A Molecular Orbital Study of the Configuration, Protonation, and Hydrogen Bonding of Secondary Amides

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Abstract: The CNDO/2 and EHT methods have been employed to examine the configurations of formamide and N-methylacetamide (NMA); reasonable values have been obtained for the barrier heights to rotation about the C–N bond. The charge densities, Mulliken overlap populations, and dipole moments of the *cis* and *trans* isomers of NMA are comparable. CNDO/2 calculations have been carried out on protonated NMA; the O–H bond in the protonated form appears to be *cis* with respect to the C–N bond. The energies of the protonated species of the *cis* and *trans* isomers of NMA are nearly the same. The CNDO/2 method gives acceptable values for the energies of hydrogen bonds in the dimers of formamide and NMA. Hydrogen bonds in the trimer of formamide are apparently stronger than the hydrogen bond in the dimer. The proton potential functions in these hydrogen bonded dimers have also been examined.

Although the *trans* configuration of the peptide bond in polypeptides and proteins is generally the more prominent configuration, the *cis* configuration has also been proposed in residues of certain fibrous proteins.[2] N-Monosubstituted amides being the simplest molecules containing the peptide bond, several workers have investigated these systems with a view to understanding the structure of proteins. Spectroscopic and other physical studies have shown that the *trans* configuration of N-monosubstituted amides predominates over the *cis* configuration.[3–7] Although simple linear secondary amides generally exist in the *trans* configuration, there is evidence for the presence of small proportions of the *cis* isomers in certain amides.[4,7] Very few linear amides are all *cis*, but some derivatives such as urethanes and hindered secondary amides consist of large proportions of the *cis* form.[4,7,8] The only model compounds available where the peptide bond is totally *cis* are the small ring lactams.[9,10]

The enthalpy, $\Delta H°$, associated with *cis–trans* equilibria is of the order of 1.0 kcal/mol,[4] while the barrier height to rotation is anywhere between 15 and 25 kcal/mol.[11,12] In spite of the extensive experimental studies on the configuration of amides, theoretical studies on these molecules have been limited. We have presently carried out a molecular orbital study of the rotational isomerism in amides, employing the extended Hückel (EHT) theory of Hoffmann[13] and the semiempirica SCF CNDO/2 method of Pople and coworkers.[14]

Another aspect of interest to us was to carry out a molecular orbital (CNDO/2) study of the protonation behavior of *cis* and *trans* amides. The protonation behavior of polypeptides is of importance in understanding the helix–coil transitions in these macromolecules and there is considerable controversy in the literature on the protonation of polypeptides and amides.

There have been several reports in the literature[15,16] on the hydrogen bonding in amides and reliable data are available for the energies of hydrogen bonds formed by the self-association of primary and secondary amides. However, there have been no extensive studies of the hydrogen bonds in amides by molecular orbital methods; the only MO study on these systems is by Pullman and Berthod,[17] who have examined the hydrogen bonds in the dimers of formamide. These workers have not minimized the energies of the dimers with respect to the N—H···O distance, nor have they calculated the potential function for the proton. In the light of our earlier MO studies of the hydrogen bond,[18] we felt that it would be useful to carry out a detailed investigation of the hydrogen bonds in the dimers of formamide and N-methylacetamide (NMA) by both the EHT and the CNDO/2 methods. Such studies would be of value in understanding the nature of hydrogen bonds in proteins and other biopolymers.

Methods of Calculation

In the EHT method,[13] we consider all the valence electrons and evaluate the overlap integrals, S_{ij}. The expression of a molecular orbital as a linear combination of atomic orbitals, $\psi_i = \Sigma_j C_{ij}\phi_j$, yields (on minimizing the total energy) a secular determinant $|H_{ij} - ES_{ij}| = 0$. The basis set consists of a 1s Slater or-

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[1] To whom all correspondence should be addressed.

