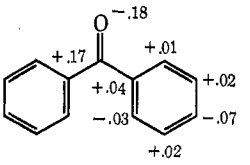

excited-state charge distribution

The charge redistribution in the excited state is not very great. This is the consequence of an "n" orbital which is not localized at oxygen, but significantly delocalized thoughout the molecule. The absence of charge redistribution of a magnitude consistent with the classical picture of a fully localized oxygen lone pair is supported by recent measurements of the dipole moments of benzophenone excited states.[28]

Benzaldehyde has been assumed to have a planar conformation since there is no steric interaction preventing such a conformation. Extended Hückel calculations confirm this assumption. The potential energy curves for the rotation of the aldehyde group away from the plane of the phenyl ring for the ground state and the excited state of benzaldehyde arising from the carbonyl (n,π^*) transition are shown in Figure 7. The calculated barrier to rotation is 0.22 eV for the ground state and 0.79 eV for the excited state. The theoretical analysis is just like that presented for benzophenone, with a predicted higher barrier to internal rotation in the (n,π^*) excited state compared to the ground state.

Acknowledgment. This work was supported by the Petroleum Research Fund of the American Chemical Society and the Public Health Service (GM 13468).

(28) R. M. Hochstrasser and T. S. Lin, *J. Chem. Phys.*, **49**, 4929 (1968).

Energy Parameters in Polypeptides. II. Semiempirical Molecular Orbital Calculations for Model Peptides[1,2]

by J. F. Yan, F. A. Momany,[3] R. Hoffmann, and H. A. Scheraga[4]

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The EHT and CNDO/2 methods have been used to compute charge distributions, dipole moments, energies for internal rotation, electronic orbital configurations, and electronic spectra of formamide, N-methylformamide, N,N-dimethylformamide, acetamide, N-methylacetamide, N,N-dimethylacetamide, and acetyl-L-proline amide. The CNDO/2 method gives more reliable charge distributions and dipole moments than the EHT procedure. However, the EHT procedure is better for treating internal rotation and provides a physical picture for the preference of the *trans* form of the amide group in peptides. Calculations are also carried out for the changes in the charge distributions, dipole moments, energies for internal rotation, electronic orbital configurations, and electronic spectra of these model compounds as the amide group departs from planarity. Some of the data for acetyl-L-prolineamide are represented in the form of a ψ–ω energy contour diagram.

Introduction

At the present time, conformational energy calculations are being carried out for polypeptides, using *empirical* methods.[5] In conjunction with these studies, an examination is being conducted[6,7] of the underlying theoretical basis of the empirical approaches.

In the first paper[8] of this series (designated here as paper I), a semiempirical method was employed to obtain some of the parameters required for the conformational energy calculations. The method of Del Re[9–11] was used to obtain the σ charges, and dipole moment data (as well as computed values of Pullman and Pullman[12]) were used to obtain the π charges. The resulting total charges on all the atoms of the amino acid residues which commonly occur in proteins were then obtained. A similar calculation of the

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(2) Presented before the Division of Biological Chemistry at the 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969.

(3) Special Fellow of the National Institute of General Medical Sciences, National Institutes of Health, 1968–1969.

(4) To whom requests for reprints should be addressed.

(5) See, *e.g.*, H. A. Scheraga, *Advan. Phys. Org. Chem.*, **6**, 103 (1968).

(6) K. D. Gibson and H. A. Scheraga, *Physiol. Chem. Phys.*, **1**, 109 (1969).

partial charges in amino acids had been carried out earlier by Del Re, *et al.*,[13] who computed only the σ charges.[14] In the present paper, we apply more rigorous LCAO–MO methods to various model peptide molecules and compute the charge distributions and resulting dipole moments, the energies for rotation about bonds (including the peptide bond, thereby obtaining the energy barrier and the energy difference between the *cis* and *trans* forms[15]), the electronic orbital configuration, and the electronic spectra of these simple amides.

The extended Hückel theory (EHT) of Hoffmann[16] and the approximate SCF–MO theory (CNDO/2) of Pople and Segal[17] are both used in the computations. These methods, which are reasonably good approximations to exact quantum mechanical calculations, can be applied to molecules of the kind considered here. A comparison of the calculated properties obtained with the EHT and CNDO/2 methods provides a narrow bracketing range of the results one might hope to obtain from exact quantum mechanical calculations. They also provide the physical insight required to establish the validity of *empirical*[18,19] conformational energy calculations for polypeptides, the latter molecules being too large for application of even the approximate EHT and CNDO/2 methods.

The molecules treated in this paper are formamide, N-methylformamide, N,N-dimethylformamide, acetamide, N-methylacetamide, N,N-dimethylacetamide, and acetyl-L-prolineamide. Their structural formulas and the nomenclature conventions[15] are illustrated in Figures 1–3.

Method

The EHT and CNDO/2 methods, both of which attempt to approximate a Hartree–Fock solution of the many-electron problem, are described in detail in the original publications.[16,17] These two approximations differ considerably and thus give rise in some cases to differences in physical properties which, however, constitute a narrow range, as indicated above. The EHT theory treats all valence electrons and includes overlap integrals, but neglects all electron repulsion integrals. The CNDO/2 theory is an SCF method which also treats all valence electrons, employs zero differential overlap, but includes electron interactions explicitly.

The input data for the computer programs[20,21] are given in Table I (atomic coordinates, expressed in terms of bond lengths and bond angles given in Table I) and Table II [(1) Slater orbital exponents, (2) values of s and p Coulomb integrals, and (3) bonding parameters, β]. The molecular geometry of the first six molecules was taken from a compilation of peptide structural data in the literature.[5] The experimental values for formamide[22–24] show the largest deviation from the data in ref 5; however, we have used the data of ref 5 for consistency with all the other molecules. For acetyl-L-

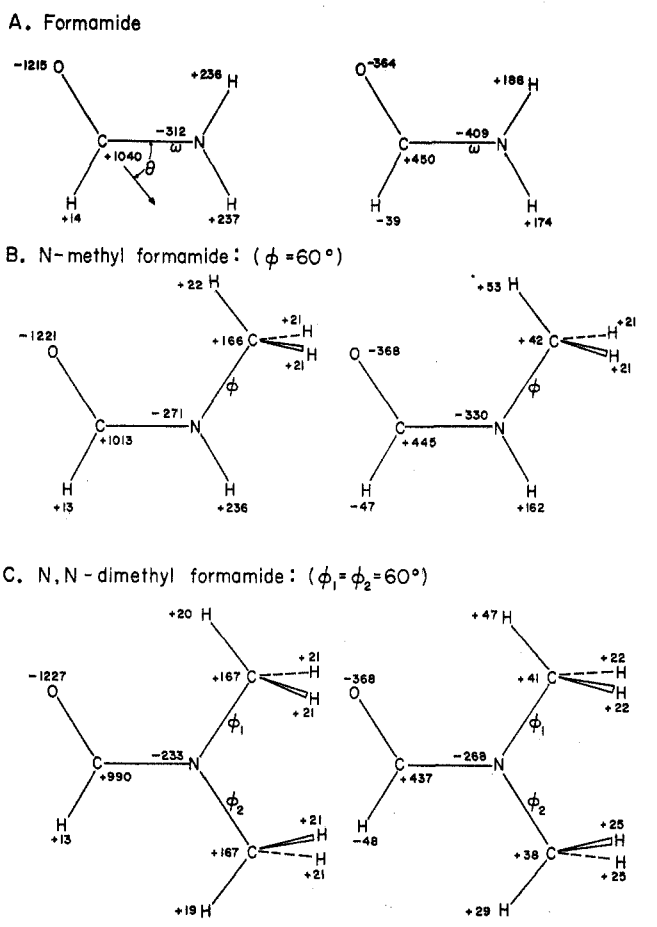

Figure 1. Computed partial charges ($\sigma + \pi$) for the molecules and conformations shown; where not designated explicitly, the conformation is planar; left, EHT (ON); right, CNDO/2 (ON). The values shown should be divided by 100 to obtain electronic charge units. The *trans* conformation (*i.e.*, ω = 0°) is shown in B. The direction of the dipole moment (θ) with respect to the C–N bond is indicated in A; this definition of θ is used for all the molecules considered here.

(7) N. Gō and H. A. Scheraga, *J. Chem. Phys.*, in press.

(8) D. Poland and H. A. Scheraga, *Biochemistry*, **6**, 3791 (1967).

(9) G. Del Re, *J. Chem. Soc.*, 4031 (1958).

(10) G. Del Re, *Theoret. Chim. Acta*, **1**, 188 (1963).

(11) G. Del Re, "Electronic Aspects of Biochemistry," Academic Press, Inc., New York, N. Y., 1963, p 221.

(12) B. Pullman and A. Pullman, "Quantum Biochemistry," Interscience, New York, N. Y., 1963, pp 321 and 661.

(13) G. Del Re, B. Pullman, and T. Yonezawa, *Biochim. Biophys. Acta*, **75**, 153 (1963).

