **6**, which after an intramolecular 1,3-H-shift

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[15] Miertus, S.; Scrocco, E.; Tomasi, J. *Chem. Phys.* **1981**, *55*, 117.

Table 4. Calculated Relative Energies (kJ·mol^{-1}) for the Alcoholysis of $HN{=}C{=}O$, All Corrected by Zero-Point Vibrational Energies (ZPE)

	MP2[a] 6-31G**	MP2[a] 6-311++G**
$HN{=}C{=}O + CH_3OH$	0	0
TS N=C (**TS3**)	122	135
NH_2COOCH_3 (**4**)	−90	−75
TS C=O (**TS5**)	162	173
$HN{=}COHOCH_3$ (**6**)	−5	6
$HN{=}C{=}O + 2CH_3OH$	0	0
$HN{=}C{=}O{\cdot}2CH_3OH$ (N=C) (**7**)	−51	−42
TS N=C (**TS8**)	8	27
$NH_2COOCH_3{\cdot}CH_3OH$ **9**	−128	−103
$HN{=}C{=}O{\cdot}2CH_3OH$ (C=O) (**10**)	−42	−33
TS C=O (**TS11**)	37	60
$HN{=}COHOCH_3{\cdot}CH_3OH$ (**12**)	−52	−30
$HN{=}C{=}O + 3CH_3OH$	0	
$HN{=}C{=}O{\cdot}3CH_3OH$ (N=C) (**13**)	−103	
TS N=C (**TS14**)	−50	
$NH_2COOCH_3{\cdot}2\ CH_3OH$ (**15**)	−127	
$HN{=}C{=}O{\cdot}3CH_3OH$ (C=O) (**16**)	−91	
TS C=O (**TS17**)	−29	
$HN{=}COHOCH_3{\cdot}2CH_3OH$ (**18**)	−57	

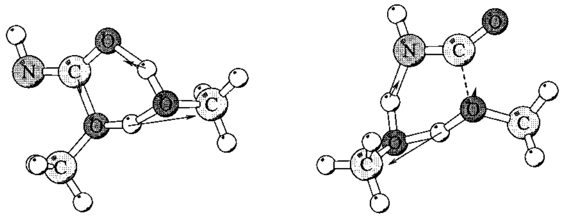
[a] Based on MP2/6-31G(d,p) geometries.

Table 5. Comparison between Energy Barriers (kJ·mol^{-1}) for Both Hydrolysis and Alcoholysis of $HN{=}C{=}O$, All Calculated at the MP2/6-311++G(d,p)//MP2/6-31G(d,p) + ZPE Level of Theory

	hydrolysis[a]	alcoholysis[b]
one reactant molecule		
TS N=C	167	135
TS C=O	212	173
two reactant molecules		
TS N=C	75	69
TS C=O	104	93
three reactant molecules		
TS N=C	41	53[c]
TS C=O	59	62[c]

[a] Values taken from ref 12. [b] Present work. [c] Due to computational costs, only with a 6-31G(d,p) basis set.

Chart 1



TS8 across **C=O** (1200 i cm^{-1}) **TS11** across **N=C** (1297 i cm^{-1})

finally yields to the same urethane product. The preference of attack on the N=C bond of isocyanate can be understood in terms of Fukui functions, as already discussed in previous work[12] on the addition of water to isocyanates.

In Table 5, a comparison is made to the hydrolysis of isocyanate, in particular concerning the energy barriers. In fact, the addition of alcohol can be seen as that of water perturbed by an alkyl substituent. It seems that the variation of substituent (ROH, with $R = CH_3$ instead of H for the hydrolysis) changes the energy barrier significantly. For the uncatalyzed C=O addition, the energy barrier is lowered by 39 kJ·mol^{-1} in going from water to methanol at the same level of theory (212 → 173 kJ·mol^{-1}). For the N=C addition, a reduction of 32 kJ·mol^{-1} is found when a methanol instead of a water molecule is included (167 → 135 kJ·mol^{-1}). As the CH_3 group is a strong electron donor, the oxygen atoms in the ring are more polarized than the corresponding ones without the electron-donating effect of a CH_3 group. This phenomenon increases the polarization of the bonds and results in improved hydrogen-bonding interaction energy. The final energetical balance will therefore be more favored in the alcoholysis case. However, the present calculations indicate that it is unlikely that any substantial fraction of the actual gas-phase alcoholysis of isocyanate passes through either **TS3** or **TS5** due their large energy barriers. Each transition structure presumably contains a certain amount of strain in its cyclic structure. This strain could be relieved by incorporation of additional alcohol molecule(s) into the cyclic hydrogen-bonded supermolecule.