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[18] (a) A. S. N. Murthy, R. E. Davis, and C. N. R. Rao, *ibid.*, **13**, 81 (1969); (b) A. S. N. Murthy and C. N. R. Rao, *Chem. Phys. Lett.*, **2**, 123 (1968).

bital for hydrogen and the 2s and 2p Slater orbitals for the second-row elements The diagonal element (Coulomb integral), H_{ii}, is equated to the negative value of the ionization potential of the corresponding valence state of the neutral atom. The off-diagonal element (resonance integral), H_{ij}, is evaluated by the method of Wolfsberg and Helmholz

$$H_{ij} = {}^1\!/_2 K S_{ij}(H_{ii} + H_{jj}) \qquad (1)$$

with $K = 1.75$. The following H_{ii} values (eV) have been used in the calculations: H_{ii}(C, 2s), −21.43; H_{ii}(C, 2p), −11.42; H_{ii}(O, 2s), −35.50; H_{ii}(O, 2p), −17.76; H_{ii}(N, 2s), −26.00; H_{ii}(N, 2p), −13.40; and H_{ii}(H, 1s), −13.60. The Slater orbital exponents used are H, 1.000; C, 1.625; N, 1.950; and O, 2.275. The computer program described by Hoffmann[19] was used by us for our calculations.

In the CNDO/2 method, the product of two different atomic orbitals, $\phi_i(1)\phi_j(1)$, associated with electron 1 is neglected in all electron interaction integrals. The atomic orbitals ϕ_i and ϕ_j belong to atoms A and B, respectively. The LCAO SCF Hartree–Fock matrix elements are approximated by

$$H_{ii} = -{}^1\!/_2(I_i + A_i) + [(P_{AA} - Z_A) - {}^1\!/_2(P_{ii} - 1)]\gamma_{AA} + \sum_{B\neq A}(P_{BB} - Z_B)\gamma_{AB} \qquad (2)$$

and

$$H_{ij} = \beta_{AB}S_{ij} - {}^1\!/_2 P_{ij}\gamma_{AB} \qquad (3)$$

Here, I_i and A_i are the atomic ionization potentials and electron affinities, respectively, associated with ϕ_i. Thus, the first term in eq 2 represents the Mulliken electronegativity of the orbital. P_{AA} is the total charge density on atom A and is given by $P_{AA} = \Sigma_i^A P_{ii}$. Z_A is the effective valence core charge of atom A and γ_{AB} is the Coulomb repulsion integral between a valence electron on A and another on B. Thus the middle term of eq 2 gives the destabilizing effect of a net excess electronic charge on atom A (if $P_{AA} > Z_A$), and the final term gives the Coulomb potential at ϕ_i due to net excess charges on other atoms in the molecule. The off-diagonal elements given in eq 3 use a semiempirical resonance integral proportional to the overlap, the constant of proportionality β_{AB} depending on the nature of atoms A and B. The second term in eq 3 is a correction to the off-diagonal elements due to electron repulsion. The molecular dipole moments are obtained as a sum of two parts

$$\mu(Z) = \mu_Q(Z) + \mu_{\text{pol}}(Z)$$

where Z is the appropriate Cartesian coordinate, $\mu_Q(Z)$ is the contribution from net atomic charge densities, and $\mu_{\text{pol}}(Z)$ is the contribution from mixing 2s and 2p orbitals on each atomic center. The CNDO/2 calculations were performed by us by using the computer program of Segal.[20]