(14) See ref 5, footnote 1, p 133, for further discussion of the differences between the methods of Del Re, *et al.*,[13] and Poland and Scheraga.[8]

(15) J. T. Edsall, P. J. Flory, J. C. Kendrew, A. M. Liquori, G. Nemethy, G. N. Ramachandran, and H. A. Scheraga, *J. Mol. Biol.*, **15**, 399 (1966).

(16) R. Hoffmann, *J. Chem. Phys.*, **39**, 1397 (1963); **40**, 2474, 2480, 2745 (1964).

(17) J. A. Pople and G. A. Segal, *ibid.*, **44**, 3289 (1966).

(18) Further refinement of the computed parameters is being carried out by empirical calculations of crystal structures.[19]

(19) F. A. Momany, G. Vanderkooi, and H. A. Scheraga, *Proc. Natl. Acad. Sci. U. S.*, **61**, 429 (1968).

(20) The version used is substantially that of R. Hoffmann, "EXTHUC—Extended Hückel Theory Calculations," No. 30, QCPE, Indiana University.

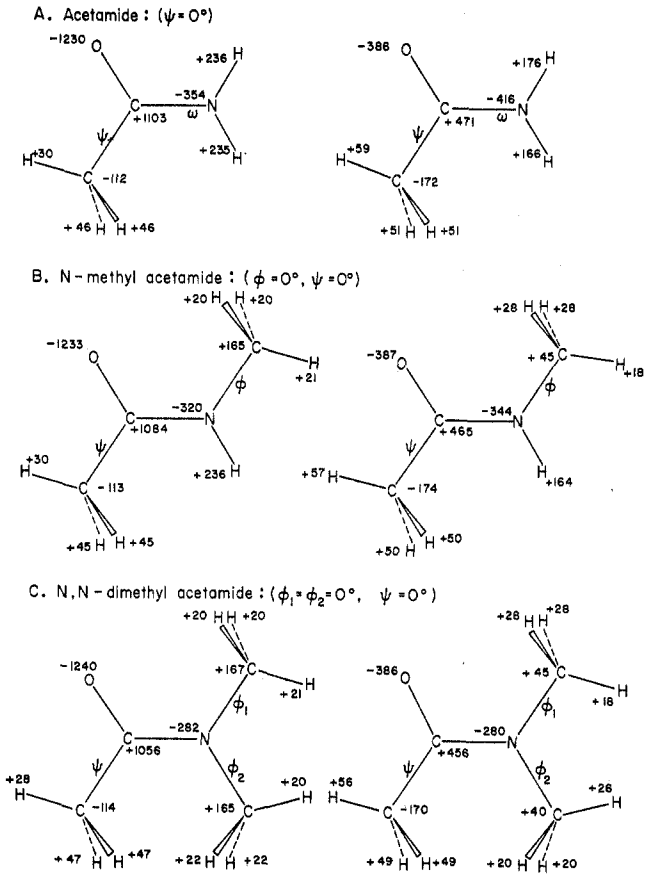

Figure 2. Computed partial charges ($\sigma + \pi$) for the molecules and conformations shown; where not designated explicity, the conformation is planar; left, EHT (ON); right, CNDO/2 (ON). The values shown should be divided by 1000 to obtain electronic charge units. The *trans* conformation (*i.e.*, ω = 0°) is shown in B.

Table I: Molecular Geometry[a,b] of Acetyl-L-prolineamide

Bond distances		Bond angles	
Bond	Bond length, Å	Bond angle	Value, deg
C^{α}_{acetyl}–H	1.09	$\tau[C'C^{\alpha}H]_{acetyl}$	109.5
C^{α}_{acetyl}–C'_{acetyl}	1.53	$\tau[C^{\alpha}C'O]_{acetyl}$	121.0
C'_{acetyl}–O_{acetyl}	1.24	$\tau[C^{\alpha}C'N]_{acetyl}$	118.0
C'_{acetyl}–N	1.34	$\tau[C'NC^{\alpha}]$	121.0
N–C^{α}	1.45	$\tau[NC^{\alpha}C^{\beta}]$	105.0
C^{α}–H	1.00	$\tau[C^{\alpha}C^{\beta}C^{\gamma}]$	106.6
C^{α}–C^{β}	1.50	$\tau[C^{\beta}C^{\gamma}C^{\delta}]$	111.3
C^{β}–C^{γ}	1.47	$\tau[C^{\gamma}C^{\delta}N]$	104.1
C^{γ}–C^{δ}	1.45	$\tau[C^{\delta}NC']$	126.0
C^{δ}–N	1.46	$\tau[NC^{\alpha}C']$	111.0
$C^{\beta,\gamma,\delta}$–H	1.09	$\tau[HC^{\alpha}C^{\beta}]$	112.0
C^{α}–C'_{amide}	1.53	$\tau[HC^{\alpha}C']$	104.0
C'_{amide}–O_{amide}	1.24	$\tau[C^{\alpha}C'O]_{amide}$	120.0
C'_{amide}–N_{amide}	1.32	$\tau[C^{\alpha}C'N]_{amide}$	115.0
N_{amide}–H	1.00	$\tau[C'NH]_{amide}$	123.0

[a] The geometry in this table was maintained fixed for all values of the dihedral angles of internal rotation. The proline ring is planar. [b] The data for all compounds except acetyl-L-prolineamide were taken from Tables 5 and 6 of ref 5, except that the aliphatic C–H bond length was taken as 1.09 Å.

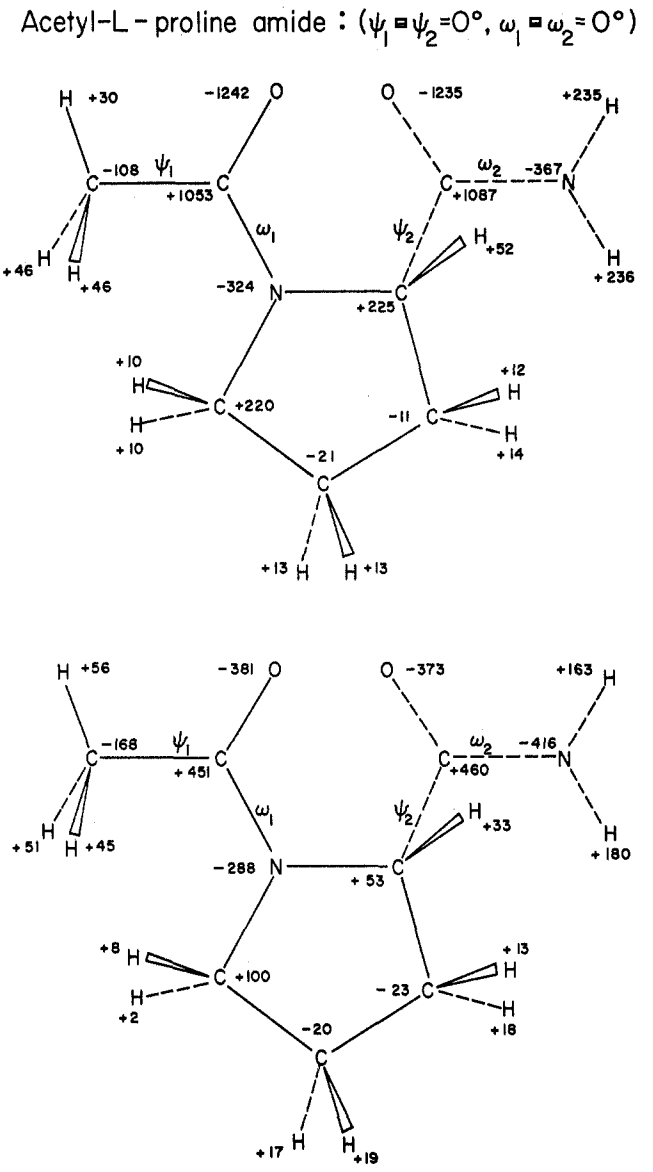

Figure 3. Computed partial charges ($\sigma + \pi$) for the molecules and conformations shown. The portion indicated by the solid lines is planar; top, EHT (ON); bottom, CNDO/2 (ON). The values shown should be divided by 1000 to obtain electronic charge units. The conformation about ω_1 is the *trans* one.

prolineamide, the parameters were selected from a composite of available X-ray data.[25–29] All bond angles

(21) Our version of the CNDO/2 method was written by P. Clark and J. Swenson. A similar program is available; see G. A. Segal, "CNDO/2—Molecular Calculations with Complete Neglect of Differential Overlap," No. 91, QCPE, Indiana University.

(22) C. C. Costain and J. M. Dowling, *J. Chem. Phys.*, **32**, 158 (1960).

(23) R. J. Kurland and E. B. Wilson, *ibid.*, **27**, 585 (1957).

(24) J. Ladell and B. Post, *Acta Cryst.*, **7**, 559 (1954).

(25) Y. C. Leung and R. E. Marsh, *ibid.*, **11**, 17 (1958).

(26) J. Fridrichsons and A. McL. Mathieson, *ibid.*, **15**, 569 (1962).

(27) J. Zussman, *ibid.*, **4**, 493 (1951).

(28) J. Donohue and K. N. Trueblood, *ibid.*, **5**, 419 (1952).

(29) S. Arnott and S. D. Dover, *ibid.*, **B24**, 599 (1968).

