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## The Importance of One-Electron Effects in Conformation and Protonation of Acetamids\*

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The CNDO/2 method was used to compute relative stabilities of various configurations and conformations of acetamide, N-methylacetamide and diacetamide and their protonated forms. It was found that: (a) nonbonded interactions play important roles in determining structural preferences of the compounds, (b)  $n-\sigma^*$  "throughbond" interactions always favor *cis*-protonation (relative to C-N).

In recent years, theoretical<sup>1</sup> as well as experimental<sup>2</sup> investigations have been conducted to determine conformational preferences of acetamides. Although some molecular orbital studies have been reported, the factors contributing to the conformational preferences have never been adequately clarified.

In the Hartree-Fock self-consistent field (SCF) framework, the total energy changed,  $\Delta E_T$ , associated with various conformational variations can be decomposed into separate contributions,  $\Delta\epsilon_i$ ,  $\Delta V_{ee}$  and  $\Delta V_{nn}$  in the form

$$\Delta E_T = \Delta(2\sum\epsilon_i) - \Delta V_{ee} + \Delta V_{nn}$$

where an orbital energy  $\epsilon_i$  is an eigenvalue of the effective one electron operator,  $\Delta V_{ee}$  is the sum of electron-electron repulsion energies and  $\Delta V_{nn}$  is the sum of internuclear repulsion energies. Two important factors which control stereochemical preferences in molecules can thus be distinguished; (a) a one-electron factor,  $\Delta(2\sum\epsilon_i)$ , which is responsible for "through-bond" and "through-space" interactions<sup>4</sup>; (b) steric factors,  $\Delta V_{ee}$  and  $\Delta V_{nn}$ , which are responsible for sterically repulsive interactions.

One of us recently introduced<sup>5</sup> simple rules for predicting "through-space" nonbonded effects qualitatively based on the frontier orbital (FMO) concept<sup>6</sup>: (a) nonbonded interaction is significant only in a conjugated (or *iso*-conjugate) chain with two end atoms in close proximity; (b) the mode and extent of nonbonded interactions are dependent upon number of electrons in the conjugative chain and on the distance between the two end atoms. It was found convenient to adopt a notation of  $(n\pi/m)$  representing  $n\pi$  electrons delocalized over  $m$  atoms (or centers) of a chain forming a

crowded structure, only systems with  $n \geq 4$  and  $m \geq 3$  being worth considering. It was shown that: (a) nonbonded interaction is attractive in decreasing order of  $4N+2$ ,  $4N+1$ , and  $4N-1$  electron systems, while it is repulsive in a  $4N$  electron system; (b) the closer the two ends approach, the stronger the nonbonded interaction becomes.

We report here results of MO studies on the rotational isomerism in acetamide, N-methylacetamide and diacetamide employing the CNDO/2 method. We have also carried out computations to investigate their protonation behaviors. We have stressed the importance of one-electron effects<sup>4</sup> in determining the conformational preferences applying our rules wherever possible.

### Calculations

All calculations were carried out using the CNDO/2 method. For acetamide and N-methylacetamide experimental values of bond lengths and angles were used, while for diacetamide the CNDO/2 optimized geometry of Capparelli<sup>6</sup> was used.

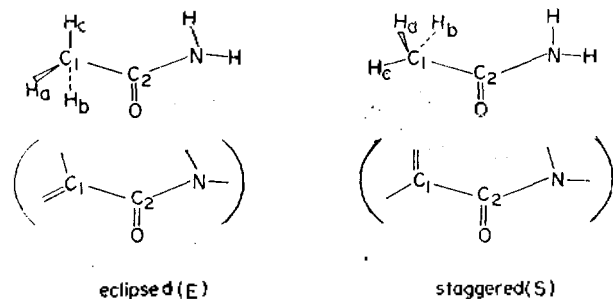
O-protonation only was considered<sup>8</sup>, with a proton at 0.99Å from O with 120° angle in the plane of NCO frame. Nitrogen was assumed to take planar form of  $sp^2$  hybrids.

