plexes.[21] The above examples are illustrative of the importance of an inversion process associated with a rotational movement to reach again a true energy minimum state.

Unfortunately, the present unavailability of the model compound $H_3P{=}C(CH_2)_2$ precludes further cross-checking of the calculated data by experiments. Photoelectron spectroscopy and dipole moment studies would be the obvious means of control. Nevertheless, data from simple homologues may well be sufficient to probe some of the expected or unexpected details.

Acknowledgment. This research was supported by Fonds der Chemischen Industrie, Frankfurt, Main, and by Deutsche Forschungsgemeinschaft, Bonn-Bad Godesberg. A travel grant to A.S., by Proctor & Gamble, European Office, Brussels, is gratefully acknowledged. Dr. D. Neugebauer is thanked for establishing the computer drawings presented in the Figures. M.A.V. and H.F.S. were supported by the Director, Office of Energy Research, Office of Basic Energy Sciences, Chemical Sciences Division of the U.S. Department of Energy under Contract DE-ACO3-76SF00098. The calculations were carried out on a Harris H800 minicomputer supported by the National Science Foundation, Grant CHE-8009320.

Registry No. $H_3P{=}C(CH_2)_2$, 31918-06-6.

Ab Initio Study of the Hydration of Ketenimine ($CH_2{=}C{=}NH$) by Water and Water Dimer

Minh-Tho Nguyen*[†] and Anthony F. Hegarty*[‡]

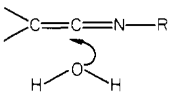
Contribution from the Department of Chemistry, University of Leuven, Celestijnenlaan, 200F, 3030 Heverlee, Belgium, and the Department of Chemistry, University College, Belfield, Dublin 4, Ireland. *Received September 20, 1982*

Abstract: The detailed reaction pathway for the hydration of the ketenimine $CH_2{=}C{=}NH$ by H_2O and by $(H_2O)_2$ has been investigated by ab initio methods using STO-3G, 4-31G, and 6-31G** basis sets. The optimized geometries of the points on the reaction surface were determined by the gradient method. The preferred reaction pathway is with the water dimer through a "preassociation" mechanism where a small amount of initial bonding occurs via attack (by oxygen) at the central carbon of the ketenimine. Proton transfer (to the β-carbon) then occurs at or just after the transition state without any appreciable changes in the C–O bond distance. The reaction (which is calculated to have an activation barrier of 22 kcal mol^{-1} in 4-31G) is therefore concerted but highly asynchronous.

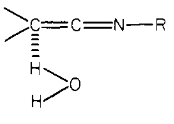
Ketenimines (>C=C=N–), which are tautomeric with aliphatic nitriles (>CC≡N), belong to the general class of cumulenes (>C=C=X).[1] They are in general highly reactive and undergo electrophilic and nucleophilic substitution, together with cycloaddition reactions. They have also attracted attention (when generated in situ) as condensation agents in peptide[2] and related syntheses. In these reactions, the ketenimine, in effect, becomes hydrated to the corresponding amide (>CHCONH–).

We have previously reported on the kinetics of the addition of water to ketenimines.[3] With simple *N*-alkylketenimines reaction occurs via rate-determining proton transfer to the terminal carbon (C_β) from H_2O (pH >7) or from H_3O^+ (pH <7) or from other general acids (such as CH_3CO_2H, RNH_3^+) that are present. The evidence for rate-determining protonation on carbon (rather than on nitrogen) was indirect, coming largely from structural studies. The preferred carbon site is supported by ab initio calculations[4] on the protonation of the model ketenimine $CH_2{=}C{=}NH$ (**1**) that show that $CH_3C{\equiv}NH^+$ (**2**) is the most stable species compared to $CH_2{=}C{=}NH_2^+$ (**3**) or $CH_2{=}CH{=}NH^+$ (**4**).

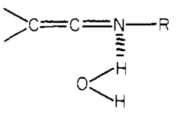
From the basis set 4-31G, the β-protonated ketenimine **2** is calculated to be 10.5 kcal mol^{-1} more stable than the N-protonated form ($CH_2{=}C{=}NH_2^+$ (**3**)). Although this energy difference is less than that calculated for β-C protonation of ketene compared with O-protonated form (37 kcal mol^{-1}),[5] it is sufficient to indicate with confidence the thermodynamically favored site of protonation. The large pH-independent rate of reaction shown by *N*-alkylketenimines in the region pH 7–13 could be due to water acting as a nucleophile at the central carbon (see **5**) or acting as a general acid to protonate carbon (**6**) or nitrogen (**7**). Alternatively one or more water molecules may be acting in a concerted fashion in which two or more processes occur in the transition state. We have now examined the reaction pathway in detail using ab initio methods using the simple model ketenimine $CH_2{=}C{=}NH$ and one or two water molecules as the reactants.