Table II: Parameters for EHT and CNDO/2 Methods[a]

Atom	Slater orbital exponent	α(2s)	α(2p)	α(1s)	β
		EHT[b]			
C and C′	1.625	−21.400	−11.400		
O	2.275	−32.300	−14.800		
N	1.950	−26.000	−13.400		
H	1.300			−13.600	
		(CNDO/2)[c]			
C and C′	1.625	−14.051	−5.572		−21.00
O	2.275	−25.390	−9.111		−31.00
N	1.950	−19.316	−7.275		−25.00
H	1.300			−7.176	−9.00

[a] The α's are the usual valence state ionization potentials in the EHT method and are the averages of the ionization potentials and electron affinities in the CNDO/2 method. The α's and β are expressed in electron volts. β is an estimate of the resonance integral. [b] Reference 16. [c] Reference 17.

and bond lengths were maintained constant (rigid geometry) in the calculations reported here, to avoid increase in computational time, even though it is recognized (and confirmed from some preliminary calculations with flexible geometry) that the results will be somewhat altered by this restriction. All other input data are given in the original papers.[16,17]

The output from the programs includes (1) the calculated energy levels and total energy of the molecule; (2) the wave functions; (3) the partial charges localized on each atom;[30,31] and (4) the bond order or overlap population. Since these results are obtained for each set of values of the dihedral angles of rotation, it is possible to study the variation of the energy, partial charges, dipole moments, and electronic orbital distributions, with changes in the dihedral angles.

The computational times on an IBM 360/65 computer ranged from 5–20 sec for a single EHT calculation to several minutes for a CNDO/2 calculation. The longer times and cost made it necessary to limit the number of conformations studied by the CNDO/2 method; however, a sufficient number of calculations were performed to map out all the necessary conformational information and to make critical comparisons of the results.

Results and Discussion

The results of the calculations are presented and discussed in five sections: (1) charges, (2) dipole moments, (3) energies for internal rotation, and (4) electronic spectra. All of the molecules, except acetyl-L-prolineamide, are considered together as a group so that differences between these similar molecules may be compared easily; acetyl-L-prolineamide will be treated in section 5.

1. Charges. The computed total charges ($\sigma + \pi$) for the seven molecules considered here, in given conformations, are shown in Figures 1–3. Two features are of interest. First, the charges computed by the two methods differ, in some cases even as far as the sign is concerned; in all cases, the EHT method gives very high charge separation for the carbonyl groups, while the CNDO/2 method gives values for the charges on this group in reasonable agreement with our earlier[8] theoretical studies. Both methods give nearly equivalent charge distributions on the methyl groups and around the nitrogen atom. Second, as found in paper I,[8] the hydrogen atoms of the methyl groups have significant charges.

Since formamide has been examined quite extensively by a number of theoretical approaches, we consider the charge distribution for this molecule in some detail and compare it with that obtained by other methods (see Table III). It can be seen that the CNDO/2 calculations are sensitive to variations in geometry and in the Slater orbital exponent of the hydrogen atom. Differences also arise from the use of the overlap-normalized (ON) Mulliken population analysis as compared to the CNDO/2 population analysis. For example, in the calculations of Pullman and Berthod,[32] the observed differences are due only to experimental differences in geometry from microwave[22] and crystal structure[24] studies. Similarly, in the "*ab initio*" calculations of Basch, *et al.*,[33] differences in charges arose because of

(30) There are two distinct ways in which charges may be assigned to atoms, depending on whether or not the overlap is included in the normalization of the molecular orbitals. The primary output of a CNDO/2 calculation is an electron density derived with the assumption of neglect of overlap. To compare such charges to the Mulliken gross atomic populations,[31] which are computed by the EHT program, it is possible to transform the CNDO/2 electron densities to an overlap-normalized basis (which will be designated as ON throughout this paper). We will have occasion to refer to both types of CNDO/2 population analysis in the course of our discussion.

(31) R. Mulliken, *J. Chem. Phys.*, **23**, 1833, 1841, 2338, 2343 (1955).

(32) A. Pullman and H. Berthod, *Theoret. Chim. Acta*, **10**, 461 (1968).

Table III: Various Charge Distributions for Formamide,[a] in Electronic Units

Atom	EHT[b-d]	(CNDO/2)[b-d]	(CNDO/2)[b,e-g]	(CNDO/2)[e-h]	(CNDO/2)[b-e]
O	−1.215	−0.365	−0.338	−0.336	−0.373
C′	1.040	0.450	0.358	0.356	0.441
N	−0.312	−0.409	−0.236	−0.237	−0.424
H(C′)	0.014	−0.039	−0.046	−0.046	−0.027
H_1	0.236	0.188	0.142	0.120[i]	0.204
H_2	0.237	0.174	0.120	0.142[i]	0.178
	(CNDO/2)[f,g,i,k]	(CNDO/2)[f,g,k,l]	(*ab initio*)[i,m]	(*ab initio*)[i,n]	(*ab inito*)[n,o]
O	−0.354	−0.306	−0.41	−0.377	−0.429
C′	0.348	0.367	0.36	0.258	0.295
N	−0.223	−0.262	−0.86	−0.758	−0.745
H(C′)	−0.044	−0.055	0.17	0.152	0.134
H_1	0.146	0.132	0.37	0.368	0.383
H_2	0.127	0.123	0.37	0.357	0.362

[a] H_1 and H_2 refer to the hydrogen atoms which are *cis* and *trans*, respectively, to the oxygen atom. [b] This work. [c] Exponent for Slater orbital of hydrogen atom = 1.3. [d] Mulliken population analysis (ON) (ref 31). [e] Pople–Gordon geometry (ref 34). [f] Exponent for Slater orbital of hydrogen atom = 1.2 (chosen for comparison with Pople and Gordon data[h]). [g] CNDO/2 population analysis. [h] Calculation by Pople and Gordon (ref 34). [i] We believe that these were interchanged in the Pople–Gordon paper (ref 34). [j] Geometry from microwave data (ref 22). [k] Calculation by Pullman and Berthod (ref 32). [l] Geometry from X-ray data (ref 24). [m] Calculated using a Gaussian orbital basis set (ref 56). [n] Calculated using a Gaussian orbital basis set (ref 33). [o] Geometry from microwave data (ref 23).

Table IV: Charge Distribution around Peptide Bond, in Units of Electronic Charge

Atom	EHT[a,b]	(CNDO/2)[a,c]	(CNDO/2)[a,b]	Ooi, *et al.*[d]	Poland–Scheraga[e]	Brant, *et al.*[f]	Schellman and Oriel[g]
C′	+1.08	+0.36	+0.47	+0.45	+0.32	+0.39	+0.43
O	−1.23	−0.36	−0.39	−0.42	−0.42	−0.39	−0.39
N	−0.32	−0.18	−0.34	−0.30	−0.20	−0.28	−0.30
H(N)	+0.24	+0.10	+0.16	+0.27	+0.20	+0.28	+0.26

[a] For N-methylacetamide in the *trans* form; all other data also pertain to the *trans* conformation. [b] Mulliken population analysis (ON).[30,31] [c] CNDO/2 population analysis. [d] Reference 35. [e] Reference 8. [f] Reference 36. [g] Reference 37.

differences in two reported sets of microwave geometries.[22,23] Likewise, in the calculations reported here and in those of Pople and Gordon,[34] there is an influence of geometry on the resulting charges. However, the results of all the CNDO/2 calculations are in reasonable agreement with each other, while the "*ab initio*" and EHT charges differ from those obtained by the CNDO/2 method. It is clear from previous experience with the EHT method that it tends to exaggerate charge separation in polar molecules. It should also be noted that the size of the basis set and the degree of approach to Hartree–Fock accuracy significantly influence the charge distribution obtained by "*ab initio*" methods. The CNDO/2 results, though sensitive to the parameters and geometry used, appear to provide the most reasonable estimate of the charge distribution in formamide as well as in the other molecules considered here.

Using N-methylacetamide as a model for the polypeptide chain, we obtain the data of Table IV for the charge distribution around the peptide bond. For comparison, the results of other workers are also included in Table IV. The CNDO/2 results are in general agreement with data from the literature,[8,35–37] whereas the EHT data differ considerably. In all the results obtained here, the sum of the peptide group charges is negative, in agreement with the results of paper I.[8] Again, it seems valid to conclude that the charges obtained by the CNDO/2 method are reasonable ones and may be used in conformational energy calculations[5] in which Coulomb's law is applied to point-charge distributions. The most serious omission in the calculation of electrostatic energies in earlier calculations[5] would seem to be the assignment of zero charge to carbon atoms and to the hydrogen atoms

(33) H. Basch, M. B. Robin, and N. A. Kuebler, *J. Chem. Phys.*, **47**, 1201 (1967).

(34) J. A. Pople and M. Gordon, *J. Amer. Chem. Soc.*, **89**, 4253 (1967).

(35) T. Ooi, R. A. Scott, G. Vanderkooi, and H. A. Scheraga, *J. Chem. Phys.*, **46**, 4410 (1967).

(36) D. A. Brant, W. G. Miller, and P. J. Flory, *J. Mol. Biol.*, **23**, 47 (1967).

(37) J. A. Schellman and P. Oriel, *J. Chem. Phys.*, **37**, 2114 (1962).

