Non-stereospecificity in Neutral 1,1-Addition to Isocyanides. An *Ab Initio* Study of the Reactions of HNC with Water, Ammonia, Water Dimer, Ammonia Dimer, and the Water–Ammonia Complex

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Ab initio calculations showed that the insertion reaction into the N–H bond of ammonia and the O–H bond of water with HNC as substrate is not stereospecific. Both reactions are mildly exothermic, but the energy barrier is high (*ca.* 67 kcal mol^{-1} for H_2O at MP4SDQ/6-31G**).† Addition of polarization functions to the basis set increase and correlation energies decrease the barrier. These effects essentially cancel so that the simple basis set (3-21G) gives a good estimate of the transition state energy barrier. Such large energy barriers render these additions unlikely. However when a second molecule of H_2O or NH_3 is present to act as a catalyst then addition takes place *via* a compact five-membered ring. For the addition of NH_3, H_2O is the favoured catalyst (rather than a second NH_3 molecule). With $(H_2O)_2$ addition to HNC to give formimidic acid, the proton transfers are synchronous while formamidine formation with ammonia is asynchronous [*e.g.* for $(NH_3)_2$, the second NH_3 acts as a basic catalyst while for $NH_3{\cdot}H_2O$ addition, H_2O acts as an acid]. In all reactions considered, the transition structures can have either *Z*- or *E*-configuration with respect to the C–N bond, but the corresponding C–N–H bending mode (responsible for the nitrogen inversion) is quasi-free. Both isomers can be formed when the transition state is passed on the reaction pathway, implying that the relevant addition is not stereospecific, as experimentally observed.

The stereochemistry of nucleophilic 1,1-addition of HX to isocyanides (RNC)[1] leading to the formation of substituted imines (XCH=NR) has recently been shown to be dependent upon the nature of nucleophiles and the reaction medium.[2,3] In the absence of solvent and with AgCl as catalyst[2] or when the reaction involves anionic nucleophiles,[3] it is stereospecific giving the *Z*-isomer of the imine as the kinetic adduct. In aqueous solution and without catalysts, the situation is different. We first summarize some experimental results on the addition under the latter conditions.[4]

Isocyanides (**2**) ($\lambda_{max.}$ *ca.* 320 nm) were generated from formimidoyl chlorides (**1**) ($\lambda_{max.}$ *ca.* 375 nm) in aqueous NaOH over a wide range of pH (7—11). When the reaction was performed in aqueous morpholine (HX) the amidines (**3**) ($\lambda_{max.}$ *ca.* 410 nm) were isolated. The second step (**2**) $\longrightarrow$ (**3**) was observed to be dependent upon the concentration of morpholine and pH-independent $\{k_{obs.} = k[\text{morpholine}]$ with $k = 0.067$ s^{-1} M^{-1} in the presence of chloride anion (KCl $\mu = 1.0$)$\}$.

Without added salt, rates for morpholine addition were 4—7 times slower in aqueous solution and 20—30 times slower in a 1:1 water–dioxane medium. In this case, the initial product (**3**) was in fact a mixture of two compounds in *ca.* equimolar amounts. On standing, the more polar of the two isomers disappears involving the conversion of (*Z*)-(**3**) to (*E*)-(**3**) (see Scheme).

Thus the addition of the amine to isocyanides (**2**) $\longrightarrow$ (**3**) involves neutral morpholine as a nucleophilic reagent and possibly water as catalyst and is not stereospecific in contrast to the direct addition of anionic nucleophiles.

In order to rationalize these experimental findings, we have now carried out a theoretical study on some model reactions. These involve hydrogen isocyanide (isocyanic acid, HNC) with the following nucleophilic species: water (H_2O), ammonia (NH_3), water dimer [$(H_2O)_2$], ammonia dimer [$(NH_3)_2$], and the water–ammonia complex ($NH_3{\cdot}H_2O$). We were particularly interested in searching for the reason for the non-stereospecificity of this addition.

Calculations

The geometry optimization has been carried out at the SCF level of theory making use of the 3-21G basis set[5] throughout. The stationary points on each energy surface have been located by minimizing the energy gradients norm while checking the eigenvalues of the Hessian matrices. The former were computed analytically and the latter numerically by gradient differences with use of a modified version of the VA05AD[6] subroutines. To consider the influence of the polarization and correlation effects on the thermodynamic parameters, we have then recalculated single-point energies, as a test case, of the three stationary points of the HNC + H_2O reaction with more accurate wavefunctions. For that purpose, four additional basis sets have been employed: 6-31G, 6-31G** (including a set of polarization functions *d* for C, N, and O and *p* for H),[7] 6-311G** (plus an additional set of *sp*-functions and 6-31++G** (++ denotes a set of diffuse functions *s* and *p* for C, N, and O and *s* for H).[8] The correlation energies were calculated by the Møller-Plesset perturbation theory to second-, third-, and fourth-order.[9] Finally, the centroids of the localized orbitals were obtained using the Foster–Boys[10] procedure. All calculation procedures were implemented in the MONSTERGAUSS[11] and GAUSSIAN 82[12] programs.