5



6



7

Table I. Calculated (4-31G) Energies (in au) for the Ketenimine in Deformed Geometries[a]

structure[b]	α, deg 170	α, deg 155
8	−131.67249	−131.66265
9	−131.66925	−131.65361
10	−131.67103	−131.65345
11	−131.66606	−131.64374

[a] Total energy of ketenimine is −131.67308 au. [b] See Figure 1.

Experimental Section

Calculation Methods. The three basis sets of Pople were used for the ab initio SCF calculations: the minimal STO-3G,[6] the split valence set 4-31G,[7] and the basis set with polarization functions, 6-31G**.[8] The STO-3G and 4-31G were used to optimize the geometry of stationary points on the energy surfaces. With these geometries we have then

---

[†] University of Leuven.

[‡] University College, Dublin.

(1) Barker, M. W.; McHenry, W. E. In "The Chemistry of Ketenes, Allenes and Related Compounds"; S., Patai, Ed.; Wiley: New York, 1980; Part 2, pp 702–720.

(2) Woodward, R. B.; Olofson, R. A. *J. Am. Chem. Soc.* **1961**, *83*, 1007.

(3) McCarthy, D. G.; Hegarty, A. F. *J. Chem. Soc., Perkin Trans. 2* **1980**, 579.

(4) Ha, T. K.; Nguyen, M. T. *J. Mol. Struct.* **1982**, *87*, 255.

(5) Yarkony, D. R.; Schaeffer, H. F., III *J. Chem. Phys.* **1975**, *63*, 4317.

(6) Hehre, W. J.; Stewart, R. F.; Pople, J. A. *J. Chem. Phys.* **1969**, *51*, 2652.

(7) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257.

(8) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213.

0002-7863/83/1505-3811$01.50/0

Table II. Energies of *C*-Methylhydroxyimine in Different Basis Sets

structure	total energy, au			rel energy, kcal/mol		
	STO-3G//STO-3G	4-31G//4-31G	6-31G**//4-31G	STO-3G	4-31G	6-31G**
12	−205.26990	−207.64256	−207.96682	0.00	0.00	0.00
13	−205.26558	−207.63713	−207.96140	2.71	3.41	3.40
14	−205.25841	−207.62582	−207.95361	7.21	10.50	8.29
15	−205.26494	−207.63575	−207.95988	3.11	4.27	4.35

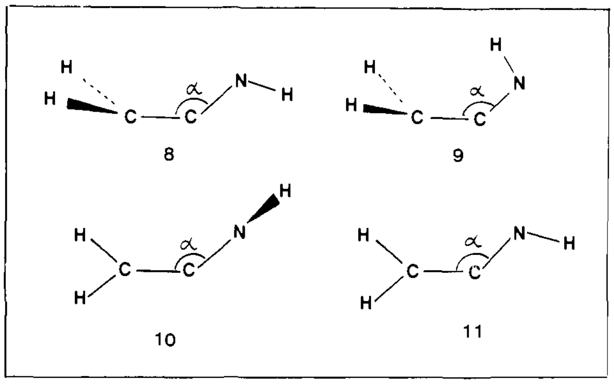


Figure 1. Four ketenimine structures, deformed from the most stable geometry.

recalculated some of these points with 6-31G** in order to obtain more precisely the energies. It has been shown by others[9] that in an organic reaction in which the number of pairs of electrons does not change, the use of a configuration interaction does not modify the qualitative results obtained by using SCF results alone. The molecular geometries have been optimized by the force method with analytical slopes[10] adapted from the MONSTERGAUSS-80 program.[11] Finally the charge centroids of the localized orbitals were obtained by using the method of Foster–Boys[12] using BOYLOC program.[13] We have shown previously[6,14] that the analysis of the change in the position of these charge centers, as the reaction proceeds, allows an unambiguous interpretation of the electron movement.