### Result and Discussion

#### (I) Conformation

*Acetamide*. Two forms are possible depending on the arrangement of methyl group relative to C-N bond; the *E* form has a system,  $(H_{ab}C_1C_2O)$ ,  $\pi$ -isoconjugate to *cis* butadiene, a  $(4\pi/4)$  system, which is both sterically and end-to-end repulsive,<sup>11</sup> while the *S* form contains a  $(5\pi/4)$  system,  $(H_{ab}C_1C_2N)$ , which should have "through-space"

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nonbonded attractive effect. Table 1 shows that the (rigid) rotational barrier of methyl rotation is 0.6 kcal/mol and the relative energy is dominated by one-electron factor.

*Protonated Acetamide.* *Cis* and *trans* (relative to C-N) protonations on both the *S* and *E* forms are considered.

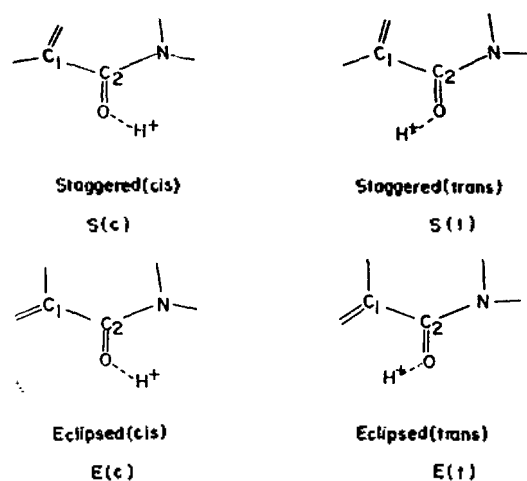


Table 2 shows that steric factors favor staggered over eclipsed form, whereas one-electron factors favor *cis*-over

*trans*-protonation. Thus the most preferred protonated form is the *S(c)* form.

It has been shown that the strongest vicinal bond-antibond interactions occur between lone pairs and L-polar antibond<sup>3,12</sup> when they are oriented in a mutually *trans* relationship. The stabilizing one-electron effect in the *cis*-protonation can be attributed to such a "through-bond" *n-σ\** conjugative effect; a proton on *cis* relative to C-N leaves another  $\sigma$  lone pair of oxygen oriented *trans* to the C-N (an L-polar pair).<sup>12</sup> The stabilization of *cis*-protonated form is provided by the conjugative interaction of the lone pair on the oxygen atom with the  $\sigma^*$  orbital of the C-N bond which is oriented *trans* to the oxygen lone pair. Predicted population changes in the *n-σ\** interaction are well borne out in our CNDO/2 calculations<sup>13</sup> as shown in Table 3. Of course electrostatic interactions also favor the *cis*-protonation.<sup>14</sup>

Another interesting point to note is that the protonation causes changes in one-electron effect such that the eclipsed form is favored over the staggered form;  $\Delta(2\sum\epsilon_i) (S(c) \rightarrow E(c)) = -12.1$  kcal/mol;  $\Delta(2\sum\epsilon_i) (S(t) \rightarrow E(t)) = -12.4$  kcal/mol. Since before protonation one-electron effect favored the staggered over the eclipsed form,  $\Delta(2\sum\epsilon_i) (S \rightarrow E) = 0.6$  kcal/mol, this implies that the protonation causes substantial changes in nonbonded interactions. This can be explained as follows: the protonation will induce the  $\pi$  lone pairs of N to delocalize further to O, thereby effectively transforming the repulsive ( $4\pi/4$ ) system in the eclipsed form to a ( $5\pi/4$ ) system which is attractive, while the attractive ( $5\pi/4$ ) system originally present in the staggered form is transformed to a ( $4\pi/4$ ) system which is repulsive. Thus the protonated staggered form now has unfavorable one-electron effect compared with the protonated eclipsed form.

