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A Note on the Torsional Potential Function $V(\phi)$ in the Dipeptide Model*

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The studies made on N-methyl acetamide (NMA), N-ethyl acetamide (NEA), N-isopropyl acetamide (NIA), using semi-empirical quantum chemical methods have indicated that NMA is not the proper model compound for arriving at the form of $V(\phi)$, whereas NEA and NIA molecules are suggested as model systems for arriving at the form of the potential function $V(\phi)$. The present calculations have indicated that $V(\phi)$ is of the form $\frac{1}{2}V_\phi(1+\cos 3\phi)$ and not $(1-\cos 3\phi)$; however the value of barrier height V_ϕ was found to be very small. So it is suggested that there is no need of separately adding the $V(\phi)$ term in empirical potential energy calculations.

Key words: Torsional potential function $V(\phi)$ – Dipeptide model

1. Introduction

In the classical partitioned potential energy approximation on a dipeptide model of a polypeptide chain, the total potential energy is decomposed into different *a priori* contributions. These contributions are generally expressed in the form of empirical formulae, which are derived from simple model molecules and are then summed up to obtain the total potential energy. The total potential energy is generally expressed as

$$V_{\text{tot}} = V_{\text{nb}} + V_{\text{es}} + V_{\text{hb}} + V(\phi) + V(\psi),$$

where V_{nb} denotes the interaction between nonbonded atoms, V_{es} denotes the electrostatic interaction and V_{hb} the hydrogen bond energy, $V(\phi)$ and $V(\psi)$ the intrinsic torsional potentials about the adjoining single bonds.

The intrinsic torsional potential is usually given by

$$V(\theta) = \frac{V_0}{2}(1 \pm \cos m\theta),$$

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where V_0 is the value of the barrier height, m is the integer which depends on the rotational symmetry of the torsional potential and θ represents the torsional angle. The forms of these functions are usually derived from comparison with experimental data on model compounds and from semiempirical quantum mechanical calculations on these compounds. In our earlier communication [1] we have discussed the form of $V(\psi)$, derived from available crystal structure data of simple peptides, proteins, IR studies on amides and from quantum chemical calculations made on model compounds. In the case of $V(\phi)$, both the forms $V_0/2(1+\cos 3\phi)$ and $V_0/2(1-\cos 3\phi)$ have been used in the literature [2–6]. The value of V_0 is usually small and varies from 0.6 to 1.5 kcal/mole.

In order to throw some light on the form of the torsional potential function $V(\phi)$, we report in this note the results of our calculations made on simple amides such as N-methyl acetamide (NMA), N-ethyl acetamide (NEA) and N-isopropyl acetamide (NIA), using semi-empirical quantum chemical methods such as IEHT [7], CNDO/2 [8] and INDO [9].

2. Results

The molecule NMA is usually considered to be a good model compound for the purpose of obtaining the torsional potential about the N–C^{α} bond in a dipeptide. Thus, several groups have applied semi-empirical [6, 10, 11] and *ab initio* [12, 13] quantum chemical methods to arrive at a minimum energy conformation for NMA as well as the barrier to rotation about the single bond. As is now well-known, the results obtained from these quantum chemical methods depend on input geometry of the small molecule as well as the assumptions involved in the methods and hence lead to controversial conclusions. For instance, the calculations carried out by Pullman and others using *ab initio* [12] and PCILO [6] methods showed that the molecule NMA in its planar conformation has the minimum energy when a C–H bond of the C-methyl group *eclipses* the C=O bond and similarly the C–H bond of the N-methyl group *eclipses* the N–H bond as shown in Fig. 1a. However, the results of the calculations carried out by Shipman and Christoffersen [13], using their *ab initio* method, showed that the molecule would have minimum energy when the N–H bond and one of the C–H bonds of the methyl group are in the staggered conformation (as shown in Fig. 1b), while the C=O *eclipses* the C–H of the C-methyl group. The only difference between Fig. 1a and b is in the conformation of N-methyl group. To resolve this apparent discrepancy in the conformation of N-methyl group we have done calculations on NMA molecule initially using the geometry of the peptide skeleton as given by Ramachandran and Sasisekharan [2]. This would correspond approximately to the Pauling-Corey [14] geometry for the peptide unit. The calculations were performed using different semi-empirical quantum chemical methods such as IEHT, CNDO/2, and INDO. The energy of the molecule was calculated using these methods for different values of the dihedral angles ϕ and ψ. The results obtained are given in Table 1, which clearly show that all these methods give energy minima for the same values of ϕ irrespective of the value of ψ. For comparison we have also given the results of Shipman and Christoffersen [13] in Table 1,