Reaction between $H{-}N{=}C{=}O$ and Two Molecules of CH_3OH. Chains with two methanol molecules were modeled, and the calculated results are also shown in Tables 3 and 4. While for the hydrolysis reaction[12] only transition structures and product complexes could be located, the alcoholysis initially starts through a preassociation complex, thus organizing all atoms in a manner that easily sets in the transition state. All stationary points including preassociation complexes **7** and **10**, transition structures **TS8** and **TS11**, and products **9** and **12** for both C=O and N=C additions are shown in Figure 5. It is obvious that in the hydrogen-bond chains the second methanol molecule serves as a proton transporter being proton donor to the isocyanate and proton acceptor to the original methanol. As inclusion of an extra reactant molecule in a cyclic cluster reduces the energy barriers for both additions by more than 100 kJ·mol^{-1}, a clear catalytic effect can be credited. Results reported in Table 7 undoubtedly point out the preference for a N=C addition. The thermodynamic stability of the stable product **9** might give perhaps a clue for a reason for the concerted mechanism across the isocyanate N=C bond. Indeed, the urethane product **9** lies about 67 kJ·mol^{-1} lower in energy than the enol intermediate **12**. Nevertheless, it is certainly not a general trend. Hydrolysis and aminolysis of ketenes (>C=C=O) have been found to invariably lead to C=O addition, even though the primary enol adducts are the less stable isomers.[16−20] As shown in Table 5, the addition of alcohol to isocyanate, in comparison to water, exhibits energy barriers remarkably affected by change in substituents, as could already be seen in the uncatalyzed case. For **TS8** and **TS11**, respectively, the imaginary frequencies of 1297i and 1200i cm^{-1} were found for the reaction coordinate vibrational mode, whose atomic displacement vectors are shown below by the arrows in Chart 1. In both cases, the dominant motions are those of the endocyclic protons, which are transferred between the oxygen atoms and, respectively, the N and O center in isocyanate. It has also to be noted that the two CH_3 groups present in either **TS8** or **TS11** lie in a staggered position to each other in order to prevent steric hindrance.

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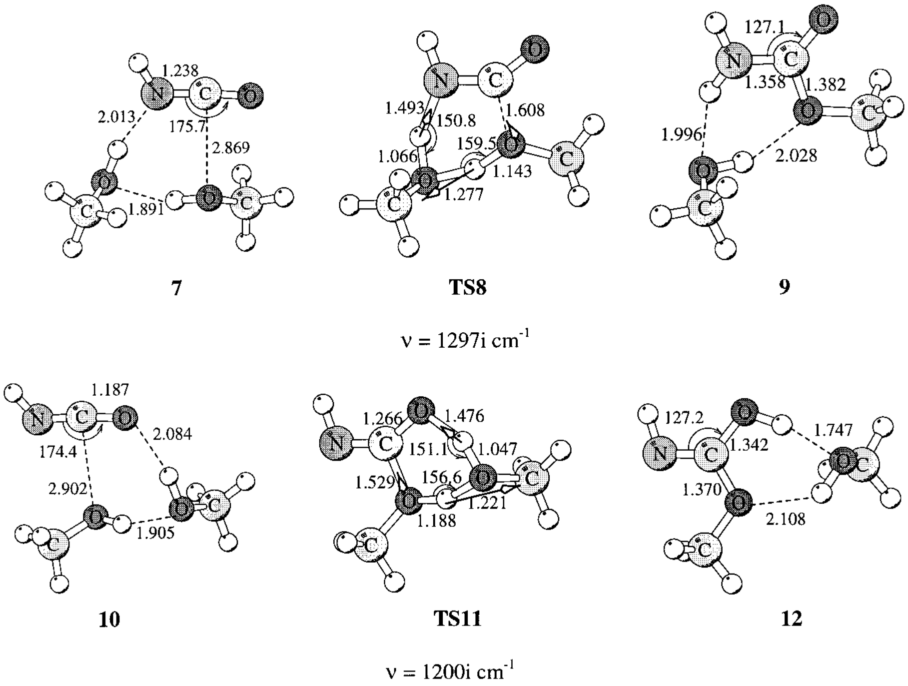