Results and Discussion

We have previously presented data listing the optimal geometry and other molecular properties of ketenimines.[4,15,16] Before describing the geometric and electronic changes that accompany the approach of an electrophile or nucleophile to a ketenimine, it was important initially to establish the ease of deformation of the molecule. There are two basic modes of deformation: as the CCN angle is reduced, the CH_2 group or the NH group may lie either in the CCN plane or above this plane (Figure 1).

In order to determine the most favored deformation, we have optimized the geometries of these structures using 4-31G with two fixed values for the CCN angle (α) of 170 and 155°. The energies obtained are recorded in Table I. From this it is clear that the deformation in mode **8** is the more favorable. This deformation has two characteristics: the C_s symmetry of the ketenimine is retained, and the two groups CH_2 and NH are on the same side of the C=C bond. For small α, the structure **9** is clearly disfavored, due no doubt largely to the interaction between the NH and CH_2 hydrogens. Overall the molecule is relatively easily deformed; closing the angle α by 25° requires only 6.5 kcal mol^{-1} (using 4-31G). In Figure 2 are given the various configurations and conformations of the (initial) reaction product formed from the ketenimine and water, viz, the hydroximic acid $CH_3C(OH)=NH$.

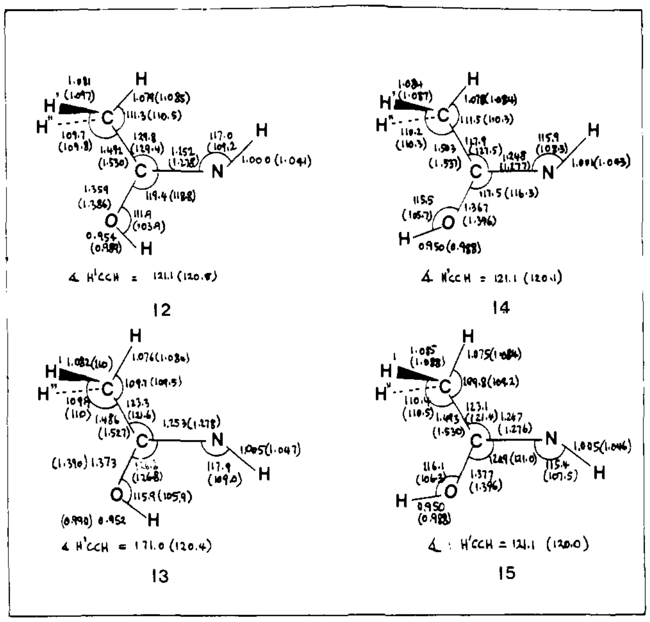


Figure 2. Optimized geometries of the hydroxyimine product in 4-31G (and STO-3G) basis sets. Distances are in angstroms and angles in degrees.

This molecule can exist in *Z* or *E* configurations with respect to the double bond, in *s*-cis and *s*-trans with respect to the C–O single bond, and in a staggered and eclipsed conformation for the methyl group. In order to simplify the calculations, we have used only the eclipsed conformations (using a dihedral angle for HCCN of 0°). As has been previously shown[17] the use of staggered conformations corresponds to an energy difference of only 1–2 kcal mol^{-1}.

Using the various basis sets, we have found that the bond lengths do not vary from one to another while the bond angles vary only by a few degrees. The use of 4-31G gives values of CC, CN, and CO bond lengths a little less (0.03–0.04 Å) than those obtained with STO-3G. On the other hand this split-valence basis set gives values of the CNH and COH angle that are significantly (7–10°) larger. In Table II are compared the relative energies of the various structures. The order of stability of the various structures remains the same with each basis set, STO-3G, 4-31G, and 6-31G**. The relative stabilities of the structures are in line with the expected interactions between the hydrogens of the three groups NH, OH, and CH_3, although lone pair–lone pair repulsions and lone pair–hydrogen attractions are also probably important. Note that in the most stable structure (**12**) the OH group occupies the same position as in the imine HC(OH)=NH. The *Z*-*E* isomerization and *s*-cis–*s*-trans isomerization of imines have already been the subject of a detailed study.[14,18]

Reaction of the Ketenimine with One Molecule of Water. In Figure 3 we have presented the optimized geometries of several

---

(9) Leroy, G.; Sana, M.; Burke, L. A.; Nguyen, M. T. In "Quantum Theory of Chemical Reactions"; Daudel, R., et al., Eds.; Reidel, 1980; Vol I, pp 91–144.