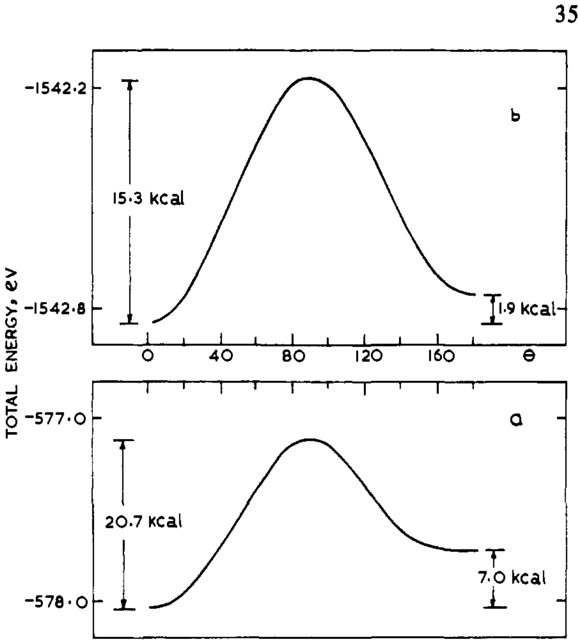

Figure 1. Variation of the energy of N-methylacetamide as a function of the angle of rotation: (a) by the EHT method and (b) by the CNDO/2 method.

Results and Discussion

Configuration of Amides. We first calculated the energy of formamide as a function of the angle of rotation, θ, about the C–N bond, taking the structural parameters of formamide from the microwave studies of Costain and Dowling.[21] The barrier height for rotation in this molecule was obtained as the difference between the energies of the two configurations where $\theta = 0$ and 90°. The barrier thus calculated was 17 and 13 kcal/mol by the EHT and CNDO/2 methods, respectively. The experimental value for the barrier in the liquid state is 19 kcal/mol, while it is about 17 kcal/mol in acetone or dioxane solutions.[12] Encouraged by the results on formamide we next examined the configuration of NMA as a function of θ. Here θ was taken as 0° for the *trans* form and as 180° for the *cis* form. The energy of NMA as a function of θ is shown in Figure 1. The CNDO/2 method provides an acceptable value for the energy difference (1.9 kcal/mol) between the two isomers as well as for the barrier height (15 kcal/mol); only the barrier height comes out to be reasonable (21 kcal/mol) by the EHT method. Miyazawa[22] has estimated the barrier height in NMA to be 14 kcal/mol.

The CNDO charges in the *trans* and *cis* isomers of NMA are shown in Table I along with those in butyrolactam (which has the *cis* configuration of the peptide bond). It can be seen that the oxygen and nitrogen atoms in NMA are σ donors and π acceptors. EHT calculations, however, show that the oxygen atom is both a σ and π acceptor, while the nitrogen atom is a σ donor and a π acceptor. The σ densities (from EHT calculations) at O and N are −0.499 and +0.215, while the π densities are −0.885 and −0.667, respectively. The EHT charges appear to be a little exaggerated in the case of electronegative atoms.

CNDO charges at the various atoms of the peptide bond for the *cis* form of NMA are close to those in butyrolactam (Table I). Further, the charge densities, dipole moments, and Mulliken overlap populations of the *cis* and *trans* rotamers of NMA are not significantly different. The dipole moments of *trans*-NMA and

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(19) R. Hoffmann, Quantum Chemistry Program Exchange (QCPE 30), Indiana University, Bloomington, Ind.

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Table I. CNDO Charges on Different Atoms in Amides and Their Dimers

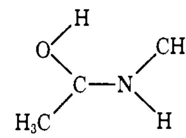
Molecule		Charges on C[a]	N[b]	O	H[c]
trans-N-Methylacetamide	σ	+0.164	+0.605	+0.050	+0.102
	π	+0.202	−0.811	−0.393	
cis-N-Methylacetamide	σ	+0.168	+0.606	+0.042	+0.117
	π	+0.204	−0.810	−0.395	
Formamide	σ	+0.161	+0.552	+0.044	+0.122
	π	+0.203	−0.807	−0.345	
Butyrolactam	σ	+0.152	+0.577	+0.067	+0.109
	π	+0.207	−0.772	−0.425	
trans-N-Methylacetamide (dimer)	σ	+0.166	+0.560	+0.065	+0.162
	π	+0.207	−0.799	−0.430	
Formamide (cyclic dimer)	σ	+0.129	+0.544	+0.055	+0.192
	π	+0.232	−0.839	−0.392	
Formamide (open dimer)	σ	+0.136	+0.558	+0.052	+0.166
	π	+0.222	−0.852	−0.371	

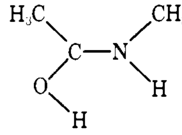
[a] Carbon of the donor carbonyl group. [b] Nitrogen of the acceptor N–H bond. [c] Hydrogen of the N–H bond.