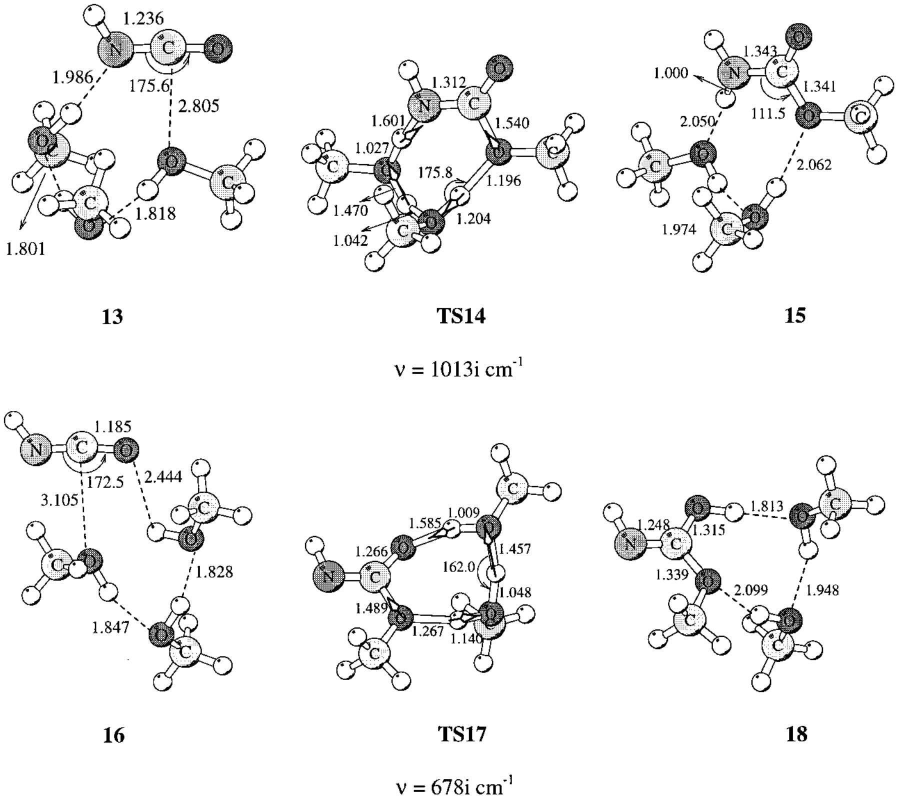
7 TS8 9

ν = 1297i cm^{-1}

10 TS11 12

ν = 1200i cm^{-1}

Figure 5. Optimized structures of the stationary points along the alcoholysis path of isocyanic acid with two CH_3OH molecules across both C═O and N═C bonds.



13 TS14 15

ν = 1013i cm^{-1}

16 TS17 18

ν = 678i cm^{-1}

Figure 6. Optimized structures of the stationary points along the alcoholysis path of isocyanic acid with three CH_3OH molecules across both C═O and N═C bonds.

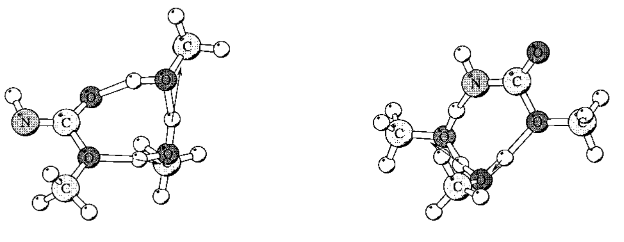
Reaction between HN═C═O and Three Molecules of CH_3OH. Here, our attention will be focused on the inclusion of three methanol molecules participating actively in the process. Figure 6 illustrates the structural incorporation of a third reactant molecule in a cyclic cluster performing the addition. Corresponding energetical parameters, given in Tables 3 and 4, emphasize the prominent role of the methanol trimer among the many possible oligomers that may be considered in alcohol solution. A cluster of three methanol molecules is expected to further enlarge the acid−base properties of the methanol molecule and gives rise to a more easily deformable species. As a matter of fact, the trimer moiety in **TS14** can be regarded as a zwitterion CH_3O^-·