TABLE 1: Energy Components of Acetamide (in a.u. Except the Relative Values which are in kcal/mol)

	Staggered	Eclipsed
$E_T$	-48.092	-48.0083
$2\sum\epsilon_i$	-21.8180	-21.8138
$V_{ee}$	94.5901	94.6119
$V_{nn}$	68.3989	68.4174
$\Delta E_T$	0.00	0.56
$\Delta(2\sum\epsilon_i)$	0.00	2.63
$\Delta V_{nn} - \Delta V_{ee}$	0.00	-2.07

TABLE 2: Energy Components For Protonated Acetamide (in a.u. Except the Relative Values which are in kcal/mol)

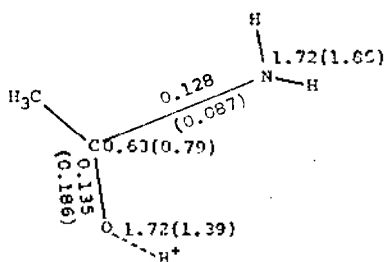
	<i>S(c)</i>	<i>S(t)</i>	<i>E(c)</i>	<i>E(t)</i>
$E_T$	-48.5118	-48.5074	-84.5086	-48.5045
$2\sum\epsilon_i$	-29.9300	-29.9196	-29.9492	-29.9394
$V_{nn}$	75.2489	75.2583	75.3104	75.3113
$V_{ee}$	93.8307	93.8461	93.8698	93.8764
$\Delta E_T$	0.0	2.8	2.0	4.6
$\Delta(2\sum\epsilon_i)$	0.0	6.5	-12.1	-5.9
$\Delta V_{nn} - \Delta V_{ee}$	0.0	-3.8	14.1	10.5

TABLE 3: Populations and Relative Energies For Protonated Acetamide

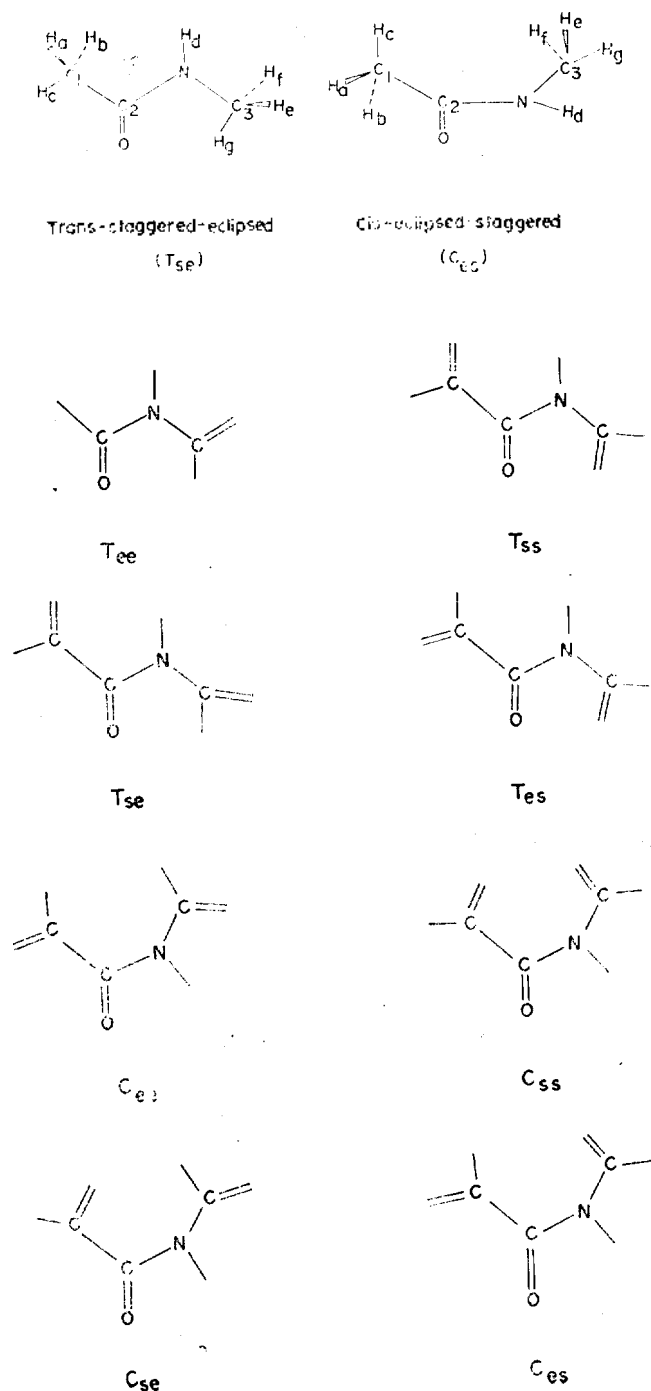
Property <sup>a</sup>	Predicted from <i>n-σ*</i> effect	Staggered		Eclipsed	
		<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>
O negative charge	<i>cis</i> < <i>trans</i>	-0.132	-0.140	-0.134	-0.141
N negative charge	<i>cis</i> > <i>trans</i>	-0.209	-0.195	-0.206	-0.192
$P_{OC}^2$	<i>cis</i> > <i>trans</i>	0.7168	0.7166	0.7169	0.7165
$P_{CN}^2$	<i>cis</i> < <i>trans</i>	0.7095	0.7110	0.7095	0.7110
$\Delta E_T$	<i>cis</i> < <i>trans</i>	0.0	2.8	0.0	2.6