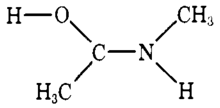
butyrolactam calculated by the CNDO/2 method are 3.65 and 3.60 D, respectively; these values are in excellent agreement with the experimental values[23] (3.60 D for NMA and 3.55 D for butyrolactam). The calculated n → π* transition energies for the *trans* and *cis* isomers of NMA are 5.63 and 5.87 eV, respectively. The observed n → π* energy of NMA (which is a *trans* amide) is 5.6 eV.[24]

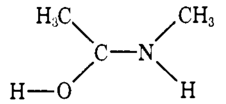
Preliminary calculations indicated that the energies and barrier heights in NMA are very sensitive to the rotation of the two methyl groups. Thus, in an unfavored configuration where the C–CH_3 group was rotated by 54° 44′ with respect to the stable configuration, the barrier height was calculated to be nearly twice that shown in Figure 1; the relative stabilities of the *cis* and *trans* isomers were, however, not affected. We feel that the overlap of hydrogens of the two methyl groups may play an important role in determining the energies of the different configurations. It would be interesting to calculate the energy of NMA as a function of θ, by taking into account the averaged contributions from the rotations of the two methyl groups.

Protonation of Secondary Amides. Spectroscopic studies have shown that oxygen is the protonation site in amides; the protonated species seem to possess the oxonium ion structure.[25,26] The configurational dependence of the protonation of amides has been examined by Balasubramanian and Balaram[27] in this laboratory, who find little difference *per se* in the protonation behavior of the *cis* and *trans* peptides. We have calculated the energies of the *cis* and *trans* forms of protonated NMA by the CNDO/2 method assuming that the carbonyl oxygen is the protonation site.[28] For this purpose, we first calculated the energy of the protonated *trans* NMA (IIIa) by varying the C–O, C–N, N–H, and O–H distances and found the structural parameters for the minimum energy configuration to be C–O, 1.34; C–N, 1.31; O–H, 1.04; and N–H, 1.06 Å. Comparison of these distances with those in the parent NMA[29] indicates a slight increase in the C–O distance and a decrease in the C–N distance. The O–H distance is appreciably longer than the normal O–H bond in alcohols. In the protonated NMA, the O–H bond can be *cis* or *trans* with respect to the central C–N bond. The protonated species can thus have any of the four possible structures shown below along with their energies (kcal/


IIIa, −35,945


IVa, −35,943


IIIb, −35,944


IVb, −35,943

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(23) A. L. McClellan, "Tables of Experimental Dipole Moments," W. H. Freeman and Co., San Francisco, Calif., 1963.

(24) (a) C. N. R. Rao, "Ultraviolet and Visible Spectroscopy—Chemical Applications," 2nd ed, Butterworth and Co. (Publishers), Ltd., London, and Plenum Press, New York, N. Y., 1967; (b) K. Kaya and S. Nagakura, *Theor. Chim. Acta*, **7**, 117, 124 (1967).

(25) T. Brichall and R. J. Gillespie, *Can. J. Chem.*, **41**, 2642 (1963).

(26) J. L. Sudmeier and K. E. Schwartz, *Chem. Commun.*, 1646 (1968).

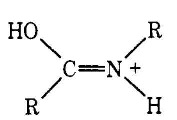
(27) P. Balaram, M.S. Thesis, Indian Institute of Technology, Kanpur, 1969.

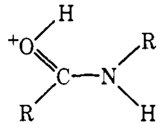
(28) We have also calculated the energy of NMA protonated at the nitrogen site. The energy of this protonated species is very much higher (−35,894 kcal for the minimum energy configuration wth an r_{NH} of 1.08 Å) than the energy of the oxygen protonated species.