(10) Schlegel, H. B.; Wolfe, S.; Bernadi, F. *J. Chem. Phys.* **1975**, *63*, 3632.

(11) Peterson, M. R.; Poirier, R. A.; Csizmadia, I. G. "Monstergauss-80", Toronto.

(12) Boys, S. F. *Rev. Mod. Phys. Phys.* **1960**, *32*, 296.

(13) Peeters, D. "Boyloc", *QCPE* **1977**, *No. 330.*

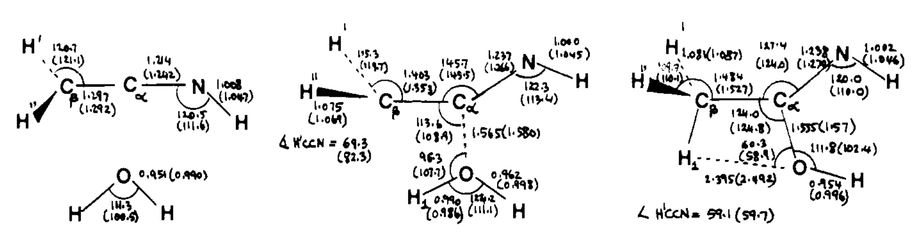
(14) Nguyen, M. T.; Sana, M.; Leroy, G.; Dignam, K. J.; Hegarty, A. F. *J. Am. Chem. Soc.* **1980**, *102*, 573.

(15) Kaneti, J.; Nguyen, M. T. *J. Mol. Struct.* **1982**, *87*, 205.

(16) A preliminary account of this work has been presented at the 13th Congress of Theoretical Chemists of Latin Expression, Sardinia, Italy, 1982. Nguyen, M. T.; Hegarty, A. F. *J. Mol. Struct.*, in press.

(17) Pross, A.; Radom, L.; Riggs, N. V. *J. Am. Chem. Soc.* **1980**, *102*, 2253.

(18) Leroy, G.; Nguyen, M. T.; Sana, M.; Villaveces, J. L. *Bull. Soc. Chim. Belg.* **1980**, *89*, 1023.



16 17 18

Figure 3. Optimized geometries for different points along the reaction pathway for the reaction between $H_2C{=}C{=}NH$ and H_2O with 4-31G (and STO-3G) basis sets.

Table III. Calculated Energies for the Reaction between $CH_2{=}C{=}NH$ and H_2O with Different Wave Functions[a]

	16	17[b]	18	activation barrier[c]	heat of reaction[d]
STO-3G//STO-3G	−204.14481	−205.05337	−205.24648	57.36	−74.77
4-31G//STO-3G	−207.57255	−207.46443		66.57	−36.63
4-31G//4-31G	−207.58173	−207.47376	−207.62025	67.73	−34.75
6-31G**//STO-3G	−207.88753	−207.77878		68.20	−40.46
6-31G**//4-31G	−207.89660	−207.78601		69.37	−39.77

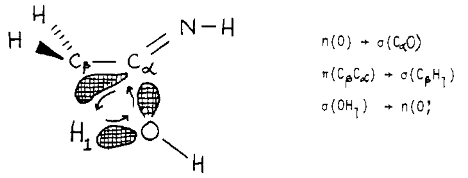
[a] Total energies in au and relative energies in kcal/mol. [b] Transition state. [c] Relative to the isolated reactants (9). [d] With respect to the C-methylhydroxyimine (6) in its staggered conformation.

particular points on the energy surfaces using the basis sets STO-3G and 4-31G. The actual position of transition-state **17** is located by the calculation of second derivatives of the energy with respect to all the structural parameters of the supramolecule. In this structure (**17**), all the gradients are zero and there is one negative value among the second derivatives, which effectively corresponds to the structure of the transition state.

Structure **18** is obtained by fixing the distance C_α–O at 1.57 (STO-3G) or 1.555 Å (4-31G), which represents a point involving a variation of 0.01 Å after the transition state. This allows one to show how the nuclear and electronic movements evolve as the transition state is passed.