<sup>a</sup> $P_{X,Y}^2$ : sigma overlap population between X and Y.<sup>13</sup>  $\Delta E_T$ ; in kcal/mol.

The results of our calculation indicate that the protonation causes considerable delocalization of  $\pi$  electrons from N to as shown below with the  $\pi$ -overlap and atomic populations for unprotonated molecule in parenthesis.



*N*-Methylacetamide. The rotations of the two methyl groups, C-methyl and N-methyl, in the *trans* and *cis* isomers give 8 distinct rotamers of interest, which are shown below



with definitions and numbering schemes of atoms to be used.

Average energy difference of 1.7 kcal/mol between *trans* and *cis* isomers, i.e.,  $1/3 [\Delta E(T_{ss} \rightarrow C_{ss}) + \Delta E(T_{se} \rightarrow C_{se}) + \Delta E(T_{es} \rightarrow C_{es})]$  excluding the sterically most unfavorable forms,  $\Delta E(T_{ee} \rightarrow C_{ee})$ , agrees well with the experimental value of 1.6 kcal/mol<sup>22</sup> and the value of 1.9 kcal/mol obtained theoretically by Murthy *et al.*<sup>1a</sup> Direct comparison with the latter may not be justified since it is not clear as to what conformations they used in their computations for the two methyl groups.

Table 4 shows that the relative order of stability for the *trans* forms is  $T_{se} > T_{ss} > T_{ee} > T_{es}$ , which obviously is a result of the delicate balance of the two factors, steric and one-electron factors. The same factor which favored staggered over eclipsed acetamide discussed above is again responsible in determining the stability of the C-methyl group in the *trans* form. In fact the barrier to C-methyl rotation is a constant 0.6 kcal/mol in the two cases of  $\Delta E(T_{se} \rightarrow T_{ee}) = \Delta E(T_{ss} \rightarrow T_{es}) = 0.6$  kcal/mol. This indicates that a *trans* N-methyl substitution has no effect upon C-methyl rotational barrier.<sup>15</sup> For N-methyl group, however, eclipsed form is preferred to staggered form, and has a rotational barrier of 0.1 kcal/mol;  $\Delta E(T_{se} \rightarrow T_{ss}) = \Delta E(T_{ee} \rightarrow T_{es}) = 0.1$  kcal/mol. This preference of the eclipsed form for N-methyl group is dominated by steric factors: although nonbonded interaction between  $H_{ef}$  and O in a  $(6\pi/5)$  system,  $(OC_2NCH_{ef})$ , favors the staggered conformation, the eclipsed conformation becomes preferred owing to the dominant steric factor.

The order of nonbonded (stabilizing) interaction predicted based on the composite  $\pi$  systems of each conformer,  $T_{ss} > T_{se} > T_{ee} > T_{es}$ , is in excellent agreement with the order of one-electron (stabilizing) effect,  $\Delta(2\sum\epsilon_i)$ . This suggests that the one-electron effect in the *trans* form is mainly the nonbonded interaction type.