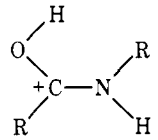
(29) A CNDO/2 calculation on the parent *trans* NMA gave the following structural parameters for the minimum energy configuration: C–O, 1.27; C–N, 1.38; and N–H, 1.06 Å. These values of the bond distances do not agree closely with the experimental values.[30] This is not surprising since the CNDO/2 method is not entirely satisfactory when energy variations are calculated with respect to bond length changes.

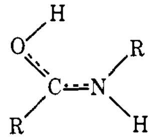
(30) L. E. Sutton, Ed., "Tables of Interatomic Distances and Configurations in Molecules and Ions," Special Publication No. 11, the Chemical Society, London, 1958.

mol). In both the *cis*- and *trans*-NMA, the structures with the *cis* O–H bond (IIIa and IVa) are slightly more stable than the corresponding structures with the *trans* O–H bond (IIIb and IVb). Among the four structures, the most stable one is found to be IIIa. The CNDO/2 charges of IIIa and those of the parent NMA provide an interesting comparison. (i) The negative charge of the nitrogen decreases markedly (~50%), the positive charge on the central carbon also increases (~30%). (ii) The negative charge on oxygen decreases appreciably (~50%). (iii) There is appreciable positive charge on the hydrogen of the O–H bond. Considering these charges as well as the bond distance in IIIa, we feel that structures V and VI are most significant among the structures given below. Structure VIII seems to satisfactorily describe all the features of protonated NMA as pointed out by Gillespie.[25] We have calculated the barrier to rotation about the C–N bond in protonated NMA (IIIa) and found it to be around 36 kcal/mol, a value much higher than that in NMA. The barrier height seems to increase markedly with decreasing C–N bond distance. This is expected since the lifetimes of both the *cis* and the *trans* configurations would be increased with a shorter C–N bond in the protonated species.[31]


V, immonium ion


VI, oxenium ion


VII, oxocarbonium ion


VIII

The present studies seem to indicate that there is no configurational dependence in the protonation of secondary amides. Any observed differences in the protonation behavior of *cis* and *trans* secondary amides in acid media may actually arise from the solvent-induced shifts in the *cis–trans* equilibria of the amide.[32] It is, however, possible that in some secondary amides protonation is sterically favored by one of the rotamers; there is some evidence for the operation of such steric effects when trifluoroacetic acid is used as the protonating agent.[27] It has been similarly reported in the literature[33] that the energies of hydrogen bonds formed by *cis* and *trans* amides are not significantly different; the magnitude of hydrogen bonding is, however, determined by steric effects of the substituents.

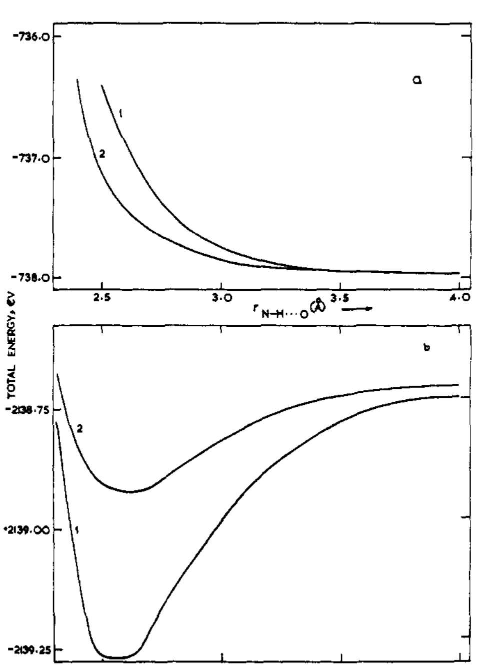
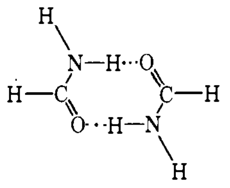
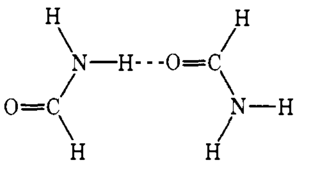
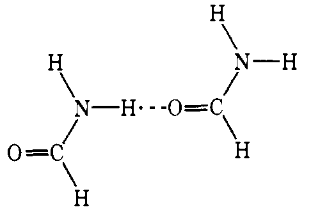


Figure 2. Variation of the energy of the dimers of formamide as a function of the N—H···O distance: (a) by the EHT method and (b) by the CNDO/2 method. 1 refers to the cyclic structure IX and 2 refers to the linear structure Xa or Xb.