The geometries obtained by using both basis sets are quite close. The intermolecular bond length C_α–O is quite short (1.565 Å) compared with that in the product (1.373 Å). This implies that the transition state is reached late in the reaction coordinate. During the reaction the ketenimine deforms in the mode that was found (see above) to be most favorable as the water molecule approaches in the CCN plane toward the central (C_α) carbon. As the transition state is passed, a proton is transferred toward the terminal carbon (C_β), so that by the point corresponding to **18**, the imine is virtually formed. The conformation formed (**13**) is not the most stable; other conformations or configurations may be formed by subsequent interconversions of **13** (Figure 2). In Table III are summarized the calculated energies for different structures. The activation barrier is quite large: 57.4 kcal mol^{-1} in STO-3G, 67.7 kcal mol^{-1} in 4-31G, and 69.4 kcal mol^{-1} in 6-31G**. We can conclude that the inclusion of polarization functions has only a minimal effect (2 kcal mol^{-1}) on the calculated value of the activation barrier. At the transition state the angle CCN has become 146°. This deformation alone requires 10–15 kcal mol^{-1} (according to the basis set used), which represents 15–20% of the activation barrier height. This is very much smaller than the contribution previously observed (approximately 70%) that the deformation energy of HCNO contributed to the overall barrier in the reaction of HCNO with H_2O.[14] This energy is of the same order of magnitude as the activation barriers for the intramolecular 1,3-roton transfer in compounds such as formic acid, vinyl alcohol, and hydroxyimine,[19] which lie in the range 60–80 kcal mol^{-1} (4-31G).

The analysis of the movement of charge centers on localized orbitals shows that the redistribution of electron pairs occurs as follows:



In Table III it is also noted that there is a dramatic fall in energy when the supermolecule passes from structure **17** to structure **18** (a change that involves only a 0.01-Å shortening of the C_α–O bond length). From the geometric (rather than from the energetic) point of view, the transfer of the proton H_1 occurs just after the transition state.

Reaction of the Ketenimine with Two Molecules of Water. Given the size of the supermolecule in this case ($CH_2{=}C{=}N$-$H{\cdot}2H_2O$), we have optimized the geometry only with the minimal basis set STO-3G. From the results in Table III, we can reproduce equally well the energy parameters by recalculating with 4-31G using the geometries derived from STO-3G (4-31G//STO-3G). In Figure 4 we have reproduced the geometric parameters for several points on the energy surface. Apart from transition-state **20**, the points corresponding to the geometries **19** and **21** were obtained by fixing the intermolecular geometry C_α–O_1 at 2.00 and 1.92 Å (0.07 and 0.01 Å before and after the transition state, respectively, on this coordinate).

The calculations show that as the transition state is approached, the two molecules of water move in the form of a dimer toward the ketenimine. The water dimer has a linear structure, which has been shown[20] to be the most stable among the possible structures for the dimer. In the course of the approach, the oxygen atom O_1 moving toward the central carbon atom (C_α) while the second oxygen atom of the dimer (O_2) is on the same side as the terminal carbon atom (C_β), so that is correctly situated to facilitate proton transfer to this carbon (C_β) rather than to the terminal nitrogen atom of the ketenimine.

The C_α–O_1 distance in the transition state is markedly greater than that observed above for the reaction with one molecule of

---

(19) Nguyen, M. T.; Sana, M.; Leroy, G. *Bull. Soc. Chim. Belg.* **1981**, *90*, 681.

(20) Leroy, G.; Louterman-Leloup, G.; Ruelle, P. *Bull. Soc. Chim. Belg.* **1976**, *85*, 205, 393.

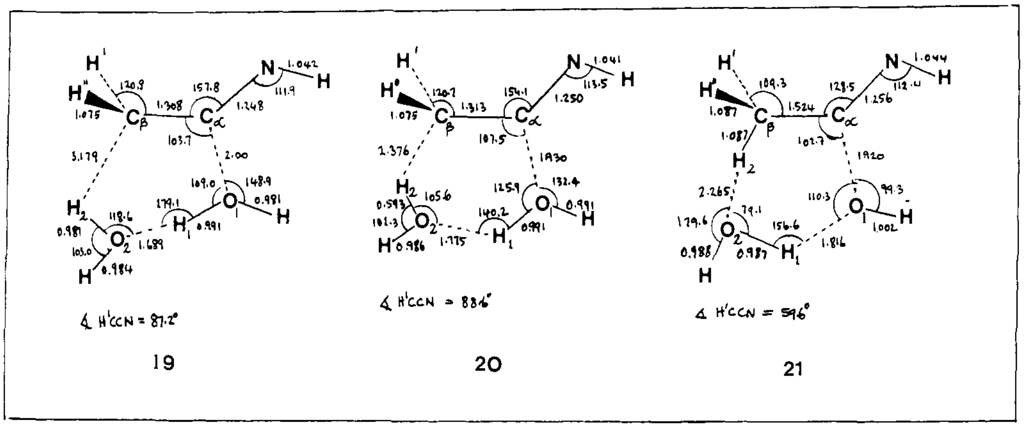


Figure 4. Optimized geometries (STO-3G) for different points on the reaction pathway for $CH_2{=}C{=}NH$ with two molecules H_2O (angles in degrees, bond lengths in angstroms).