For the *cis* forms, the relative stability is in the order,  $C_{ss} > C_{se} > C_{ee} > C_{es}$ . Remarkable increases in both steric repulsion and stabilizing one-electron effect are to be noted in the *cis* forms compared to those of the *trans* forms due to the closer approach of the end atoms in the *cis* forms. This is a kind of compensating effect widely observed in other physico-chemical processes.<sup>17</sup>

Here again staggered forms are preferred for the C-methyl group by the same reason as in acetamide. For N-methyl group also staggered forms are now favored over eclipsed;  $\Delta E(C_{ss} \rightarrow C_{se}) = 2.3$  kcal/mol,  $\Delta E(C_{es} \rightarrow C_{ee}) = 16.4$  kcal/mol.

The order of one-electron stabilizing effect,  $\Delta(2\sum\epsilon_i)$ , is again well reproduced by the order of nonbonded attraction effect expected from the composite  $\pi$  systems<sup>16</sup> of each conformations;  $C_{se} > C_{ss} > C_{es} > C_{ee}$ . Relative stabilities are however the result of the balance of steric and nonbonded effects. In the  $C_{ee}$  form one can identify a sigma aromatic,  $(6\sigma/6)$ , system but this seems to have very small attractive effect as the  $\pi$  over  $\sigma$  rule predicts.<sup>5</sup>

*Protonated N-Methylacetamide.* Four representative protonated forms are considered:  $T_{se}(C)$ ,  $T_{se}(T)$ ,  $T_{ss}(C)$ ,

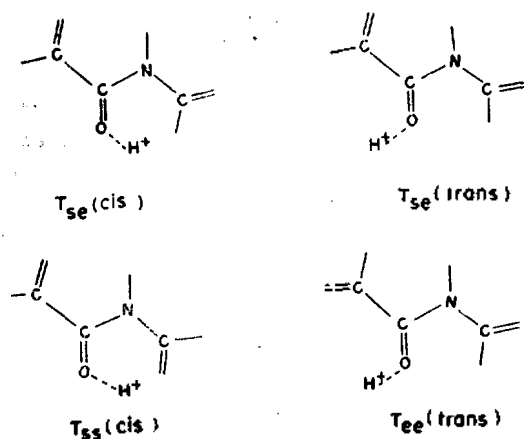
TABLE 4: Energy Components and Composite  $\pi$ -Systems for N-methyl acetamide (a.u.)

(a)	$T_{ss}$	$T_{ss}$	$T_{ss}$	$T_{ss}$	$C_{ss}$	$C_{ss}$	$C_{ss}$	$C_{ss}$	$C_{ss}^b$
$E_T$	-56.7026	-56.7035	-56.7036	-56.7025	-56.6727	-56.7031	-56.6995	-56.6988	-56.6919
$2\sum\epsilon_i$	-27.3472	-27.3552	-27.3512	-27.3490	-27.4022	-27.4298	-27.4376	-27.4230	-27.4154
$V_{nn}$	101.3786	101.2942	101.3593	101.3137	102.5830	102.2884	102.4003	102.3979	102.4284
$V_{ss}$	130.7340	130.6425	130.7116	130.6671	131.8538	131.5617	131.6622	131.6737	131.7049
$\Delta E_T$	0.6	0.1	0.0	0.7	19.4	0.3	2.6	3.0	7.3
$\Delta(2\sum\epsilon_i)$	2.5	-2.5	0.0	1.4	-32.0	-49.3	-54.2	-45.0	-40.3
$\Delta(V_{nn}-V_{ss})$	2.0	2.6	0.0	-0.7	51.3	49.5	56.7	48.0	47.6
Composite <sup>c</sup>	(5 $\pi$ /4)	(6 $\pi$ /5)	2 $\times$ (5 $\pi$ /4)	(6 $\pi$ /5)	(5 $\pi$ /4)	(7 $\pi$ /6)	(6 $\pi$ /5)	(6 $\pi$ /5)	
$\pi$ -system	(4 $\pi$ /4)	(5 $\pi$ /4)		(4 $\pi$ /4)	(4 $\pi$ /4)			(4 /4)	

<sup>a</sup>Relative energies are in kcal/mol. Standard is the  $T_{ss}$  form. <sup>b</sup>A gauche-gauche form, which was obtained by rotating both methyl groups by 30° from the  $C_{ss}$  form. <sup>c</sup>Composite crowded  $\pi$  structures which can contribute to nonbonded interactions. Common structural features are excluded.