Hydrogen Bonding in Secondary Amides. The energies of the cyclic (IX) and the linear dimers (Xa and Xb) of formamide were calculated as a function of N—H···O distance and the results from both the EHT and the CNDO/2 methods are shown in Figure 2. The EHT method fails to show a minimum energy configuration for the dimers, while the CNDO/2 method clearly shows the cyclic structure to be more stable. Further, there is little difference in the energies of the two open dimers Xa and b. The energy of the hydrogen bond by the CNDO/2 method in the open dimer is 5.0 kcal/mol, while it is 6.5 kcal/mol in the cyclic dimer. The N—H···O distance in the minimum energy configurations of both the linear and cyclic dimers is 2.6 Å; the experimental value in solid formamide[34] is, however, 2.9 Å.


IX


Xa


Xb

An examination of the σ and π densities in the monomer and the cyclic dimer (Table I) reveals that there is a net gain of electrons by the donor and acceptor atoms on hydrogen bond formation. The nitrogen atom shows a gain of both σ and π electrons and the oxygen atoms shows a loss of σ electrons and gain of π electrons. This observation differs slightly from that of Pullman and Berthod.[17] It appears that the charge transfer from oxygen to nitrogen is mainly of σ type.

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(31) G. Fraenkel and C. Franconi, *J. Amer. Chem. Soc.*, **82**, 4478 (1960).

(32) We have evidence from infrared and nmr studies to show that *cis–trans* equilibria in secondary amides are affected appreciably by the solvent medium.[8]

(33) (a) K. R. Bhaskar and C. N. R. Rao, *Biochim. Biophys. Acta*, **136**, 561 (1967); (b) R. L. Jones, *Spectrochim. Acta*, **20**, 1879 (1964).

(34) J. Ladell and B. Post, *Acta Crystallogr.*, **7**, 559 (1954).

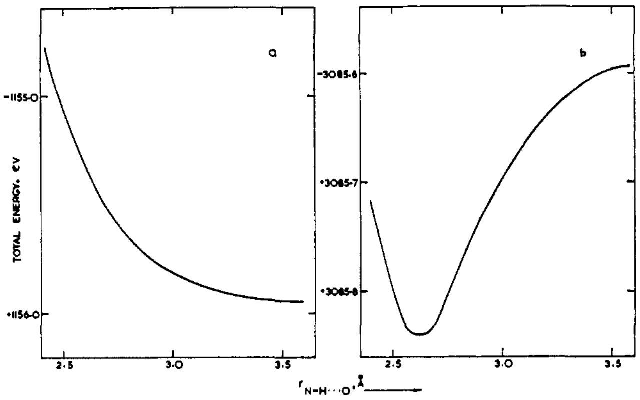
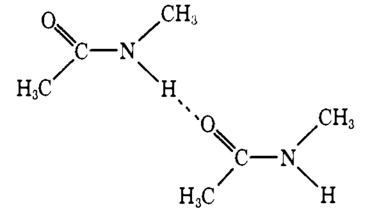


Figure 3. Variation of the energy of the linear dimer of *trans*-N-methylacetamide as a function of the N—H···O distance: (a) by the EHT method and (b) by the CNDO/2 method.

The Mulliken overlap population of the C=O bond is lower, as expected in the dimer.