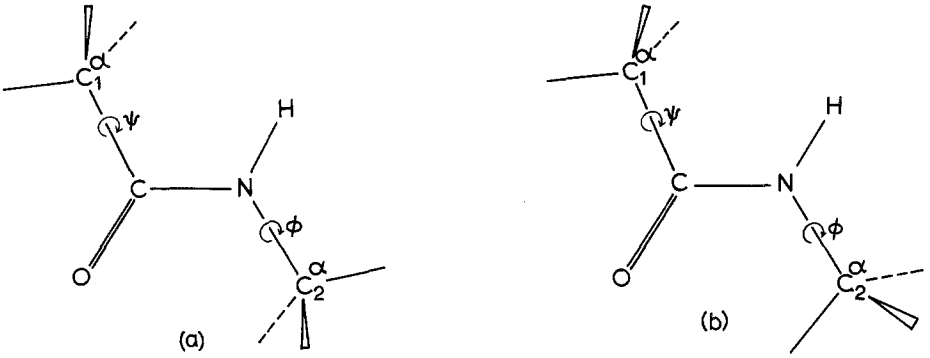

Fig. 1a and b. Conformation of the N-methyl acetamide molecule. (a) $\phi = 180°$ and $\psi = 180°$, the equilibrium conformation corresponding to Refs. [6] and [12]. (b) $\phi = -120°$ and $\psi = 180°$, the equilibrium conformation corresponding to Ref. [13] and present calculations

Table 1. Energy values in kcal/mole for NMA with Pauling-Corey geometry for the peptide skeleton. The energy of the conformation (−120°, 180°) was taken to be 0.0 kcal/mole

(ϕ, ψ) in deg.	Method used			
	CNDO/2	INDO	IEHT	*ab initio* from Ref. [13]
(−120, 180)	0.00	0.00	0.00	0.00
(180, 180)	0.37	0.35	0.74	0.69
(−120, −120)	0.41	0.39	0.94	1.10
(180, −120)	0.78	0.67	1.29	1.82

who have used the same geometry for the peptide skeleton. Thus, these calculations show that as long as the input geometry of the molecule is the same, at such gross level, the positions of minima obtained from these semi-empirical quantum chemical methods are not different. So, for convenience further calculations were carried out using only the CNDO/2 method.

The CNDO/2 method was employed for calculating the conformational energy of NMA with different geometries of the peptide skeleton. The geometries used were (1) as given in the Ref. [6] by Pullman's group, (2) as given in Ref. [15], and (3) as given in Ref. [2]. The angle ϕ was varied at 30° intervals and ψ was kept fixed at 180°. The results obtained are given in Table 2. The energy minimum in the first column corresponds to $\phi = -180°$ which agrees with the calculations reported earlier, made using PCILO [6] and *ab initio* methods [12], for this geometry. However, the energy minimum in the other columns, which have different input geometries, is at $\phi = -120°$. The fact that the application of the CNDO/2 method leads to the same results as that obtained using the PCILO method, would indicate that the apparent discrepancies between the results reported by Pullman and others are only due to the differences in the geometry of the peptide skeleton and not because of the different methods used.