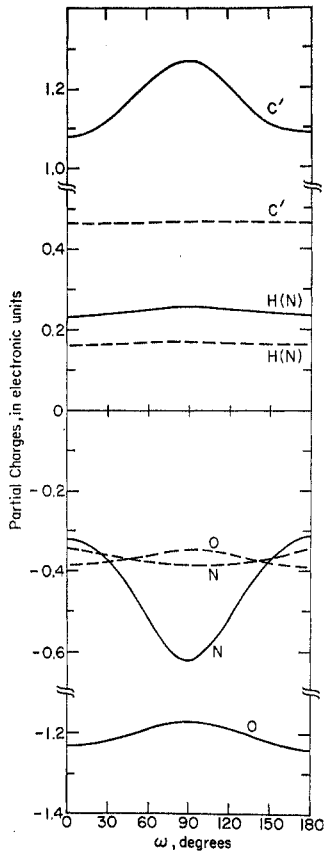

Figure 4. Variation of partial charges on the atoms of the amide group [C′, O, H, H(N)] with ω, for N-methylacetamide. The solid and dashed lines are EHT and CNDO/2 results, respectively.

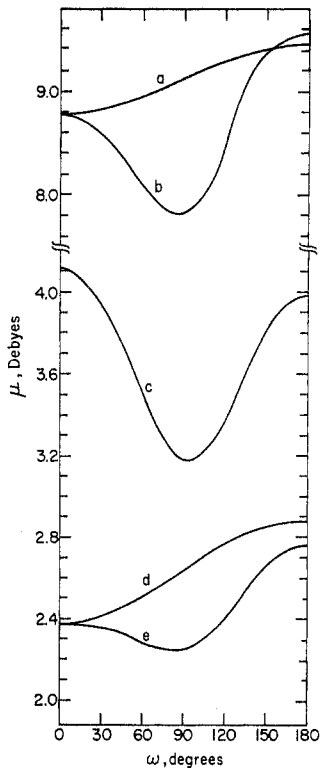

Figure 5. Variation in the dipole moment of N-methylacetamide with ω. Curve a, monopole calculation with EHT charges taken as constant and equal to those of the conformation $\phi = 60°$, $\psi = 0°$, $\omega = 0°$; curve b, monopole calculation with EHT charges as obtained for the conformation of lowest energy for each value of ω; curve c, monopole calculation with CNDO/2 charges and Pople-Segal correction[39] as obtained for the conformation of lowest energy for each value of ω; curve d, monopole calculation with CNDO/2 (ON) charges taken as constant and equal to those of the conformation $\phi = 60°$, $\psi = 0°$, $\omega = 0°$; curve e, monopole calculation with CNDO/2 (ON) charges as obtained for the conformation of lowest energy for each value of ω.

attached to them; this point will be considered in a later paper of this series.

If ω, the dihedral angle for rotation around the peptide bond, is allowed to vary and the calculations repeated for specific values of ω, we obtain the variations of charge with ω shown in Figure 4. The variations of charge with ω are greater in the EHT than in the CNDO/2 results. The charges on the C′ and N atoms vary most upon rotation about the peptide bond; thus, assuming that the two theoretical methods show the extremes of variation of the partial charges, it appears that a study of the C^{13} chemical shift of the carbonyl carbon may provide information about the electronic distribution as a function of ω. Using our computed bond orders for N-methylacetamide and Pople's theory of carbon chemical shifts,[38] we predict a maximum nmr shift (EHT) of 30 ppm (from $\omega = 0°$ to $\omega = 90°$) and a minimum shift (CNDO/2) of 0.3 ppm. We would expect the true value to lie somewhere between these limits, and that such nmr studies would detect changes in ω by approximately 15° or more. Another conclusion from the data of Figure 4 is that the partial charges are nearly identical at $\omega = 0°$ (*trans*) and $\omega = 180°$ (*cis*) for both methods. This result confirms the use of equivalent charge distributions for conformational calculations for both *cis* and *trans* forms.

It is of interest to note that the charge on the carbonyl oxygen atom decreases as ω departs from 0 and 180°. Assuming that a hydrogen bond contains an electrostatic contribution, one might expect a departure of ω from 0 and 180° to lead to a reduced strength of a hydrogen bond involving this oxygen atom. An opposite, although weaker effect appears at the amide hydrogen atom, whose charge increases slightly; this might enhance the strength of a hydrogen bond involving this hydrogen atom. These points will be considered in detail in later papers of this series, where their possible effects on helix formation as well as their influence on solvent interactions will be discussed.

The geometrically nonequivalent hydrogens of the methyl groups carry slightly different charges, which *change* by about 0.01 electron upon rotation of the methyl group. These *changes* may most probably be ignored in conformational energy calculations;[5] however,

(38) J. A. Pople, *Mol. Phys.*, 7, 301 (1964).

Table V: Dipole Moments in Debye Units[a,b]

Molecule	EHT (ON)	CNDO/2	CNDO/2 (corrected)[c]	θ,[d] deg	μ, (exptl)[e]	θ (exptl), deg
Formamide	8.75 (T)	2.46 (T)	4.00 (T)	−37.7	3.71[f]	−39.6[f]
N-Methyl-formamide	8.85 (T)	2.40 (T)	3.97 (T)	−38.8	3.82[g]	
N,N-Dimethyl-formamide	9.59 (T)	2.52 (T)	3.83 (T)	−37.8	3.80[g]	
Acetamide	8.78 (T)	2.53 (T)	4.15 (T)	−44.3	3.75,[g] 3.72[h]	
N-Methyl-acetamide	8.80 (T)	2.40 (T)	4.12 (T)	−44.3	3.71 (T),[g] 4.39 (T)[i]	
	9.50 (C)	2.61 (C)	3.98 (C)	−42.5	3.40 (C)[i]	
N,N-Dimethyl-acetamide	9.60 (T)	2.51 (T)	3.97 (T)	−44.3	3.80[g,h]	

[a] Dipole moments were calculated classically, using the charges of the minimum-energy conformation. [b] T and C refer to *trans* and *cis* conformations, respectively. [c] Contribution to the dipole moment due to the displacement of atomic electron charges away from the center of the atom (see ref 34 and 39). [d] See Figure 1 for direction of dipole moment. This column was computed from the CNDO/2 (corrected) results. [e] The value of μ in ref 23 was obtained from microwave data. The values of μ given in footnote *h* of this table may be considered as experimental values since they were calculated from dielectric constants of solutions; the values from footnote *i* of this table and ref 40 are estimates from bond moments. [f] Reference 22. [g] Reference 39. [h] R. M. Meigham and R. H. Cole, *J. Phys. Chem.*, **68**, 503 (1964). [i] W. D. Kumler and C. W. Porter, *J. Amer. Chem. Soc.*, **56**, 2549 (1934).

the significance of the *magnitudes* of these proton charges for conformational energy calculations and for other physical properties, such as proton nmr spectroscopy and ORD, may have to be taken into account.

2. *Dipole Moments.* As a general check on the validity of the computed charges, we may use them to compute dipole moments, μ, which may be compared with experimental values. Dipole moments, computed from the calculated charges, are listed in Table V, together with experimental values. The dipole moments were calculated classically from the EHT and CNDO/2 charges of the minimum energy conformation, taking into account the charges on all of the atoms. Those calculated using the CNDO/2 basis were corrected by adding a term primarily due to the lone-pair electrons, using equations of Pople and Segal.[39] The dipole moments computed with this correction then seem to show the best agreement with experimental results, as was demonstrated earlier[34] for a large number of other molecules, providing additional confidence in the charges computed by the CNDO/2 method.

Figure 5 shows the variation of μ with ω for N-methylacetamide. Different results are obtained depending on whether the charges on each atom are kept constant (at the values for the *trans* form) or are allowed to vary as ω varies. Since we expect the charges to vary with ω (see Figure 4), the usual procedure of ignoring the variation of charge with ω in empirical conformational energy calculations[5] (*i.e.*, the use of curves a or d) is clearly erroneous. However, as already pointed out, the charges are similar at $\omega = 0$ and 180° (although the values of μ differ because of the different geometry); thus, the *same* charges can be used in a comparison of *cis* and *trans* forms in empirical calculations,[5] *provided ω does not depart from these values.* Since curve c gives the closest agreement with the *limited* experimental data, we again conclude that the CNDO/2 method provides the best estimate of the charge distribution.

3. *Energies for Internal Rotation.* The effect of steric interactions and conjugation on barriers to rotation has been well documented,[16,41] and the vast amount of literature in this field will not be reviewed here. However, it is necessary to consider the approximations which have been made in treating rotation potentials and nonbonded interactions to use them in conformational analyses of polypeptides and proteins. Hopefully, use of the theoretical methods applied in this paper will shed some light on this very difficult problem. One should expect that most features usually associated with steric interactions will manifest themselves in the computed rotational barriers since interactions among *all* the atoms of the molecule are included in both the EHT and CNDO/2 calculations; however, in the procedures used here, it is not possible to separate out those energies associated with any given type of interaction. Also, while the approximate molecular orbital methods used here do not appear to include the attractive portion of the van der Waals interactions between nonbonded atoms, nevertheless it will be shown that

(39) J. A. Pople and G. A. Segal, *J. Chem. Phys.*, **43**, S136 (1965).