Results and Discussion

The molecular structures of isolated species, namely HNC, H_2O, NH_3, $(H_2O)_2$, $(NH_3)_2$, and ($NH_3{\cdot}H_2O$), have been extensively studied in previous works. For simplicity, we refer to reference 13 for their 3-21G-optimized geometries. For geometrical parameters, bond lengths are given in (Å) and bond angles in (°).

The HNC + H_2O *Reaction.*—In searching the transition structure for this reaction, the stationary point (**4**) has been

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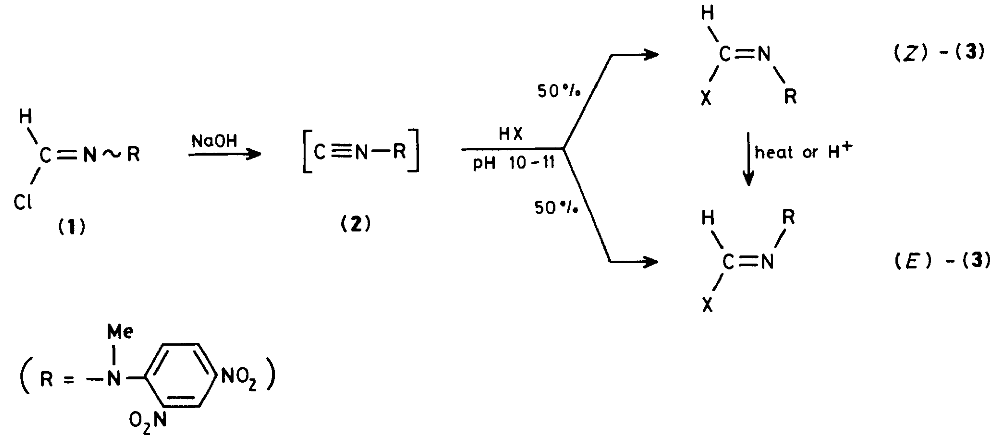
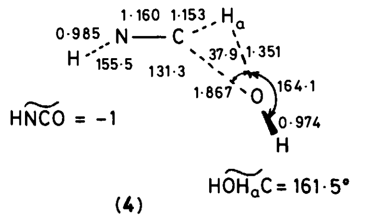
† Non-S.I.-units employed: 1 cal. = 4.184 J.

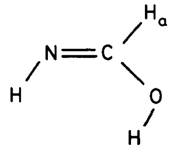


Scheme.

located. Separate analytic second derivatives show that (**4**) has two imaginary frequencies. The first frequency of 1 413i cm^{-1} is composed of both the CO and CH stretching modes whereas the second (*ca.* 150i cm^{-1}) describes the motion of the H(C) atom. Extensive attempts to locate the true transition state failed partly because the region of the energy surface corresponding to the HNC bond angle and torsion parameters is extremely flat. It can be expected that the true transition structure for the insertion reaction exhibits a somewhat larger HNCO dihedral angle but the energy difference between it and (**4**) is very small. Therefore we consider (**4**) as the transition state for the reaction being considered.



(**4**)



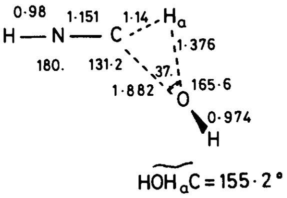
(**5**)

In (**4**), the C–H$_a$ bond is virtually formed (1.153 Å) while the C–O distance is still large (1.867 Å). It may be regarded as involving an interaction between HCNH$^+$ and OH$^-$ species. Although the C–N bond length in (**4**) remains unchanged with respect to that in the free HNC, the corresponding stretching frequency is slightly reduced from 2 032 cm^{-1} in HNC to 1 866 cm^{-1} in (**4**) (3-21G values, Figure 1). All bending and torsion modes in (**4**) are shown to be much easier (with smaller frequencies) than those of minima structures.

An interesting feature of the transition structure (**4**) is that the H(N) atom and the OH group are found to be situated on the same side of the C–N. This leads to the formation of the (*Z*)-*s*-*trans*-formimidic acid (**5**) as product. A detailed conformational and configurational analysis of the formimidic acid has previously been computed at HF/3-21G level.[14] Accordingly, structure (**5**) is the second most stable isomer, lying only 3.2 kcal mol^{-1} above the global minimum, the (*Z*)-*s*-*cis*-form.

It should be pointed out that no stationary point in which the H(N) atom and the OH group have an *E*-conformation with respect to C–N can be located. In order to assess the ease of the H(N) atom movement in (**4**), we have optimized the geometry of structure (**6**) in which the H–N–C is kept in a straight line. Structure (**6**) does not correspond to any stationary point but can indicate the energy of the HNC bending mode. At the HF/3-21G level, it lies only 0.9 kcal mol^{-1} above (**4**).*

Thus, it can be expected that in the region immediately after the transition state, the supermolecule can have either the *Z*- or *E*-form by means of just an easy vibrational HNC bending. If the less favoured form can survive later on the reaction pathway where the inversion motion becomes more difficult both isomers can consequently be formed.