TABLE 5: Energy Components For Some Protonated N-Methylacetamide. (in a.u. Except the Relative Values which are in kcal/mol)

	$T_{ss}(C)$	$T_{ss}(T)$	$T_{ss}(C)$	$T_{ss}(T)$
$E_T$	-57.2089	-57.2046	-57.2094	-57.2044
$2\sum\epsilon_i$	-36.4510	-36.3450	-36.4476	-36.3416
$V_{nn}$	109.5456	109.0745	109.4433	109.0855
$V_{ss}$	130.3035	129.9340	130.2051	129.9483
$\Delta E_T$	0.3	3.0	0.0	3.1
$\Delta(2\sum\epsilon_i)$	-2.1	64.4	0.0	66.5
$\Delta V_{nn}-\Delta V_{ss}$	2.5	-61.3	0.0	-63.4



and  $T_{ss}(T)$ . The energy component analysis is given in Table 5.

The  $T_{ss}$  form was shown to be the most stable form for the unprotonated N-methylacetamide (Table 2) but it is the  $T_{ss}(C)$  form which is the most preferred protonated form (Table 5). *Cis*-protonated forms are always preferred to *trans*-protonated forms, as it was the case with protonated acetamide, owing to the much favorable one-electron effect; the stabilization is again provided by overlap of a lone pair on the oxygen atom with  $\sigma^*$  orbital of the C-N bond which is oriented *trans* to the oxygen lone pair.<sup>3</sup>

Predicted changes<sup>3</sup> in atomic and overlap populations based on the  $n-\sigma^*$  conjugative effect are consistent with the results of our computations<sup>13</sup> in Table 6.

Table 5 shows that the  $T_{ss}(C)$  is less favorable sterically but has more favorable one-electron effect over the  $T_{ss}(C)$ . Since both are the *cis*-protonated forms, the

TABLE 6: Populations and Relative Energies for the Protonated  $T_{ss}$  Forms of N-Methylacetamide

Property <sup>a</sup>	Predicted from $n-\sigma^*$ effect	Calculated	
		<i>cis</i>	<i>trans</i>
O Negative charge	<i>cis</i> < <i>trans</i>	-0.142	-0.147
N Negative charge	<i>cis</i> > <i>trans</i>	-0.144	-0.127
$P_{oc}^s$	<i>cis</i> > <i>trans</i>	0.718	0.717
$P_{cn}^s$	<i>cis</i> < <i>trans</i>	0.702	0.704
$\Delta E_T$	<i>cis</i> < <i>trans</i>	0.0	2.7

<sup>a</sup> $P_{oc}^s$  and  $\Delta E_T$  are as described in Table 3.<sup>13</sup>

origin of the difference in one-electron effect can only be of nonbonded interaction type; inspection of  $\pi$ -systems in the two forms shows that the  $T_{ss}(C)$  has a (6 $\pi$ /4) system while the  $T_{ss}(T)$  has a (7 $\pi$ /5) system, the former being more stabilizing according to our 4N+2 over 4N-1 rule.<sup>5</sup>

**Diacetamide.** Total of ten distinct rotamers can be considered for three configurations, *trans-trans*(TT), *trans-cis*(TC), and *cis-cis*(CC), of this compound. Isoconjugate