(40) S. Mizushima, T. Simanouti, S. Nagakura, K. Kuratani, M. Tsuboi, H. Baba, and O. Fujioka, *J. Amer. Chem. Soc.*, **72**, 3490 (1950).

(41) For recent work, see: L. C. Allen, *Chem. Phys. Lett.*, **2**, 597 (1968); W. H. Fink and L. C. Allen, *J. Chem. Phys.*, **46**, 2261, 2267 (1967); J. P. Lowe and G. Parr, *ibid.*, **44**, 3001 (1966); for earlier work, see R. M. Pitzer and W. N. Lipscomb, *ibid.*, **39**, 1995 (1963), and references cited therein.

they do give the essential features of the rotational energy functions.

For the purpose of considering the rotational energies, we provide in Table VI a listing of the total energies computed for several conformations. For each molecule, the conformation of lowest energy has been assigned the energy zero.

The energies for rotation about the peptide bond in N-methylacetamide, acetamide, and N-methylformamide, respectively, are shown in Figure 6. The

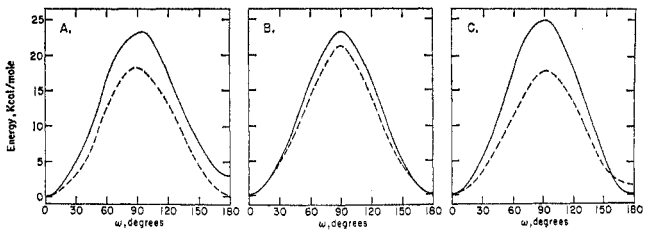

Figure 6. Energy for rotation about the peptide bond in (A) N-methylacetamide, (B) acetamide, and (C) N-methylformamide. The solid and dashed lines are EHT and CNDO/2 results, respectively.

EHT and CNDO/2 methods both give similar shapes and magnitudes for the rotational energy. The energy scales have been normalized to agree at $\omega = 0°$ (the *trans* conformation); hence, the difference in energy between the *cis* and *trans* conformations appears at $\omega = 180°$ (the *cis* conformation). The calculated results are in reasonable agreement with the experimental values shown in Table VII. Unfortunately, there is so much deviation in the experimental results for a given molecule that it is impossible to make any but a qualitative comparison.

In addition to the well-known preference of synthetic and natural polypeptides for the *trans* conformation around the peptide bond, there exists some fragmentary evidence for a *trans* preference in the model compounds N-methylformamide[42] and N-methyl acetamide.[43,44] Neither EHT nor CNDO/2 methods reproduce the somewhat uncertain experimental quantities, but the trend predicted from the EHT calculations, namely a small *trans* preference in N-methylformamide and a greater differential in N-methylacetamide, appears most consistent.

The preference for the *trans* conformation of N-methylformamide may actually be due to consequent proximity of the methyl substituent and the carbonyl oxygen. In the *trans* conformation, the methyl group is *cis* to the carbonyl group. The peptide unit, as a four π-electron system, is isoelectronic with the allyl anion. There exists experimental evidence for the greater stability of a *cis*-methyl allyl anion.[45] Other examples of the stabilization of alkyl substituents *cis* to a four π-electron system are cited by Owen.[46] A theoretical rationalization of the preference for *cis*-methyl groups has been presented.[47] On this basis, we would expect the methyl group to be *cis* to the oxygen in the N-methylformamide (*trans* conformation of the peptide).

In analyzing the still greater preference of N-methylacetamide for a *trans* conformation, one is inclined to attribute a significant role to a destabilization of the *cis* conformation as a consequence of the steric repulsion of the *cis*-methyl groups. The simple steric argument gains support from the following set of numerical observations (Table VI).

1. The barriers to internal rotation of the single methyl groups in N-methylformamide and in acetamide remain small (less than 1 kcal/mol) regardless of the rotation of the amide group out of planarity (see Figure 7).

2. The barriers to internal rotation of the two methyl groups of N-methylacetamide remain small and comparable to the corresponding barriers in N-methylformamide and in acetamide *only* when the angle of twist of the amide, ω, is less than 120°. At greater angles of twist, as the *cis* conformation of N-methylacetamide is approached, the methyl group barriers rise sharply. This magnification of methyl group barriers, obtained by both EHT and CNDO/2 methods, is highly indicative of a sharpening of the potential walls due to steric repulsions.

The steric effect appears to dictate a peculiar geared motion which couples methyl group internal rotations to amide twisting in N-methylacetamide. The data in Table VI yield the following itinerary of optimum ϕ and ψ for a given range of ω.

ω	ϕ	ψ
0,30,60	60	0
90	0	0
120	60	0
150,180	0	0

Figure 7 shows the computed ω dependence of the methyl group rotations in N-methylformamide and in acetamide. The preferred conformations are illustrated in Figures 1B and 2A, respectively. The trends exhibited in Figure 7 result from both calculations, and so it becomes important to present an interpretation.

Both barriers are relatively small at $\omega = 0°$. The

(42) R. M. Badger and H. Rubalcava, *Proc. Nat. Acad. Sci. U. S.* **40**, 12 (1954).

(43) I. Suzuki, *Bull. Chem. Soc. Jap.*, **35**, 540 (1962).

(44) T. Miyazawa, *J. Mol. Spectrosc.*, **4**, 155 (1960).

(45) S. Bank, A. Schriesheim, and C. A. Rowe, Jr., *J. Amer. Chem. Soc.*, **87**, 3244 (1965), and references therein.

(46) N. L. Owen, *Proc. Chem. Soc.*, 264 (1963).

(47) R. Hoffmann and R. A. Olofson, *J. Amer. Chem. Soc.*, **88**, 943 (1966).

Table VI: Total Energies for Various Conformations of Several Molecules[a,b]

	Dihedral angle, deg				Energy, kcal/mol	
	ϕ_1	ϕ_2	ψ_1	ω	EHT	CNDO/2
Formamide				0	0.00	0.00
				30	5.35	
				60	17.79	
				90	25.26	20.29
N-Methylformamide	0			0	0.33	0.25
	60			0	0.00	0.00
	0			30	5.78	
	60			30	5.33	
	0			60	18.26	
	60			60	18.00	
	0			90	25.60	18.22
	60			90	25.62	18.05
	0			120	18.05	
	60			120	17.86	
	0			150	5.87	
	60			150	5.36	
	0			180	0.71	1.41
	60			180	0.09	1.18
N,N-Dimethylformamide	0	0		0	3.47	
	60	0		0	1.40	
	60	60		0	0.00	0.00
	0	0		90	28.42	
	60	0		90	26.77	
	60	60		90	25.81	15.03
Acetamide			0	0	0.00	0.00
			60	0	0.21	0.25
			0	30	5.14	
			60	30	5.41	
			0	60	16.98	
			60	60	17.51	
			0	90	24.01	21.72
			60	90	24.80	22.41
N-Methylacetamide	0		0	0	0.30	0.24
	0		60	0	0.48	0.54
	60		0	0	0.00	0.00
	60		60	0	0.18	0.30
	0		0	30	5.47	
	0		60	30	5.72	
	60		0	30	5.08	
	60		60	30	5.32	
	0		0	60	17.18	
	0		60	60	17.73	
	60		0	60	17.00	
	60		60	60	17.54	
	0		0	90	24.16	18.91
	0		60	90	24.84	19.47
	60		0	90	24.17	18.80
	60		60	90	24.90	19.39
	0		0	120	18.42	
	0		60	120	18.78	
	60		0	120	18.09	
	60		60	120	18.12	
	0		0	150	7.76	
	0		60	150	11.22	
	60		0	150	10.11	
	60		60	150	12.42	
	0		0	180	2.92	−0.09
	0		60	180	7.64	1.19
	60		0	180	6.70	0.75
	60		60	180	18.03	9.01

Table VI (*Continued*)

	Dihedral angle, deg				Energy, kcal/mol	
	ϕ_1	ϕ_2	ψ_1	ω	EHT	CNDO/2
N,N-Dimethylacetamide	0	0	0	0	2.03	
	0	0	60	0	6.76	
	0	60	0	0	0.00	0.00
	0	60	60	0	4.69	
	60	0	0	0	4.08	
	60	0	60	0	15.39	
	60	60	0	0	2.99	
	60	60	60	0	14.26	
	0	0	0	30	6.91	
	0	0	0	60	17.45	
	0	0	0	90	23.14	
	0	0	60	90	23.74	
	0	60	0	90	21.48	
	0	60	60	90	22.12	
	60	0	0	90	21.48	
	60	0	60	90	22.12	
	60	60	0	90	20.52	16.04
	60	60	60	90	21.20	

[a] The dihedral angles are those shown in Figures 1 and 2. [b] For each molecule, the zero value corresponds to the conformation of lowest energy.