Table 2. Energy values in kcal/mole for NMA molecule obtained using CNDO/2 method for different geometries of the peptide skeleton (ψ at 180°). The energy of the conformation (−120°, 180°) was taken to be 0.0 kcal/mole

ϕ	Geometry used by Pullman *et al.* Ref. [6]	P.C. geometry Ref. [2]	Average geometry Ref. [15]
180°	−0.40	+0.37	+0.25
−150°	−0.21	+0.19	+0.12
−120°	0.0	0.0	0.0
− 90°	−0.21	+0.19	+0.12

Thus, the results given in Table 2 show that the position of the energy minimum for NMA is sensitive to the input geometry, particularly at the nitrogen atom. In the geometry used by Pullman and others [6], the angles at nitrogen were significantly different from the corresponding angles at nitrogen in the geometry for the peptide unit as given by Pauling and Corey [14]. The results given in Table 1, as well as those in Table 2, also indicate that the total energy difference between the maximum and the minimum for the rotation about the N–C^{α} bond is of the order of kT, so that the N-methyl group of NMA can freely rotate. Thus NMA cannot be considered as a model compound for determining the form of $V(\phi)$, because the position of the minimum is sensitive to the choice of input geometry, and the rotation of the N-methyl group is more or less free.

The calculations are repeated for N-ethyl acetamide (NEA) using the CNDO/2 method with different peptide skeleton geometries, as has been done in the case of NMA. In the NEA molecule, the ethyl group was fixed in the usual manner with C–C = 1.53 Å and N–$\hat{C}$–C = 109°28′. The results thus obtained are given in Table 3. They indicate that the positions of the energy minima obtained by varying ϕ are not sensitive to the input geometry. The energy minima with respect to ϕ are found to be at −60°, +60°, +180°. The total energy differences between minima and maxima vary with the input geometry of the peptide, and these variations are not large in the region in which steric interactions do not play a dominant role.

Table 3. Energy values in kcal/mole as obtained using CNDO/2 method of NEA (ψ at 180°). The conformation (−120°, 180°) was taken to be 0.0 kcal/mole

ϕ	Geometry used by Pullman *et al.* Ref. [6]	P.C. geometry Ref. [2]	Average geometry Ref. [15]
180°	−0.98	−0.23	−0.40
−150°	−0.57	−0.19	−0.28
−120°	0.0	0.0	0.0
− 90°	−0.18	+0.17	+0.15
− 60°	−0.61	−0.07	−0.19
− 30°	+3.02	+0.20	+0.07
0°	+3.21	+0.06	−0.04

Table 4. Energy values in kcal/mole as obtained using CNDO/2 method for NIA. The geometry used for the peptide skeleton is that of Pauling and Corey (ψ at 180°). The energy value for the conformation (−120°, 180°) was taken to be zero

ϕ	180°	−150°	−120°	−90°	−60°	−30°	0°	+30°	+60°
Energy in kcal/mole	−0.53	−0.14	0.0	−0.13	−0.53	+0.01	+0.22	+0.21	−0.55

Similarly, the calculations on N-isopropylacetamide (NIA) gave the energy minima at $\phi = -60°$, $+60°$, 180° (see Table 4) as in the case of NEA, for the input geometry corresponding to the one given in Ref. [2]. The calculations carried out by Kopple (personal communication) using the CNDO/2 method on N-methyl formamide (NMF) N-ethyl formamide (NEF) and N-isopropyl formamide (NIF) gave similar results like NMA, NEA and NIA as far as positions of the minima and maxima are concerned.

3. Discussion

Thus, our present studies on the NMA, NEA and NIA molecules, with different geometries for the peptide skeleton, indicate that the form of the intrinsic torsional potential function $V(\phi)$ should be approximated to the form obtained either in NEA, or NIA, depending upon whether the dipeptide model has for its side chain a glycyl, or alanyl, residue. The positions of the energy minima at $\phi = -60°$, $+60°$, $+180°$ for NEA and NIA according to our calculations suggest that $V(\phi)$ is three-fold and will have the form $V(\phi) = \frac{1}{2}V_\phi(1 + \cos 3\phi)$, although, in the SCF frame of reference, the partitioning of the total energy has very little meaning. The total energy difference between minimum and maximum reported here, using the CNDO/2 method, is only of the order of 0.5 kcal/mole (when the steric interactions are not dominant). Thus, at least from our results on these simple amides, it is difficult to suggest the value for the intrinsic barrier height, which seems to be small. Therefore, we suggest that, there is no need to include an energy term $V(\phi)$ separately, in evaluating the total potential energy empirically, in the conformational studies of polypeptides.

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