(**6**)

Table 1 lists the total and relative energies of stationary points calculated at different levels of theory, along with some thermochemical data.

Firstly, one sees that, at all levels, the reaction is moderately exothermic and exhibits a high activation barrier. At 0 K and without zero-point energy (ZPE) correction, HF/3-21G calculations provide the values of 69.0 and -18.3 kcal mol^{-1} for the activation barrier and heat of reaction respectively. The HF/6-31G single-point calculation reduces them to 67.8 and -11.9 kcal mol^{-1}. In comparison with the barrier determined at HF/6-31G, it is seen that polarization functions (6-31G**) increase the barrier significantly ($+11.5$ kcal mol^{-1}) but an extra set of *s*- and *p*-functions exerts no effect on it. In contrast, diffuse functions (6-31++G**) appear to lower it slightly (-1.4 kcal mol^{-1}). Correlation energies calculated at all perturbation orders act in the opposite direction. At the MP4SDQ level, the barrier is reduced by 10.5 (with 6-31G) and by 12.8 kcal mol^{-1} (with 6-31G**). Hence, the larger the basis set, the larger the reduction by correlation energies. In addition, both corrections due to polarization and correlation effects are approximately equivalent meaning that they mutually cancel.

With regard to the heat of reaction, inclusion of polarization functions and correlation energies tend to stabilize the product although diffuse and higher *sp*-functions seem to limit such stabilization. The best estimates incorporating both basis set

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* The HF/3-21G energy of structure (**6**) is $-167.814\,25$ a.u.

Table 1. Total energies and thermodynamic parameters of stationary points in the HNC + H_2O reactions considered at different levels of calculations. Relative energies (kcal mol^{-1}) with respect to the HNC + H_2O system are given in parentheses

Method	HNC	H_2O	(**4**) (TS)	(**5**)
	Total energies[a] (a.u.)			
HF/3-21G	−92.339 72	−75.585 96	−167.815 70 (69.0)	−167.970 48 (−18.3)
HF/6-31G	−92.814 87	−75.984 53	−168.691 38 (67.8)	−168.818 29 (−11.9)
HF/6-31G**	−92.859 55	−76.022 27	−168.755 51 (79.3)	−168.911 88 (−18.9)
HF/6-311G**	−92.882 34	−76.045 39	−168.801 14 (79.4)	−168.953 59 (−16.2)
HF/6-31++G**	−92.865 44	−76.030 10	−168.771 40 (77.9)	−168.919 42 (−15.0)
MP2/3-21G	−92.530 20	−75.708 78	−168.149 94 (55.9)	−168.270 87 (−20.0)
MP2/6-31G	−93.002 98	−76.112 96	−169.029 08 (54.5)	−169.139 89 (−15.0)
MP3/6-31G	−93.000 64	−76.114 60	−169.020 46 (59.5)	−169.142 00 (−16.8)
MP4SDQ/6-31G	−93.011 22	−76.118 86	−169.038 75 (57.3)	−169.154 46 (−15.3)
MP2/6-31G**	−93.132 41	−76.219 31	−169.253 66 (61.5)	−169.393 37 (−26.1)
MP3/6-31G**	−93.140 15	−76.225 60	−169.256 27 (68.7)	−169.405 32 (−24.8)
MP4SDQ/31G**	−93.146 33	−76.228 02	−169.268 39 (66.5)	−169.412 92 (−24.2)
	Thermodynamic parameters[a]			
ZPE (kcal mol^{-1})[b]	9.9	12.3	21.5	27.8
S_{298} (cal mol^{-1} K^{-1})	48.1	45.0	61.9	59.6
C_{p298} (cal mol^{-1} K^{-1})[c]	8.5	8.0	13.2	11.2

[a] Using HF/3-21G-optimized geometries. [b] Zero-point energies are scaled by 0.9. [c] Specific heat capacities (C_p).