Table VII: Barriers to Rotation about the Peptide Bond, and *cis–trans* Energy Difference, in Kilocalories per Mole, for Minimum-Energy Values of ϕ and ψ

Molecule	Barrier (EHT)	Barrier (CNDO/2)	$\Delta E_{cis-trans}$ (EHT)	$\Delta E_{cis-trans}$ (CNDO/2)	Barrier (exptl)	$\Delta E_{cis-trans}$ (other estimates)
Formamide	25.26	20.29			18 ± 3[a] 16.8–21.3[b]	
N-Methyl-formamide	25.60 (0–90°)	18.05 (0–90°)			28.0–28.5[d]	
			0.09	1.18, 1.25[c]		>2.0[e]
	25.51 (90–180°)	16.87 (90–180°)			14.0[f]	
N,N-Dimethyl-formamide	25.81	15.03			6.5 ± 0.3[g] 22.0 ± 3[h] 9.6 ± 1.5[i] 21.0[j] 21.0[k] 20.6[l]	
Acetamide	24.01	21.72				
N-Methyl-acetamide	24.16 (0–90°)	18.80 (0–90°)				
			2.92	−0.09		3.0[d], 1.6[m]
	21.24 (90–180°)	18.89 (90–180°)			14.0[f]	
N,N-Dimethyl-acetamide	20.52	16.04			17.4[j] 18.2 ± 3[n] 19.0[h] 17.5[o]	

[a] B. Sunners, L. H. Piette, and W. G. Schneider, *Can. J. Chem.*, **38**, 681 (1960). [b] H. Kamei, *Bull. Chem. Soc. Jap.*, **41**, 2269 (1968). Values listed are E_a^{rot}. [c] Reference 32. Theoretical value by CNDO/2 method. [d] Reference 43. Estimated from spectroscopic force constants. [e] Reference 42. Estimated from infrared spectroscopic data. [f] T. Miyazawa, *J. Chem. Phys.*, **34**, 691 (1961). Estimated from spectroscopic force constants. [g] E. S. Gore, D. J. Blears, and S. S. Danyluk, *Can. J. Chem.*, **43**, 2135 (1965). Value listed is ΔH^*. [h] H. S. Gutowsky and C. H. Holm *J. Chem. Phys.*, **25**, 1228 (1956). Value listed is ΔF^*. [i] G. Fraenkel and C. Franconi, *J. Amer. Chem. Soc.*, **82**, 4478 (1960). Value listed is E_a^{rot}. [j] M. T. Rogers and J. C. Woodbrey, *J. Phys. Chem.*, **66**, 540 (1962). Value listed is ΔF^*. [k] M. Rabinovitz and A. Pines, *J. Amer. Chem. Soc.*, **91**, 1585 (1969). Value listed is ΔF^*. [l] A. Mannschreck, A. Mattheus, and G. Rissmann, *J. Mol. Spectrosc.*, **23**, 15 (1967). Value listed is ΔF^*. [m] Reference 44. Estimated from infrared spectroscopic data. [n] R. C. Neuman, Jr., and V. Jonas, *J. Amer. Chem. Soc.*, **90**, 1970 (1968). Value listed is ΔF^*. [o] G. N. Ramachandran and V. Sasisekharan, *Advan. Protein Chem.*, **23**, 365 (1968).

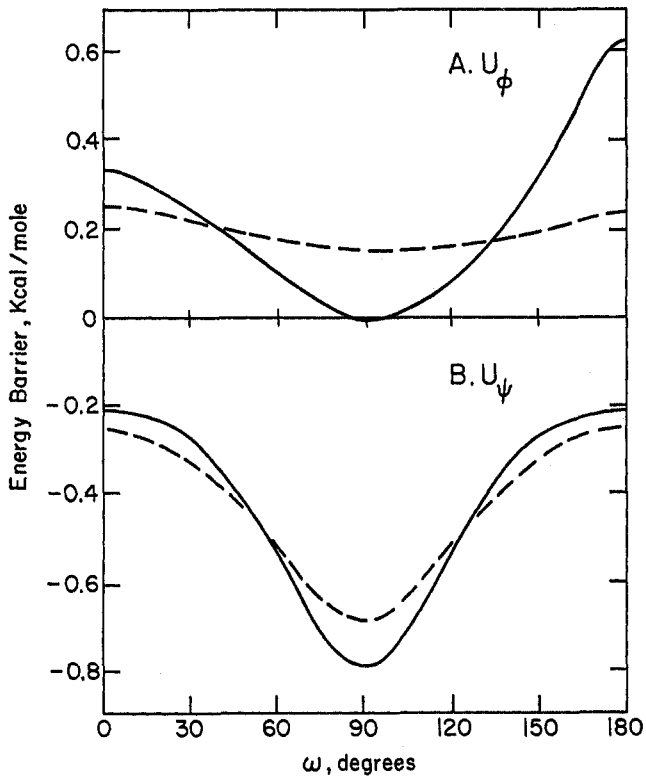

Figure 7. Barriers to rotation of methyl groups as functions of ω for (A) N-methylformamide and (B) acetamide. The solid and dashed lines are EHT and CNDO/2 results, respectively. The values of U_ϕ and U_ψ are the differences in energy $E_{0°} - E_{60°}$ for ϕ and ψ, respectively.

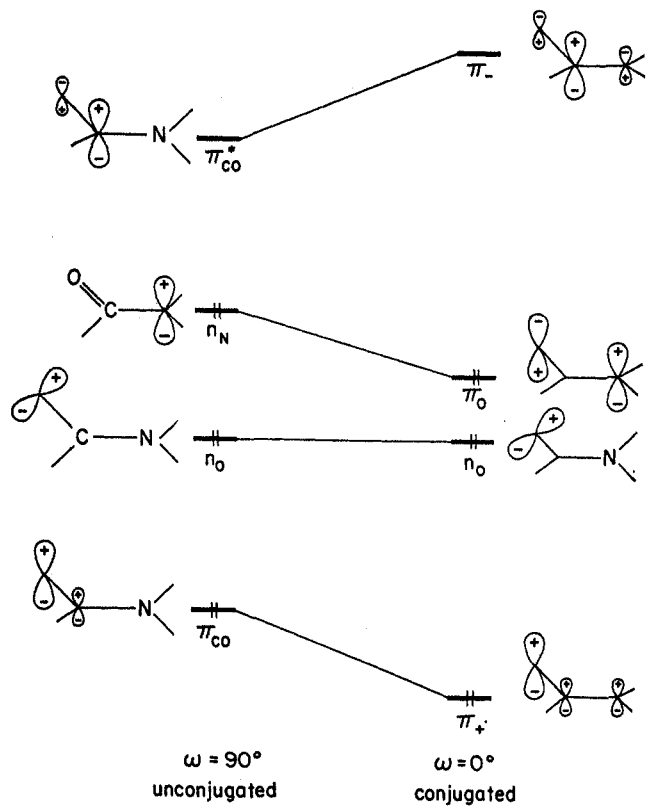

Figure 8. Qualitative description of energy position and composition of molecular orbitals of a typical peptide unit at ω = 90 and 0°. See text for derivation.

rotors are of the form CH_3–XAB with X trigonal. Were A and B equivalent, the barrier would be sixfold, and such barriers are known to be small.[48–51] When A and B are nonequivalent, a threefold component is introduced. This dominates the general barrier shape, but the barrier height generally remains small as long as the trigonal configuration at X is maintained.

The preferred conformations at ω = 0° are easily understood if one recalls that, in propylene[52,53] and acetaldehyde,[54] the conformations in which a hydrogen eclipses the C=C or C=O double bond are favored by 1.98 and 1.16 kcal/mol, respectively. The acetamide case is then entirely analogous to the model compound acetaldehyde. The rise in this barrier as ω approaches 90° may be explained as follows. Whereas the NH_2 and CO groups are conjugated at ω = 0°, the peptide delocalization is broken at ω = 90°, and the carbonyl group is unconjugated. At ω = 0° the peptide delocalization weakens the C=O bond and strengthens the C–N bond, thus making the A,B groups in the CH_3–CAB rotor (A = O, B = NH_2) more equivalent. In the N-methylformamide case at ω = 0 or 180°, the methyl hydrogens prefer to eclipse N–COH, which has partial double bond character, in analogy with propylene and acetaldehyde. As ω is changed to 90°, this double bond character is lost; thus, the NAB rotor has an A (nonconjugated COH) more like a B (H on N) than in the ω = 0° geometry, and the barrier decreases accordingly.

It is appropriate at this point to show that the information we have obtained so far concerning charges and barriers is consistent with a simple molecular orbital description of the peptide bond. The description derived below has some further important consequences for the spectral characteristics of nonplanar peptide units (considered in section 4).