The energy of the linear trimer of formamide was calculated by minimizing the total energy with respect to the second N—H···O distance. The energy of this hydrogen bond in the trimer is found to be 6 kcal/mol, which is higher than the energy of the hydrogen bond in the dimer. This is consistent with the prediction of Mizushima,[35] who has suggested that the strength of an amide hydrogen bond should increase as each monomer is added to the polymer chain. Similar results were been found earlier in the association of methanol.[18a]

The energy of the *trans* dimer of NMA (XI) is shown as a function of N—H···O distance in Figure 3; here again, only the CNDO/2 method gives a minimum in the potential energy curve. The energy of the hydrogen bond found from the curve in Figure 3 is 5 kcal/mol; the experimental value from infrared studies is 4.7 kcal/mol,[33a] while the value from nmr studies[36] is 3.3 kcal/mol.



XI

An examination of the CNDO charges (Table I) shows that on dimer formation there is a net gain of electrons by the donor (oxygen) and acceptor (nitrogen) atoms as compared to the monomer NMA. While the nitrogen atom shows a σ gain (0.045) and a π loss (0.012), the oxygen atom shows a σ loss (0.015) and a π gain (0.037). This would probably mean that the N—H···O hydrogen bond in NMA involves a donor to acceptor charge transfer of σ electrons. The calculated dipole moment of the NMA dimer is 8.3 D. The Mulliken overlap population of the C=O bond is lower in the dimer (0.71) than in the monomer (0.73); the population of the N—H remains unaffected, but that of the O···H bond is quite appreciable (0.14).

We have carried out some calculations to examine the dependence of hydrogen bond energy on the C=O···N angle. For this purpose, we calculated the total energy of the linear dimers of formamide and N-methylacetamide varying the C=O···N angle (θ') between 120 and 180°. The stability of the hydrogen bond was only slightly greater when the angle was 120°; we would expect much greater stability when $\theta' = 120°$ since the oxygen has sp^2 lone pair orbitals. The effect of bending the amide hydrogen bond was next examined by varying the C—N···O angle in the NMA dimer (keeping the C=O···N angle constant at 120°). Deviations from the tetrahedral value for the C—N···O angle are generally taken as a measure of the extent of bending.[15] Preliminary calculations indicate that bending the C—N···O angle by 10° causes little or no extra stabilization of the hydrogen bond in the NMA dimer.

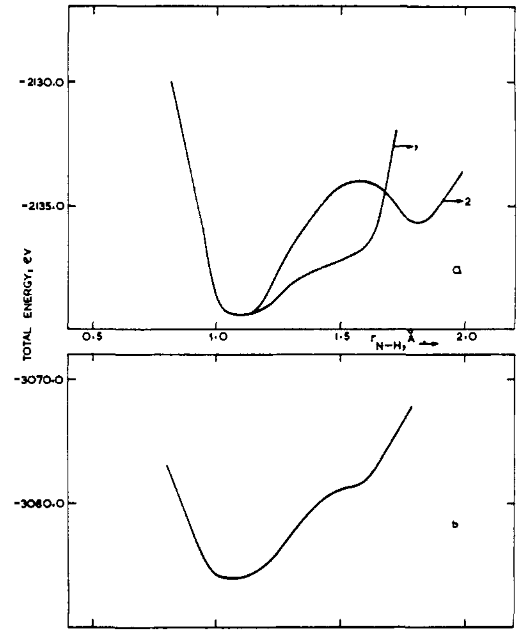


Figure 4. Total energy of amide dimers as a function of the position of the hydrogen atom by the CNDO/2 method: (a) cyclic dimer of formamide, 1 and 2 refer to N—H···O distances of 2.6 and 2.9 Å, respectively, and (b) linear dimer of *trans*-N-methylacetamide at an N—H···O distance of 2.6 Å.

The proton potential functions in the cyclic dimer of formamide and the *trans* dimer of NMA calculated by the CNDO/2 method are shown in Figure 4. The proton potential function for formamide shows a shoulder corresponding to the H···O minimum when the N—H···O distance is 2.6 Å. A clear double minimum is seen when the experimental N—H···O distance (2.9 Å) is employed; the H···O distance of 1.1 Å also appears to be reasonable. The potential function of the *trans* dimer of NMA shows both the minima around 1.0 Å when the N—H···O distance is 2.6 Å. While the shapes of the potential curves seem to be reasonable in both formamide and NMA, the barrier heights are much too large.

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