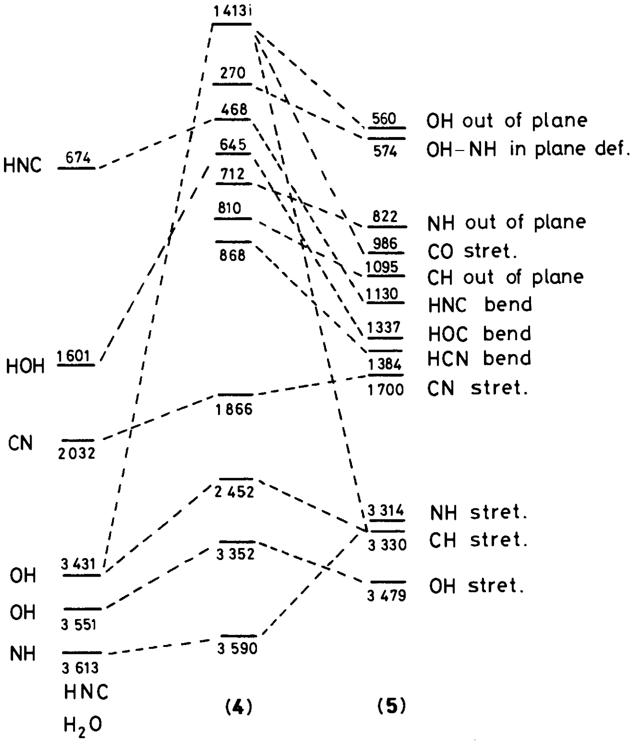


Figure 1. Vibrational frequency correlation diagram for three stationary points of the HNC + H_2O pathway calculated at HF/3-21G. Values are given in cm^{-1} (scale arbitrary)

and correlation effects yield the values of 65 and −20 kcal mol^{-1} for the activation barrier ($\Delta H^{\ddagger}$, 0 K) and heat of reaction (ΔH°, 0 K), respectively. Accordingly, these parameters could be reasonably estimated by the HF/3-21G wavefunctions.

Table 2 summarizes some thermochemical data for the HNC + H_2O addition. Both the activation and reaction entropies are calculated to be significantly large (−31.2 and −33.5 cal mol^{-1} K^{-1}, respectively). As a consequence, the entropic contribution to the free energies is in turn appreciable (*ca.* 10 kcal mol^{-1} at 298 K). The entropy values also indicate that the transition structure (**4**) is much closer to the adduct (**6**). The free energy of reaction is small (−5 kcal mol^{-1}) although the addition remains exothermic. The free energy of activation is substantial (> 70 kcal mol^{-1}) meaning that the addition of one water molecule to HNC is a difficult process.

Proceeding in the opposite direction, the decomposition of the formimidic acid (**6**) to HNC + H_2O requires a slightly smaller activation free energy (60—65 kcal mol^{-1}) due to a smaller variation of entropies.

Table 3 indicates that as the water approaches HNC, in the transition state (**4**), the lone pair or the oxygen atom is reinforced and the carbon becomes electrophilic. In fact, the H_a atom of water is actually transferred to carbon as a proton, thus resulting in an appreciable amount of negative charge (0.6 e^-) transfer to the remaining OH group. As mentioned above from geometric parameters, the transition structure (**4**) is somewhat like an unfavourable interaction between $HNCH^+$ and OH^- fragments. With respect to those in the free system, in particular HNC, the HOMOs in (**4**) are strongly destabilized (up to 3 eV, Figure 2); this can be partly responsible for the high activation energy of the addition.

Table 2. Calculated thermochemical data for the HNC + $H_2O \longrightarrow$ (**5**) reaction

Parameter^a		HF/3-21G	MP4/6-31G**
Heat of reaction:	ΔH° (0 K)	-16.4	-20.0
(kcal mol^{-1})	ΔH° (0 K with ZPE)	-10.8	-14.4
	ΔH° (298 K)	-11.8	-15.4
Entropy of reaction (cal mol^{-1} K^{-1}):	ΔS (298 K)	-33.5	(-33.5)
Free energy of reaction (kcal mol^{-1}):	ΔG° (298 K)	-1.8	-5.4
Energy barrier (kcal mol^{-1}):	$\Delta H^\ddagger$ (0 K)	69.0	65.0
	$\Delta H^\ddagger$ (0 K with ZPE)	68.3	64.3
	$\Delta H^\ddagger$ (298 K)	66.7	62.7
Activation entropy (cal mol^{-1} K^{-1}):	$\Delta S^\ddagger$ (298 K)	-31.2	(-31.2)
Free energy of activation (kcal mol^{-1})	$\Delta G^\ddagger$ (298 K)	76.0	72.0

^{a} ΔH (0 K) = calculated values from Table 1; ΔH (0 K with ZPE): including zero-point contributions; ΔH (298 K) = ΔH (0 K with ZPE) + $\int_0^{298} \Delta C_p dT$; $\Delta G = \Delta H - T\Delta S$.