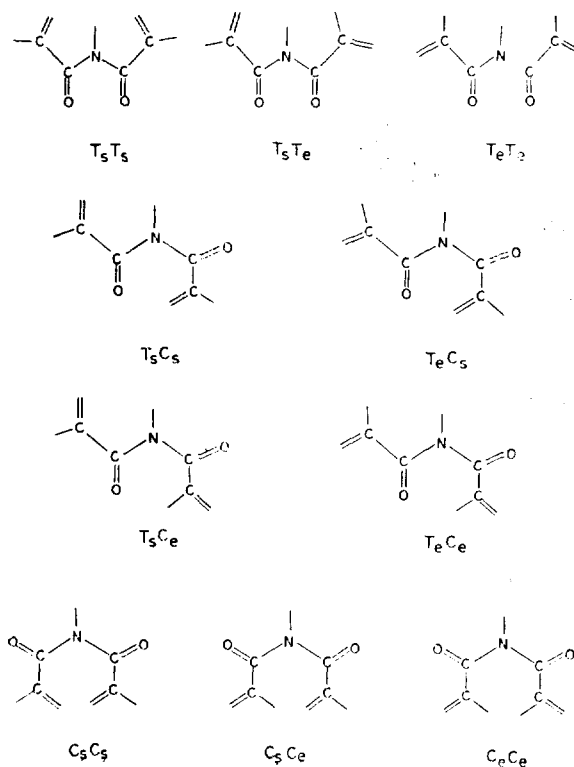


TABLE 7: Energy Component Analyses for Various Forms of Diacetamide. (In a.u. Except the Relative Values which are in kcal/mol. Values in Parenthesis are Relative to the Most Stable Form,  $T_eC_e$ )

	$T_eT_e$	$T_eT_e$	$T_eT_e$	$T_eC_e$	$T_eC_e$	$T_eC_e$	$T_eC_e$	$C_eC_e$	$C_eC_e$	$C_eC_e$
$E_T$	-82.2057	-82.2052	-82.2046	-82.2120	-82.2090	-82.2114	-82.2084	-82.2006	-82.1823	-81.9357
$2\Sigma\epsilon_i$	-36.4970	-36.4888	-36.4806	-36.5752	-36.5502	-36.5684	-36.5438	-36.8872	-36.8926	-36.8154
$V_{nn}$	161.4625	161.4754	161.4887	162.4336	162.7198	162.4464	162.7325	163.7079	164.0032	164.6478
$V_{ee}$	207.1712	207.1918	207.2127	208.0704	208.3786	208.0894	208.3971	209.0213	209.2929	209.7681
$\Delta E_T$	0.0 (4.0)	0.4	0.7	0.0	1.9	0.4	2.3	0.0 (7.2)	11.5	166.2
$\Delta(2\Sigma\epsilon_i)$	0.0 (49.1)	5.1	10.3	0.0	15.7	4.3	19.7	0.0 (-195.8)	-3.4	45.1
$\Delta V_{nn}-\Delta V_{ee}$	0.0 (-45.1)	-4.8	-9.6	0.0	-13.8	-3.9	-17.4	0.0 (202.9)	14.9	121.2
*Composite structures	$2 \times (5\pi/4)$ ( $4\pi/4$ ) ( $4\pi/3$ )	$(5\pi/4)$ ( $4\pi/4$ ) ( $4\pi/3$ )	$2 \times (4\pi/4)$ ( $4\pi/3$ )	$(7\pi/6)$ ( $5\pi/4$ )	$(6\pi/5)$ ( $5\pi/4$ ) ( $4\pi/4$ )	$(7\pi/6)$ ( $4\pi/4$ ) ( $4\pi/4$ )	$(6\pi/5)$ ( $2 \times (4\pi/4)$ ) ( $4\pi/3$ )	$(8\pi/7)$	$(7\pi/6)$ ( $4\pi/4$ )	$(6\pi/5)$ ( $2 \times (4\pi/4)$ )

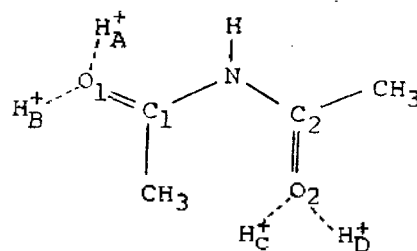
\*Structures common to a configuration are excluded.

models of each rotamer are shown below with designations, and energy component analyses are given in Table 7. We have also listed composite  $\pi$ -structures in the table in order to assess nonbonded interactions.