Table 6. Total (Hartree) and Relative Energies (kJ·mol^{-1}) of the Considered Stationary Points in Solvent ($\epsilon = 78.3$, Water, and $\epsilon = 32.6$, Methanol), Using the PCM Solvent Method

	total energies[a]		relative energies	
	$\epsilon = 78.3$	$\epsilon = 32.6$	$\epsilon = 78.3$	$\epsilon = 32.6$
$HN{=}C{=}O$ (**1**)	−168.235 54	−168.235 30		
CH_3OH (**2**)	−115.391 47	−115.391 14		
$HN{=}C{=}O + CH_3OH$	−283.627 01	−283.626 44	0	0
TS $N{=}C$ (**TS3**)	−283.578 35	−283.577 81	131	131
NH_2COOCH_3 **4**	−283.670 02	−283.669 24	−95	−94
TS $C{=}O$ (**TS5**)	−283.569 83	−283.569 12	155	155
$HN{=}COHOCH_3$ (**6**)	−283.635 30	−283.634 81	−3	−3
$HN{=}C{=}O + 2CH_3OH$	−399.018 48	−399.017 58	0	0
$HN{=}C{=}O{\cdot}2CH_3OH$ ($N{=}C$) (**7**)	−399.039 06	−399.038 98	−43	−45
TS $N{=}C$ (**TS8**)	−399.015 25	−399.009 06	19	20
$NH_2COOCH_3{\cdot}CH_3OH$ (**9**)	−399.074 47	−399.043 64	−123	−123
$HN{=}C{=}O{\cdot}2CH_3OH$ ($C{=}O$) (**10**)	−399.036 85	−399.03659	−34	−36
TS $C{=}O$ (**TS11**)	−399.010 08	−399.073 51	34	34
$HN{=}C{-}OH{-}OCH_3{\cdot}CH_3OH$ (**12**)	−399.044 48	−399.014 31	−43	−43
$HN{=}C{=}O + 3CH_3OH$	−514.409 95	−514.408 72	0	0
$HN{=}C{=}O{\cdot}3CH_3OH$ ($N{=}C$) (**13**)	−514.445 58	−514.444 42	−77	−77
TS $N{=}C$ (**TS14**)	−514.430 90	−514.429 34	−38	−37
$NH_2COOCH_3{\cdot}2\ CH_3OH$ (**15**)	−514.480 51	−514.479 30	−109	−109
$HN{=}C{=}O{\cdot}2CH_3OH$ ($C{=}O$) (**16**)	−514.441 76	−514.440 76	−63	−63
TS $C{=}O$ (**TS17**)	−514.431 26	−514.429 30	−35	−33
$HN{=}C{-}OH{-}OCH_3{\cdot}2CH_3OH$ (**18**)	−514.455 56	−514.454 18	−42	−41

[a] Based on gas-phase MP2/6-31G(d,p) geometries.

Chart 2



TS17 across **C=O** (678i cm^{-1}) **TS14** across **N=C** (1012i cm^{-1})

$(CH_3OH)_2H^+$. Such a polarization is similar to that in a water trimer when the latter is attacking, for example, carbon dioxide[21] but probably at a much smaller energy cost. As stated above, the basicity of the central oxygen atom is increased with the hydrogen-bonded system, which explains the efficiency of the bifunctional catalytic (or solvent-assisted) alcoholysis. Another point of interest is the fact that addition of the alcohol cluster on isocyanate occurs in two distinct planes. As a consequence, possible geometric constraints occurring in the dimer when the reaction requires simultaneously a positively charged hydrogen atom and a nucleophilic oxygen atom are reduced. This gives rise to an energy barrier for the N=C addition of only 53 kJ·mol^{-1}. Consistent with previous results, addition across the C=O results in a somewhat larger energy barrier amounting to 62 kJ·mol^{-1}. Due to computational cost, calculations at a level higher than the MP2/6-31G(d,p) could not be performed on the trimer systems. Imaginary frequencies of 1012i and 678i cm^{-1} were found for the reaction coordinate vibrational modes of **TS14** and **TS17**, respectively. Atomic displacement vectors are shown below by the arrows in Chart 2. Again, in both cases, the dominant motions are associated with the endocyclic protons, which are transferred between both oxygen atoms and, respectively, the N and O center in isocyanate. It must be noted that in both transition structures **TS14** and **TS17** the hydrogen has not been fully transferred yet. Nevertheless, the proton transfer along the cluster occurs in one step without any interlying intermediates.