Table 3. Net charges (HF/3-21G) along the pathway of the HNC + H_2O addition. The HF/6-311G** values are given in parentheses for comparison

Atom	HNC + H_2O	Transition state (**4**)	Product (**5**)
C	0.37 (-0.12)	0.49 (0.43)	0.44 (0.33)
N	-0.79 (-0.39)	-0.89 (-0.48)	-0.68 (-0.45)
H_a	0.43 (0.26)	0.52 (0.36)	0.27 (0.14)
O	-0.72 (-0.52)	-0.88 (-0.82)	-0.69 (-0.43)
H(O)	0.36 (0.25)	0.33 (0.22)	0.39 (0.26)

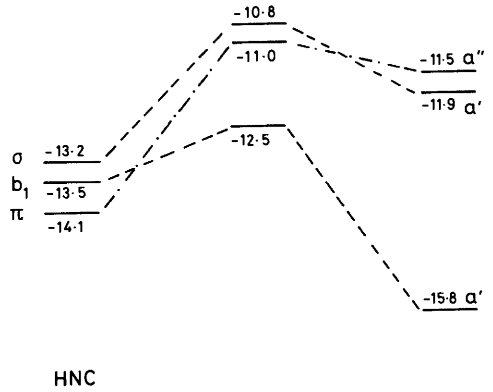
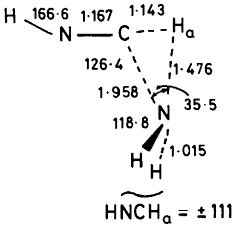


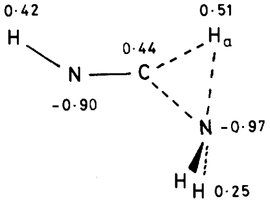
Figure 2. Correlation of three HOMOs along the HNC + H_2O addition. Values given in eV at HF/6-311G**

In summary, extensive calculations on the HNC + H_2O reaction pathways emphasize (a) that due to the ease with which the HNC bending occurs in the transition state (**4**), both *Z*- and *E*-isomer of the adduct (**5**) can be formed (if the system can reach the transition state) and (b) that the corresponding thermodynamic parameters of the reaction can be reasonably estimated at the HF/3-21G level. Concerning the latter, similar observations have previously been made on bimolecular (NH_3 + HCO_2H)[15] and trimolecular (CO + H_2O + H_2O)[16] additions. Therefore, in the following reactions only HF/3-21G calculations will be considered.

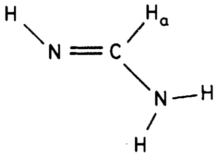
The HNC + NH_3 *Reaction*.—The transition state (**7**) was located using the 3-21G basis set. Similar observations concerning the H(N) motion have again been made, namely a second imaginary frequency (*ca.* 200i cm^{-1}) persists and the energy surface in that area is very flat. Geometric parameters in (**7**) are comparable to those in (**4**) but the relative positions of the H(N) and NH_2 groups occupy a *trans* configuration with respect to the C–N bond thus leading to the formation of the (*E*)-formamidine (**8**), in contrast to the previous case in (**4**). The interaction between hydrogen atoms H(N) and H(H_2N) seems to favour the *trans*-form (**7**).



(7)



(7a)



(8)

The first imaginary frequency of 1 800i cm^{-1} is somewhat larger than that found in the transition state (**4**) (1 413i cm^{-1}, Figure 1). The geometry of (**8**) along with a conformational analysis (at HF/3-21G) have previously been reported.[17] Accordingly, the *E*-isomer (**8**) is < 1 kcal mol^{-1} more stable than the *Z*-isomer. Some energetic and thermochemical data relevant to the addition are recorded in Table 4.

Again, the reaction is calculated to be slightly exothermic (ΔG° -3.1 kcal mol^{-1}). The entropy variations (-30 to -33 cal mol^{-1} K^{-1}) are similar to those computed for the addition of water. As suggested by the imaginary frequencies, the activation free energy in the addition of ammonia to HNC ($\Delta G^\ddagger$ 95.8 kcal mol^{-1}) is higher than that involving water (76.0 kcal mol^{-1}, see Table 2). Such a large activation energy renders this bimolecular addition unlikely.

Like the previous case, the charge distribution in the transition state as given in (**7a**) (HF/3-21G) together with its geometrical structure [see (**7**)] also show that at this stationary point the H_a atom is already shifted to the carbon atom as a proton thus yielding a non-favourable interaction between $HCNH^+$ and NH_2^- fragments.

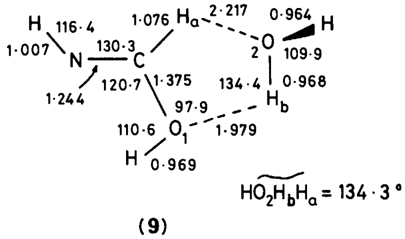
Table 4. Energetic and thermochemical data relevant to the HNC + NH_3 reaction (HF/3-21G)

Absolute values	NH_3	(**7**)	(**8**)
E (a.u.)	−55.872 20	−148.072 46	−148.237 75
ZPE (kcal mol^{-1})[a]	20.3	29.3	35.0
S (cal mol^{-1} K^{-1})	45.9	63.4	60.9
C_p (cal mol^{-1} K^{-1})	8.6	14.9	12.9
Relative values[b]			
ΔH° (298 K, kcal mol^{-1})		−12.2	
ΔS° (298 K, cal mol^{-1} K^{-1})		−30.6	
ΔG° (298 K, kcal mol^{-1})		−3.1	
$\Delta H^\ddagger$ (298 K, kcal mol^{-1})		85.9	
$\Delta S^\ddagger$ (298 K, cal mol^{-1} K^{-1})		−33.1	
$\Delta G^\ddagger$ (298 K, kcal mol^{-1})		95.8	

[a] Corrected by a factor of 0.9. [b] See Table 2 for a definition of parameters.