Consider a carbonyl π system interacting with a lone pair on an adjacent amine group. In the absence of interaction or equivalently when the amine group is twisted 90° out of the plane of the carbonyl, the orbitals of the noninteracting systems are as shown at the left of Figure 8. In order of increasing energy these are: a π_{CO} orbital of the carbonyl group which, as a consequence of the greater electronegativity of oxygen, possesses a larger contribution of the oxygen 2p orbital; a lone pair of the carbonyl oxygen, n_O; a lone pair,

(48) E. Tannenbaum, R. J. Myers, and W. D. Gwinn, *J. Chem. Phys.*, **25**, 42 (1956).
(49) W. M. Tolles, E. T. Handelman, and W. D. Gwinn, *ibid.*, **43**, 3019 (1965).
(50) R. E. Naylor and E. B. Wilson, *ibid.*, **26**, 1057 (1957).
(51) H. D. Rudolph and M. Seiler, *Z. Naturforsch.*, **20**, 1682 (1965).
(52) E. Hirota, *J. Chem. Phys.*, **45**, 1984 (1966).
(53) D. R. Lide and D. E. Mann, *ibid.*, **27**, 868 (1957).
(54) R. W. Kilb, C. C. Lin, and E. B. Wilson, *ibid.*, **26**, 1695 (1957).

assumed to be pure 2p, of nitrogen, n_N; a low-lying π^*_{CO} orbital of the carbonyl group which, in contrast to the π_{CO} level, is heavy at the carbon atom.

We then "turn on" the interaction between the carbonyl group and the amine or equivalently rotate the amine group into conjugation from its original perpendicular orientation. Perturbation theory is a powerful guide to the interaction of orbitals. As a result of interaction, the orbital energies and wave functions are modified as follows[55]

$$E_i = E_{i0} + \sum_{j \neq i} \frac{|H'_{ij}|^2}{E_{i0} - E_{j0}}$$

$$\psi_i = \psi_{i0} + \sum_{j \neq i} \frac{H_{ij}'\psi_j}{E_{i0} - E_{j0}}$$

The following set of qualitative rules emerges. (1) Orbital interactions are pairwise additive. (2) Energy levels "repel" each other. (3) The extent of interaction between two levels is approximately proportional to some function of their overlap and inversely proportional to their separation in energy. (4) The consequence of the interaction of two orbitals is a mixing of their wave functions in the following manner. The lower energy orbital mixes into itself the upper one in a bonding way, whereas the upper one mixes into itself the lower one in an antibonding manner. The extent of interaction is governed by the same factors as in (3) above.

Applying these guide lines to the case at hand, we obtain the energy shifts and delocalized wave functions shown at the right-hand side of Figure 8. These are justified in the following way. (1) π_{CO} is stabilized by interaction with n_N and mixes into itself the latter orbital in a bonding way. It becomes π_+, the lowest energy allylic orbital. (2) π^*_{CO} is destabilized by interaction with n_N and mixes into itself n_N in an antibonding way. It emerges as π_-. (3) n_O, lying in the nodal plane of the π orbitals, is (to first order) unaffected by the interaction. (4) n_N interacts with both π_{CO} and π^*_{CO}. It is difficult to weigh qualitatively the strength of the two interactions. After interaction n_N takes on the form

$$n'_N = \pi_0 = n_N + c_1\pi^*_{CO} - c_2\pi_{CO}$$

where c_1 and c_2 are the mixing coefficients. The computational methods which we have used disagree on the relative sizes of c_1 and c_2. The EHT calculations place the node in π_0 between C and O, implying $c_1 > c_2$; the CNDO/2 calculations (as well as the "*ab initio*" Gaussian computations[56]) put the node between C and N, implying $c_2 > c_1$. Both procedures agree in that n_N is stabilized as a consequence of interaction.

These qualitative arguments are confirmed in detail by examination of the calculated molecular orbitals, and the important consequences of the interaction are as follows. (1) There exists a sizable barrier to rotation of the amine group out of conjugation. This follows from the increase in energy of π_+ and π_0 as they become π_{CO} and n_N. (2) As the amine group rotates out of planarity there should be some electron transfer from the carbonyl group to the amine nitrogen. Thus, as the rotation occurs, C and O should become more positive and N more negative. This is a consequence of the strong interaction of n_N (donor) with π^*_{CO} (acceptor). On the rotated, unconjugated side, the two electrons in the n_N orbital are all on N while, in the planar, conjugated system, the two electrons in π_0 are mostly on N, but with a significant fraction in the carbonyl group.

(3) As the amine group rotates out of planarity, there should occur a significant red shift and intensity diminution of the $\pi_0 \rightarrow \pi_-$ electronic transition, the first intense band of a peptide group (1700–1950 Å). The energy shift follows from the motion of levels shown in Figure 8. The hypochromic effect follows from the transformation of a $\pi \rightarrow \pi^*$ transition in the planar form to essentially an intramolecular charge-transfer transition, $n_N \rightarrow \pi^*_{CO}$, in the rotated form. The weaker peptide transition, $n_0 \rightarrow \pi_-$, ~2200 Å, should also be shifted to lower energy on twisting, but less than the $\pi_0 \rightarrow \pi_-$ transition.

4. *Electronic Spectra.* Amides are characterized by two primary electronic transitions in the ultraviolet region. A weak transition, occurring at approximately 2200 Å, has been assigned to an $n \rightarrow \pi^*$ excitation, more specifically to $n_0 \rightarrow \pi_-$.[57,58] The intense vacuum ultraviolet transition of peptides is located in the region 1700–1950 Å, and has been assigned to the $\pi_0 \rightarrow \pi_-$ excitation.[57-59] More recently a new band has been observed between the two above-mentioned transitions and has been tentatively assigned to a $n \rightarrow \sigma^*$ excitation.[33]

In the previous section we have outlined the qualitative spectral changes we would expect in a twisted ($\omega \neq 0$ or 180°) peptide chromophore. The calculations confirm our qualitative conclusions. Figure 9 illustrates the one-electron energy gap for $n_0 \rightarrow \pi_-$ and $\pi_0 \rightarrow \pi_-$ excitations as a function of ω, as obtained from EHT calculations. Since these calculations do not include electron interaction explicitly they cannot provide accurate singlet and triplet state energies. The one-electron gap is at best considered as a configuration energy, the average of singlet and triplet states. This is the reason for the "incorrect" ordering of the $n_0 \rightarrow$

(55) J. N. Murrell, "The Theory of the Electronic Spectra of Organic Molecules," John Wiley & Sons, Inc., New York, N. Y., 1963.

(56) M. A. Robb and I. G. Csizmadia, *Theoret. Chim. Acta*, **10**, 269 (1968).

(57) H. D. Hunt and W. T. Simpson, *J. Amer. Chem. Soc.*, **75**, 4540 (1953).

(58) E. E. Barnes and W. T. Simpson, *J. Chem. Phys.*, **39**, 670 (1963).

(59) D. L. Peterson and W. T. Simpson, *J. Amer. Chem. Soc.*, **77**, 3929 (1955); **79**, 2375 (1957).

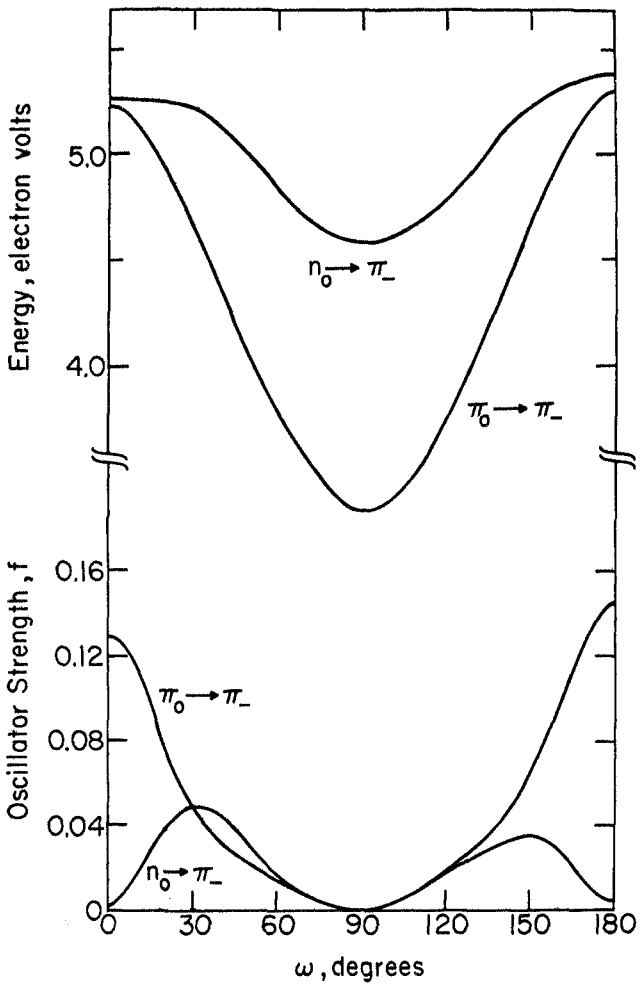

Figure 9. Computed dependence on ω of energies and oscillator strengths for $n_0 \rightarrow \pi_-$ and $\pi_0 \rightarrow \pi_-$ transitions in N-methylacetamide.

π_- and $\pi_0 \rightarrow \pi_-$ transition in Figures 8 and 9. However, *trends* in this configuration energy are, from our experience, reliable indicators of spectral shifts. Figure 9 also shows for the two transitions the calculated oscillator strengths,[60] which are proportional to the intensities of the electronic transition.

The important conclusions are as follows. Both (n,π^*) and (π,π^*) peptide transitions should be red shifted on twisting out of planarity. The effect should be more extreme for the (π,π^*) transition, and so it is likely that, at a certain angle of twist, the two bands might cross. The intensity of the (π,π^*) band should diminish sharply with twisting. The computed intensity of the (n,π^*) band has maxima around $\omega = 30$ and 150°. The latter behavior was not anticipated by our simple argument and remains to be tested experimentally.