Electrostatic Solvent Effects. Results obtained when the "supermolecule" consisting of isocyanic acid and an alcohol cluster is put in a cavity embedded in a dielectric medium are shown in Tables 6 and 7. As for prototypes, PCM calculations are performed in both aqueous ($\epsilon = 78.3$) and methanol ($\epsilon = 32.6$) solution, which lead, after all, to similar results. On the whole, the role of the surroundings seems to be less decisive than the specific action of a catalytic cluster. In fact, the considered reactions have been shown not to be greatly influenced by the presence of a continuum that does not modify the conclusions emerging from the study carried out for the gas-phase species. That is, the addition across the N=C bond of isocyanate remains consistently favored over that across the C=O.

A few experimental estimates for the activation energies have been reported, but they disagreed with each other.[6,9] While an earlier kinetic study[6] of the reaction of phenyl isocyanate with a variety of alcohols in benzene medium derived large free energies of activation, namely ($G^{\ddagger} = 95$ kJ·mol^{-1}, a more recent investigation[9] using nitrophenyl isocyanate and pentanol in CCl_4 obtained a negative enthalpy of activation ($H^{\ddagger} = -28 \pm 5$ kJ·mol^{-1}. Obviously, there is here a problem regarding the reference system. In the trimeric methanol system, both **TS14** and **TS17** lie effectively below the separated reactant limit (cf. Table 6). A positive activation energy can also be derived when considering the preassociation complexes as the starting points (cf. Table 7). In this regard, the present theoretical estimates for activation energies are rather comparable with those of Satchell et al.[9] The earlier values[6] seem to be too large.

Conclusions

In the present paper, a combined kinetic and theoretical investigation of the solvent catalyzed alcoholysis of isocyanates has been undertaken. Both experimental

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Table 7. Activation Energies (kJ·mol^{-1}) for the Hydrolyses of HN=C=O across Both C=O and N=C Bonds, Including Different Numbers of Methanol Molecules, in the Gas Phase and in Solution

	gas phase		solution	
			$\epsilon = 78.3$	$\epsilon = 32.6$
	MP2[a] 6-31G**	MP2[a] 6-311++G**	PCM-MP2[a] 6-31G**	PCM-MP2[a] 6-31G**
HN=C=O + **1**CH_3OH				
across N=C	122	135	131	131
across C=O	162	173	155	155
HN=C=O + **2**CH_3OH				
across N=C	59	69	62	65
across C=O	79	93	68	70
HN=C=O + **3**CH_3OH				
across N=C	53		39	40
across C=O	62		28	30

[a] Based on MP2/6-31G(d-p) geometries.

and quantum chemical results show that the alcoholysis reaction should be understood by invoking a multimolecular intervention of the alcohols. In agreement with earlier suggestions, it is found that either two or three molecules of the alcohol are implicated in the mechanism, while the reaction with trimers becomes dominant at high alcohol concentrations. The theoretical study concurs with this, pointing toward an active participation of three alcohol molecules in a reacting supersystem. The detailed reaction mechanism for the alcoholysis by methanol and methanol clusters (HN=C=O + $n(CH_3OH)$) ($H_2NCOOCH_3 + (n - 1)\ CH_3OH$, $n = 1-3$) was modeled by ab initio methods, both in the gas phase and in solution. The nucleophilic addition occurs in a concerted way directly across the N=C bond of the isocyanate rather than across the C=O bond. The bulk solvent effect, which is treated by a polarizable continuum model (PCM), confirms the preference for the attack of alcohol across the N=C bond. In many aspects, the alcoholysis mechanism is quite similar to the hydrolysis, except for the fact that alkyl substituents of alcohols substantially reduce the energy barriers.

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