Table IV. Calculated Energies for the Reaction of Ketenimine with Two Molecules of H_2O^a

	STO-3G//STO-3G	4-31G//STO-3G
$CH_2{=}C{=}NH + 2H_2O$	−280.10880	−283.48035
19	−280.09551	
20^b	−280.08470	−283.44521
21	−280.12119	
activation barrier^c	15.12	22.05

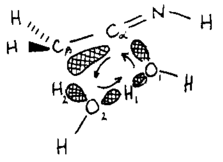
^{a} Total energies in au, relative energies in kcal/mol. ^{b} Transition state. ^{c} Relative to the $CH_2{=}C{=}NH + 2H_2O$ system.

water (1.93 against 1.58 Å). This distance is comparable to that observed for the reaction of fulminic acid with one molecule of water (HCNO + H_2O; 1.85 Å).[14] At the transition state there are two important nuclear motions: the deformation of the ketenimine, which is quite small (α(CCN) = 154°), and the closing of the $O_2H_1O_1$ angle of the dimer, which changes from 179 to 140°. These movements tend to facilitate the transfer of a proton (H_2) toward the C_β carbon. At the point corresponding to **21**, just after the transition state, the product is already clearly formed. For smaller distances of C_α–O, the HO_2H_1 forms a molecular complex of a linear structure with the O_1 oxygen.

In Table IV are summarized the energies calculated by using the different basis sets. The energy barrier varies from 15.1 (STO-3G) to 22.0 kcal mol^{-1} (4-31G). This barrier is noticeably smaller than that obtained for the reaction of the ketenimine with one molecule of water. The difference in the barriers calculated by using the different basis sets is of the same order of magnitude as previously observed. Moreover, the activation barrier for the fulminic acid reaction (HCNO + H_2O) is 23.5 kcal mol^{-1} (STO-3G). We can therefore conclude that the hydration of the simple ketenimine $CH_2{=}C{=}NH$ occurs via reaction with two (rather than one) molecules of water, which reacts in the form of a dimer. These results are in accord with the experimental measurements obtained in solution; substituent and isotope effects indicate that water acts as a general acid to protonate the C_α carbon.[3]

The deformation of the ketenimine and of the water dimer in the transition state require 6.5 and 8 kcal mol^{-1}, which represents in total about 65% of the energy barrier. In this case also the deformation occurs in the most favorable mode, creating the conditions (steric and electronic) that are most conducive to the approach of the dimer and the proton transfer.

In analyzing the movement of charge centers of localized orbitals, we can summarize the electron movement as follows:



$n(O_1) \rightarrow \sigma(C_\alpha O_1)$
$\pi(C_\alpha C_\beta) \rightarrow \sigma(C_\beta H_2)$
$\sigma(O_2H_2) \rightarrow n(O_2)$
$n(O_2) \rightarrow \sigma(O_2H_1)$
$\sigma(O_1H_1) \rightarrow n(O_1)$

Table V. Net Charges along the Pathway for the Reaction $CH_2{=}C{=}NH + 2H_2O$

atoms	reactants	trans state	products
C_α	0.160	0.241	0.246
C_β	−0.202	−0.260	−0.191
N	−0.309	−0.315	−0.339
H'(H'')	0.084	0.053	0.080
H(N)	0.183	0.180	0.124
O_1	−0.415	−0.372	−0.281
H_1	0.212	0.246	0.183
$H(O_1)$	0.159	0.156	0.193
O_2	−0.365	−0.375	−0.366
H_2	0.204	0.233	0.089
$H(O_2)$	0.204	0.156	0.183

Table VI. Overlap Populations, Bond Energies, and Degrees of Evolution of Bonds at Particular Points along the Reaction Pathway for the Reaction $CH_2{=}C{=}NH + 2H_2O$ (STO-3G)