There appear to be no proper model compounds, *i.e.*, peptides with ω deviating significantly from 0 or 180°, to test these predictions. One can devise sterically hindered molecules for this purpose, *e.g.*, derivatives of N,N-dimethylacetamide in which all three

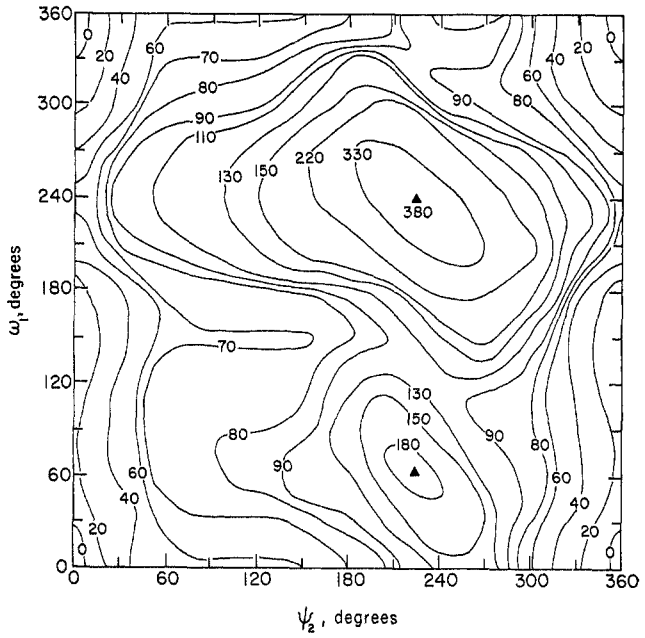

Figure 10. Conformational energy contour diagram (EHT) of acetyl-L-prolineamide for $\psi_1 = \omega_2 = 0°$ at all values of ψ_2 and ω_1. The energies are in units of kilocalories per mole relative to zero around $\psi_2 = \omega_1 = 0°$. The solid triangles refer to maxima in the energy surface.

methyl groups have bulky groups attached to them. The synthesis of some appropriate derivatives is planned in this laboratory.

5. *Acetyl-L-prolineamide.* Since poly-L-proline undergoes a *cis–trans* interconversion,[61] whereas polyamino acids having amide groups with an unsubstituted NH do not, it was of interest to see if the peptide bond in a model proline compound, acetyl-L-prolineamide, differed from that in, say, N-methylacetamide.

The charges of acetyl-L-prolineamide are shown in Figure 3. As in the case of the other N-methyl compounds of Figures 1 and 2, the charges on carbons attached to the proline nitrogen are positive. The other two carbons in the proline ring are slightly negative, as was observed in previous calculations[16] on hydrocarbons.

An energy contour map of ω_1 *vs.* ψ_2, computed at 30° intervals in both angles, using the EHT method, is shown in Figure 10. The large steric hindrances in this molecule lead to very high energies in most of the ψ–ω map. Also, in contrast to the other molecules considered here, the energy function for rotation about the peptide bond is very asymmetric, as illustrated in Figure 11.

From Figure 10, it can be seen, first of all, that, at

(60) These are computed correctly, *i.e.*, with all two-center terms included. We would like to thank J. Howell for making his transition moment program available to us. In Figure 9, the oscillator strength,[65] *f*, has been computed using the calculated transition energies.

(61) I. Z. Steinberg, W. F. Harrington, A. Berger, M. Sela, and E. Katchalski, *J. Amer. Chem. Soc.*, 82, 5263 (1960).

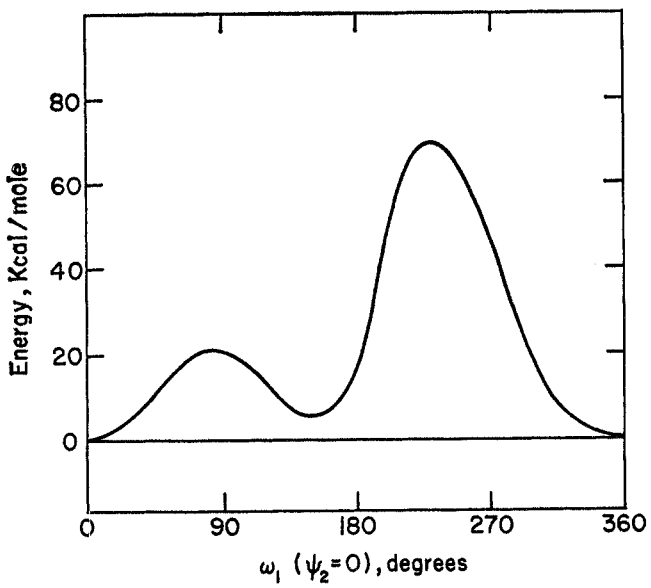

Figure 11. Variation of energy of acetyl-L-prolineamide with ω_1 at $\psi_2 = 0°$ (taken from the data of Figure 10).

$\omega_1 = 0°$ (*trans*), the energy rises rapidly as ψ_2 increases from 0 to 60° and then levels off between $\psi_2 = 60$ and 150°; these high energies are probably the result of interactions between the amine hydrogens and the C^β hydrogens. The very high energy between $\psi_2 = 240$ and 270° (at $\omega_1 = 0°$) arises primarily from interactions between the amine hydrogens and the acetyl oxygen; this bad contact can be relieved somewhat by varying ω from 0 to *ca.* −30°. Thus, for $\omega = 0°$, the range of low-energy values of ψ_2 is very small. A second point of interest in Figure 10 is that the low-energy *cis* conformation (at $\psi_2 = 0°$) lies near $\omega_1 = 150°$ rather than at $\omega_1 = 180°$ (see also Figure 11); *i.e.*, the stable *cis* conformation should be nonplanar. Planarity could be achieved (*i.e.*, the minimum-energy *cis* conformation could be brought to 180°) by changing some bond angles. Available experimental evidence[62,63] indicates that both conditions exist, *i.e.*, some variation in bond angles from "normal" values and also some departure from planarity of the amide group. As in the case of the *trans* conformation, the low-energy path for variation of ψ_2, for the *cis*-amide (*i.e.*, starting from $\omega_1 = 150°$), would involve some variation in ω_1, *viz.*, from $\omega_1 = 150$ to 120° as ψ_2 increases beyond $\sim 210°$.

The activation energy for the *cis–trans* interconversion in poly-L-proline has been found[61,64] to be 20–23 kcal/mol. While the detailed mechanism for this interconversion is not known, it is of interest to consider the activation energy for the reversible thermal *cis–trans* interconversion. Our calculations serve as a model for the latter process. Figure 11 shows the computed energy profile as ω_1 is varied at $\psi_2 = 0°$. The numerical value of the barrier between $\psi_2 = 0$ and 150° is 22.4 kcal/mol which is similar to those of amides with unsubstituted NH groups. Even though the values of $\Delta E_{cis-trans}$ (5.3 and 1.2 kcal/mol by the EHT and CNDO/2 procedures, respectively) are somewhat greater than for N-methylacetamide, poly-L-proline undergoes the *cis–trans* interconversion whereas polyamino acids with unsubstituted NH groups do not. Until we know the mechanism of the *cis–trans* interconversion, and whether stable conformations exist for *cis*-peptides, we cannot account for the difference in behavior between proline and other peptides. Calculations on prolylproline and other dipeptides in the *cis* and *trans* forms, as well as the influence of nonplanarity of the proline ring, are in progress.

Another important feature of Figure 11 is that the barriers between the *trans* (0°) and *cis* (150°) forms differ according to the path; *i.e.*, at $\psi_2 = 0°$, the *cis–trans* conversion would appear to follow a path $\omega_1 = 150°_{min} \rightarrow 90°_{max} \rightarrow 0°_{min}$ rather than the path $\omega_1 = 150°_{min} \rightarrow 240°_{max} \rightarrow 360°_{min}$. According to Figure 10, ψ_2 would probably remain at 0° as ω_1 varies, for the *fixed geometry* used in the calculation of Figures 10 and 11.

A few points on the ψ–ω energy contour diagram of acetyl-L-prolineamide were computed by the CNDO/2 method. The *cis* conformation occurs at 180° and, in general, the barriers due to nonbonded interactions (steric effects) are lower than those found by the EHT procedure.

The availability of these results for acetyl-L-prolineamide, *i.e.*, the accessibility of conformations with nonplanar amide groups, may help rationalize theoretical and experimental results on the optical rotatory properties[65] of this molecule.

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(62) G. N. Ramachandran and C. M. Venkatachalam, *Biopolymers*, **6**, 1255 (1968).

(63) G. N. Ramachandran, *ibid.*, **6**, 1494 (1968).

(64) A. R. Downie and A. A. Randall, *Trans. Faraday Soc.*, **55**, 2132 (1959).

(65) J. A. Schellman and E. B. Nielsen, "Conformations of Biopolymers," G. N. Ramachandran, Ed., Vol. 1, Academic Press, London, 1967, p 109.