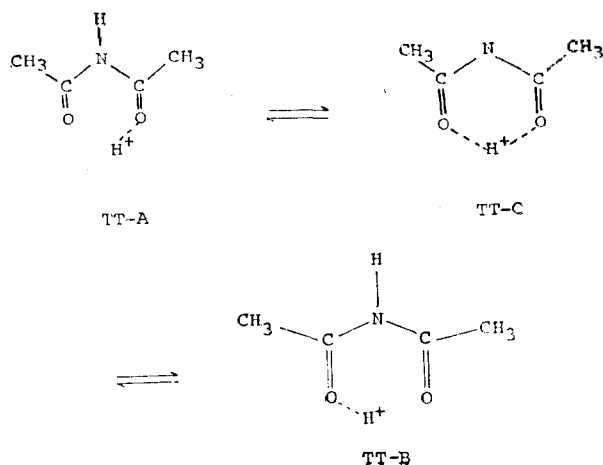
The relative stability of the three configurations is in the order,  $TC > TT > CC$ .<sup>16,1c</sup> The most preferred rotamer in each configuration is the form with both methyl groups staggered,  $T_eT_e$ ,  $T_eC_e$ , and  $C_eC_e$ , while the least favored is that with both methyl groups eclipsed,  $T_eT_e$ ,  $T_eC_e$  and  $C_eC_e$ ; this is because an eclipsed C-methyl group (methyl in an acetyl group) constitutes a  $(4\pi/4)$  system. Three rotamers of TT isomer have a  $(6\pi/5)$  system, (OCNCO), in common and the order of stability,  $T_eT_e > T_eT_e > T_eT_e$ , follows the order of one-electron stabilizing effects,  $\Delta(2\Sigma\epsilon_i)$ . On the other hand, three rotamers of CC isomer have two  $(4\pi/3)$  systems in common and steric effects dominate over one-electron effects in determining the stability;  $C_eC_e > C_eC_e > C_eC_e$ . The relative stability of four rotamers of TC isomer, which has a  $(4\pi/3)$  system in common, again follows the order of one-electron stabilizing effects. It is clearly seen that both the steric repulsions and one-electron stabilizing effects are greater in the CC while they are both smaller in the TT compared to those for the TC configuration. The relative order of one-electron effects for rotamers in each configuration agrees in general with that predicted qualitatively by using additivity of nonbonded effects of composite  $\pi$  structures.<sup>16</sup> One exception is the reversal of the order for  $T_eC_e$ - $T_eC_e$  pair: the former is expected to have greater one-electron stabilizing effect based on number of electrons in a crowded  $\pi$  conjugate chain ( $4N+2$  over  $4N-1$  rule), whereas it is expected to have less attractive nonbonded interaction based on distances between two end atoms (proximity rule)<sup>5</sup>. In fact the former has overlap population of 0.00013 with a distance of 2.6420 Å, while the latter has overlap population of 0.00094 with a distance of 2.3875 Å, between two end atoms. Methyl group in a *trans* acetyl form has a nearly constant rotational barrier of -0.4 kcal/mol;  $\Delta E = (T_eT_e \rightarrow T_eT_e) = \Delta E(T_eT_e \rightarrow T_eT_e) = \Delta E(T_eC_e \rightarrow T_eC_e) = \Delta E(T_eC_e \rightarrow T_eC_e) \cong 0.4$  kcal/mol. This value is somewhat smaller than the corresponding barrier of 0.6 kcal/mol for

methyl groups in acetamide and *trans*-N-methylacetamide; an origin of this discrepancy may well be the different sets of geometrical parameters used in the computation for the two systems as described in CALCULATION.

**Protonated Diacetamide.** For TT and CC configurations only two protonated forms need be considered; *cis*- and *trans*- (relative to C-N) protonations on  $T_eT_e$  and  $C_eC_e$  forms are examined. As expected from the previous results on protonated acetamides, *cis*-protonation was found to be favored in both cases owing to the larger  $n-\sigma^*$  conjugative interactions. For the TC configuration four possible forms, A, B, C and D, are examined with  $T_eC_e$  form. *Cis*-protonation was again found to be the preferred but order of stability was  $A > B > C > D$ . Large steric repulsion caused the C form



to be less favored by 8.0 kcal/mol than the A form. The A form of  $T_eC_e$  was however less stable by 2.1 kcal/mol than the *cis*-protonated  $T_eT_e$  form, TT-A or TT-B: thus the TT



isomer becomes more stable than the TC isomer when protonated. In this respect the protonated form assumed by Laurent *et al.*,<sup>8</sup> in their hydrolysis mechanism of diacetamides a type of protonated TT, seems reasonable.

The proton shifts from one oxygen to another, TT-A $\leftrightarrow$ TT-B, may go through an intermediate TT-C of C<sub>2v</sub> symmetry, which has a barrier height of 56 kcal/mol.

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