	C_α–C_β	C_α–O_1	C_β–H_2	O_1–H_1	O_2–H_1	O_2–H_2
	P_{AB}: Overlap Populations					
reactants	0.612	0.000	0.000	0.256	0.000	0.263
trans state	0.571	0.016	0.000	0.255	0.005	0.269
products	0.366	0.283	0.385	0.000	0.254	0.000
	E_{AB}: Bond Energies (kcal/mol)					
reactants	143.0	0.0	0.0	111.5	0.0	114.5
trans state	133.1	5.3	0.0	111.0	2.2	117.1
products	80.9	83.7	98.7	0.0	110.6	0.0
	$T^{\ddagger}$: Degree of Bond Evolution (%)					
trans state	16.1	6.4	0.0	1.5	2.0	

There are thus five electron pairs (ten electrons) implicated in this cyclic reorganization.

Note that the deformation of the ketenimine permits the pair $\pi(C_\alpha C_\beta)$ to migrate toward the C_β atom, thus creating a lone pair on this atom and reinforcing at the same time the positive charge on the C_α atom (see Table V). The oxygen atom O_1 approaches in the direction of one of the lone pairs. After the transition state the two protons H_1 and H_2 are transferred from one lone pair to another in the direction opposite to the electronic movement and the formation of the C_α–O_1 bond is complete. The charge transfer is from the dimer toward the ketenimine (about 0.05 electron).

Using the methods described in previous work[14,21] to estimate the degree of bond formation in the transition state, we obtain the values listed in Table VI for the six bonds that participate in the transformation. It should be noted that in the transition state only the C_α–O_1 bond has begun to form (if very weakly); the C_β–H_2 bond does not exist while the O_2–H_2 bond is almost nonexistent despite the presence of water as a dimer. Thus the asynchronous nature of the reaction is 100% with respect to the two bonds C_β–H_2 and O_2–H_2 relative to C_α–O_1. On the other

---

[21] Leroy, G.; Nguyen, M. T.; Sana, M. *Tetrahedron* **1978**, *34*, 2459.

J. Am. Chem. Soc. 1983, 105, 3815-3818

hand if we look at the parameters for structure **21** (just after the transition state), the two bonds C_β–H_2 and O_2–H_1 are now completely formed, while the C_α–O_1 bond remains only about 25% formed. It thus appears as if in this addition the transfer of two protons H_1 and H_2 toward O_2 and C_β, respectively, is simultaneous and occurs before the C_α–O_1 bond is complete at or just after the transition state. Thus there is no intermediate on the reaction pathway, which is thus concerted but quite asynchronous.

In conclusion, the reaction of water dimer with the ketenimine is clearly favored relative to reaction with a single water molecule and approximates closely the measured experimental parameters in aqueous solution. The calculated transition state is reached with virtually no proton transfer from water to the adjacent carbon, but the reactants enter the transition state correctly oriented for subsequent proton transfer. The reaction therefore has the characteristics of a "preassociation mechanism"[22] where although proton transfer does not contribute to the overall driving force of the reaction, the reactants are oriented in the optimal fashion to permit this in a rapid (and concerted) subsequent step.

Registry No. Ketenimine, 17619-22-6.

---

(22) Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161.

Lipophilic Lithium Ion Carriers

Abraham Shanzer,* David Samuel, and Rafi Korenstein

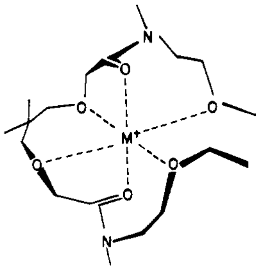
Contribution from the Departments of Organic Chemistry, Isotope Research, and Membrane Research, The Weizmann Institute of Science, Rehovot, Israel. *Received October 26, 1982*

Abstract: The design, preparation, and properties of a new series of lipophilic lithium ion carriers are described. The structure of these carriers is based on an acyclic system in which a hexafunctional lipophilic envelope is formed around the metal ion in an octahedral arrangement. The synthesis involves a series of condensation reactions using a cyclic tin–oxygen compound as an activated diol precursor. The carrier properties for lithium ions were demonstrated by in vitro experiments on liposomes using a fluorescence assay. The potential pharmacological applications of these ionophores are discussed.