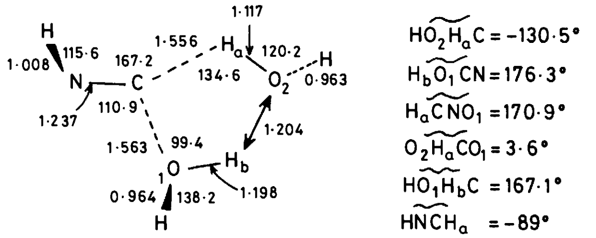
The reaction of HNC *with* $(H_2O)_2$, $(NH_3)_2$, *and* $(NH_3{\cdot}H_2O)$.—The role of a second water or ammonia molecule which acts as a catalyst in hydrogen-transfer reactions is well established. For instance, the pathways involving the water dimer or the ammonia dimer in the hydration of formaldehyde,[18] cumulenes,[19–21] or in the formation of peptide,[22] respectively, have been shown to be markedly favoured over that involving only a monomer. In the present case, because of the extremely high activation energies calculated above for the HNC + H_2O and HNC + NH_3 reactions, the question is thus as to whether two nucleophile molecules acting together constitute a reasonable model for 1,1-additions to isocyanides. We therefore considered the reactions of HNC with the water dimer and ammonia dimer. In addition, as during the reaction described for the Scheme, since the solvent molecule (water) could also participate in the process, it is appropriate to investigate the reaction of HNC with the $(NH_3{\cdot}H_2O)$ complex.

Between the HNC molecule and each of the $(H_2O)_2$, $(NH_3)_2$, and $(NH_3{\cdot}H_2O)$ species, there are some van der Waals complexes formed from the interaction between the carbon lone pair and hydrogen atoms. At the HF/3-21G level, the energy difference between these complexes and the separate systems amounts to 6—8 kcal mol^{-1} in favour of the former. Unlike the previous cases,[18–22] however, no cyclic five-membered complexes have been located. Such structures, bringing two electron lone pairs into the same region, should be unfavourable. Therefore, these complexes would probably not belong to the reaction pathways through a pre-association mechanism. For this reason, we do not report here their geometric structures. With regard to the adducts, the situation is slightly different. A cyclic complex arising from the formation of two O ··· H bonds is formed between formimidic acid and water, whereas for the formamidine such structures do not exist; only the complexes with one H ··· N or H ··· O bond are formed. The stabilization energies of the latter also amount to −6 to −8 kcal mol^{-1} (HF/3-21G). To simplify the data, we only present here (as an example) the structures of the former. The optimized geometry determined with the 3-21G basis is displayed in (**9**) (E = −243.557 27 a.u.). The complex (**9**) is 17.8 and 13.0 kcal mol^{-1} lower in energy than the isolated systems HNC + $(H_2O)_2$ and formimidic acid + H_2O, respectively. The latter value is thus about twice as large as the stabilization energy of singly hydrogen-bonded complexes. Because the stabilization due to the formation of hydrogen bonds occurs in both the reactants and products, the heats of reaction are somewhat similar to those of previous bimolecular additions.

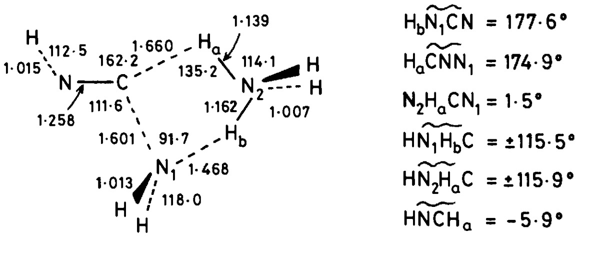


(**9**)

The 3-21G-optimized geometries of the three transition states for the addition of HNC to $(H_2O)_2$, $(NH_3)_2$, and $(NH_3{\cdot}H_2O)$ are shown in structures (**10**), (**11**), and (**12**), respectively.



(**10**)



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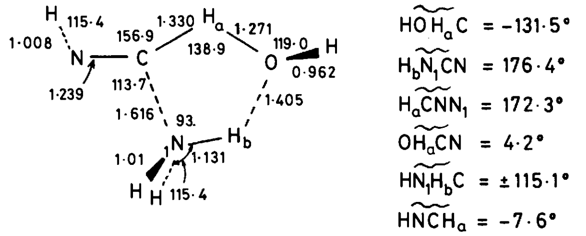


(**12**)

These transition states exhibit some similarities and some differences:

(a) In each case, a rather compact five-membered ring has been reached. It is almost planar, the distortion from planarity being <10°.

(b) The hydrogen atom of HNC adopts, in all cases, a *cis*-configuration with respect to the shifted H_a atom thus yielding the *E*-isomer of the relevant adduct. Separate calculations again show that the movement of the H(N) atom around the C–N bond in these structures is extremely easy.

(c) Of particular interest are the bond distances within the rings. In the water dimer case, the ring in structure (**10**) is almost symmetrical: the intermolecular distances C ··· O_1 and C ··· H_a, and the bond lengths O_1–H_b and O_2–H_a, are comparable. The distance between two water molecules is markedly reduced [1.204 Å in (**10**) in comparison with 1.825 Å in $(H_2O)_2$]. The C–O_1 distance of 1.563 Å is much shorter than that of 1.867 Å in the bimolecular transition structure (**4**). The bond distances C ··· H_a (1.556 Å) and O_2 ··· H_a (1.117 Å)

Table 5. Total energies and activation barriers ($\Delta H^{\ddagger}$ 0 K without ZPE) for the additions of HNC to the water dimer, ammonia dimer, and $NH_3{\cdot}H_2O$ complex (HF/3-21G)

Reactions	Transition structures	Total energies (a.u.)	Activation barriers[a] (kcal mol^{-1})
HNC + $(H_2O)_2$	**(10)**	−243.469 19	37.6
HNC + $(NH_3)_2$	**(11)**	−204.021 34	45.2
HNC + $(NH_3{\cdot}H_2O)$	**(12)**	−223.749 54	40.9

[a] With respect to the relevant reactants. The HF/3-21G total energies are: $(H_2O)_2$ = 151.189 40 a.u.; $(NH_3)_2$ = −111.753 72 a.u., and $(NH_3{\cdot}H_2O)$ = −131.475 06 a.u.

indicate that, unlike the situation in **(4)**, the H_a atom in **(10)** is not yet transferred to the carbon atom. One can thus say that, in the HNC + $(H_2O)_2$ reaction, three reactant species approach each other forming a very compact transition state but without significant alteration of their own structures. As a consequence, the hydrogen transfer should occur just after the transition state. This process can thus be expected to be highly synchronous. The transition state **(10)** has an entropy of 70 cal mol^{-1} K^{-1} (HF/3-21G) providing an activation entropy of $\Delta S^{\ddagger} \simeq -45$ cal mol^{-1} K^{-1}* for the direct transformation of the HNC + $(H_2O)_2$ system.

In the ammonia dimer case, the situation is changed. Although the carbon in (11) is also nearly equidistant from the H_a (1.660 Å) and N_1 (1.601 Å) atoms and the H_a atom is still bonded to N_2, the position within the ammonia dimer is dramatically altered. As a matter of fact, the large distances $N_1 \cdots H_b$ (1.468 Å) and the short bond N_2–H_b (1.162 Å) clearly show that the H_b atom is already shifted to the N_2 atom in the transition state (11). The reaction may be best regarded as an approach of the ionized form $(H_2\overset{-}{N} \cdots \overset{+}{N}H_4)$ to the carbon. Accordingly, the second ammonia molecule reacts as a base in order to facilitate the removal of a proton from the nucleophile NH_3. That occurs before or at the transition state, meaning that the two hydrogen transfers are quite asynchronous.

The situation in the transition state **(12)** with the presence of water to help the addition of ammonia is again different to the previous cases. While the intermolecular distance remains in the previously observed order of magnitude (1.616 Å), the $C \cdots H_a$ distance becomes substantially shorter (1.330 Å). The H_a atom is now situated approximately in the bi-sector of the C–O distance ($O \cdots H_a$ = 1.271 Å). In addition, the N–H_b bond is only slightly stretched (1.131 Å) whereas the interdistance $O \cdots H_b$ is noticeably compressed (1.405 Å against 1.865 Å in $NH_3{\cdot}H_2O$). Hence, in the transition state **(12)**, the H_a atom of water is partly transferred to carbon but the H_b remains attached to nitrogen. In this case, the water molecule plays the role of an acidic catalyst in a highly asynchronous proton transfer.

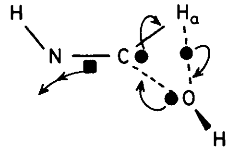
In summary, we are dealing with three different categories of catalysis: (i) the addition of $(H_2O)_2$ *via* **(10)** can be described as a synchronous bifunctional (acid–base) catalysis, (ii) that of $(NH_3)_2$ *via* **(11)** as a basic catalysis, and finally (iii) that of $(NH_3{\cdot}H_2O)$ *via* **(12)** as an acidic catalysis. The catalytic process is thus obviously dependent upon the nature of the nucleophilic reagent.