Introduction

Selective ion carriers are gaining increasing interest as tools for the analysis and separation of metal ions as well as for many biological applications. Ionophores for divalent cations and some alkali ions are well known,[1] but so far, very few carriers specific for lithium ions have been described. Lithium ion carriers could have a wide range of applications. One potential pharmacological application for such carriers would be, for instance, the enhancement of the uptake of lithium into the brain and other tissues. Lithium salts have extensively and successfully been used for the treatment of manic depression and some other neurological and psychiatric disorders.[2] A major problem in lithium therapy is, however, the slow penetration of lithium through the blood brain barrier and across other membranes.[3] This results in a delayed onset of action and necessitates the administration of relatively large doses, which may be the cause of many undesirable side effects.[4] In order to examine the potential use of ionophores and in order to enhance the penetration of lithium ions into the central nervous system, we describe here the preparation and properties of a number of such lipophilic ligands.

The design of lipophilic ionophores for lithium cations is a difficult problem owing to the fact that the ions are smaller than sodium and potassium but strongly hydrated in aqueous solution.[5] It is mainly for this reason that few lithium ionophores have been synthesized. Examples of selective ligands for lithium ions relative to sodium ions are the cryptands[6] and spherands,[7] which reached remarkable binding selectivity. Some macrocyclic crown ethers[8,9] as well as acyclic polyethers[10] and acyclic dioxa diamides[11] have also been synthesized which transport lithium ions in preference to sodium ions through artificial membranes. However, the ratio of the selectivity of these carriers proved to be rather moderate and did not exceed a value of 10.[8-11] In order to improve the transport selectivity and at the same time increase the lipophilicity, we have synthesized a series of acyclic, hexafunctional dioxa diamide derivatives. These systems were expected to wrap around the lithium ion in an octahedral arrangement using six binding sites, thus forming a lipophilic envelope of aliphatic residues. In this publication we wish to describe the preparation of such hexafunctional ionophores and to report on some of their carrier properties.



---

(1) J. M. Lehn, *Struct. Bonding (Berlin)*, **16**, 1 (1973); W. Simon, W. E. Morf, and P.Ch. Meier, *ibid.*, **16**, 113 (1973); Yu. A. Ovchinnikov, V. T. Ivanov, and A. M. Shkrab, BBA Lib. (*Membr. Active Complexones*), **12**, 1 (1974); D. J. Cram and J. M. Cram, *Acc. Chem. Res.*, *11*, 8 (1978); J. S. Bradshaw, G. E. Mass, R. M. Izatt, and J. J. Christensen, *Chem. Rev.*, **79**, 375 (1979), and references cited therein.

(2) (a) Z. Gottesfeld and D. Samuel, *Endeavour*, **32**, 122 (1973); (b) F. N. Johnson, Ed., "Lithium Research and Therapy", Academic Press, London, 1975; (c) *Psychopharmacol. Lithium, Neurosci. Biobehavioral Rev.*, **3**, 15 (1979).

(3) M. Schou, *Annu. Rev. Pharmacol. Toxicol.*, **16**, 231 (1976); M. S. Ebadi, V. J. Simmons, M. J. Hendrickson, and P. S. Lacy, *Eur. J. Pharmacol.*, **27**, 324 (1974).

(4) L. Vacaflor, ref 2b, p 211.

(5) F. A. Cotton and C. Wilkinson, "Advanced Inorganic Chemistry", Interscience, New York, 1962, p 165.

(6) J. M. Lehn and J. P. Sauvage, *J. Am. Chem. Soc.*, **97**, 6700 (1975).

(7) G. M. Lein and D. J. Cram, *Chem. Commun.*, 301 (1982).

(8) U. Olsher and J. Jagur-Grodzinski, *J. Chem. Soc., Dalton Trans.*, 501 (1981).

(9) K. M. Aalmo and J. Krane, *Acta Chem. Scand., Ser. A* **36**, 227 (1982).

(10) K. Hiratani, *Chem. Lett.*, 1021 (1982).

(11) W. Simon, E. Pretsch, D. Ammann, W. E. Morf, M. Gueggi, R. Bissig, and M. Kessler, *Pure Appl. Chem.*, **44**, 613 (1975), and references therein; R. Bissig, E. Pretsch, W. E. Morf, and W. Simon, *Helv. Chim. Acta*, **61**, 1520 (1978).

0002-7863/83/1505-3815$01.50/0