The total energies of the three transition states and the relevant activation barriers ($\Delta H^{\ddagger}$, 0 K and without ZPE corrections) calculated at the HF/3-21G level are recorded in Table 5. Like the bimolecular transformations, the activation barrier of the water dimer addition (37.6 kcal mol^{-1}) is found to be smaller than that of the ammonia dimer (45.2 kcal mol^{-1}). The latter is also larger than that predicted for the $(NH_3{\cdot}H_2O)$ addition (40.9 kcal mol^{-1}). These values indicate that during an addition of a secondary amine to isocyanides (see Scheme), in aqueous solution, the water molecule should participate as a catalyst rather than other amine molecules. This is in line with the experimental observations (see above) in which the reaction rate decreases by diminishing the water concentration.

As would be expected from earlier work,[18–22] the activation barrier of the additions is reduced by about 50% when one extra water molecule is incorporated in the process. Nevertheless, as mentioned above, these reactions carry strongly negative activation entropy ($\Delta S^{\ddagger} \geqslant -40$ cal mol^{-1} K^{-1}) implying that the relevant free energy of activation ($\Delta G^{\ddagger}$) should be appreciably larger than the present $\Delta H^{\ddagger}$ (0 K) values. In other words, the water dimer appears not to be large enough to be a suitable model for the hydration of isocyanides. More water molecules in an oligomer form $(H_2O)_n$ should be included in such a transformation.[23,24] The question of the value of the number *n* remains obviously to be answered.

Stereochemistry in 1,1-*Additions to Isocyanides*.—As stated above, the lack of stereospecificity in the neutral 1,1-additions to isocyanides can be accounted for by the ease with which the HNC bending mode takes place in the transition states of both bi- and tri-molecular transformations. A reverse situation has been found in the anionic addition[3] in which the nitrogen inversion in the intermediate adduct requires a substantial amount of activation energy leading consequently to the existence of a large stereoelectronic effect.

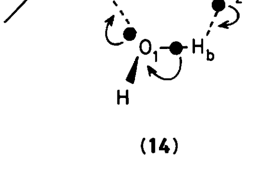
In search of a possible electronic reason for the facile HNC deformation, we have analysed the evolution of the charge centroides of the Boys localized orbitals in going from the reactants to the transition states. The reorganization of the charge distribution in the HNC + H_2O and HNC + $(H_2O)_2$ additions, for example, takes place as follows:



(13)

$$\text{(a)}\quad \pi(\text{CN}) \rightarrow n(\text{N})$$

$$\text{(b)}\ \begin{cases} n(\text{O}) \rightarrow \sigma(\text{CO}) \\ n(\text{C}) \rightarrow \sigma(\text{CH}_a) \\ \sigma(\text{OH}_a) \rightarrow n(\text{O}) \end{cases}$$



(14)

$$\text{(a)}\quad \pi(\text{CN}) \rightarrow n(\text{N})$$

$$\text{(b)}\ \begin{cases} n(\text{O}_1) \rightarrow \sigma(\text{CO}_1) \\ n(\text{C}) \rightarrow \sigma(\text{CH}_a) \\ \sigma(\text{O}_2\text{H}_a) \rightarrow n(\text{O}_2) \\ n(\text{O}_2) \rightarrow \sigma(\text{O}_2\text{H}_b) \\ \sigma(\text{O}_1\text{H}_b) \rightarrow n(\text{O}_1) \end{cases}$$

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* The entropy of the water dimer at HF/3-21G level is 67.1 cal mol^{-1} K^{-1}.

In each case [(**13**) and (**14**)] there are two somewhat separate movements of electron pairs: the first (a) is the creation of the nitrogen lone pair following the bending of HNC and the second (b) involves several electron pairs in a continuous and cyclic motion. The latter is no doubt responsible for the formation of new chemical bonds. Because the migration of the $\pi(C\equiv N)$ pair is apart from the main cyclic process governing the transformation, it can be understood that it does not produce any additional energy for the system. As shown by the tiny energy difference between (**4**) and (**5**) (see above), this electron pair seems to move rather freely from the C–N bond region of the N lone pair area. Thus, it is of no stereochemical significance whether the electron pair occupies a *cis*- or *trans*-configuration with respect to the approaching nucleophile. This phenomenon is quite opposite to the reorganization which occurs in an anionic addition where this electron pair fully participates and consequently determines the stereochemistry of the addition.[3]

Conclusion

In agreement with experimental findings, 1,1-addition to isocyanides by neutral nucleophiles is shown, by *ab initio* calculations, to be non-stereospecific. This is due to the non-participation of the ($C\equiv N$) electron pair (which becomes the N lone pair in the product) in a cyclic movement of several electron pairs creating a nearly free $R-N\equiv C$ bending mode in the transition state. The reaction of an amine in aqueous medium is also demonstrated to be preferentially catalysed by water (solvent) rather than by a second amine. Moreover, a chain of water molecules rather than one is probably involved in the hydrogen transfer. The latter can act either as a bifunctional or as an acidic catalyst (and also probably as a basic catalyst) depending upon the nature of the nucleophilic reagent. In such processes, the hydrogen transfer can be highly synchronous or quite asynchronous. Attempts to clarify the active solvent catalysis would appear to be highly desirable.

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