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Effect of the Crystalline Environment upon the Rotational Conformation about the N–C and C–C′ Bonds (Φ and Ψ) in Amides and Peptides

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SCF *ab initio* and PCILO computations indicate the intrinsic preference of the Ψ torsion angle for 60°. In the crystal structure of simple methylamides and peptides the observed values for this torsion angle lie between 0°–30°. Different procedures for computing lattice energies and total crystallographic conformational energies (lattice + torsional) utilized by other authors, failed to account for this situation. We show that the procedure developed recently in our laboratory for computing lattice energies indicates that the minima of these energies for Ψ in acetamide and N-methylacetamide correspond well to 0°–30°. Because of the low value of the barrier of the torsional potential for this angle, the total crystallographic conformational energy corresponds also to $\Psi = 0°$–30° in agreement with the experimental data.

Key words: Rotational conformation in amides and peptides – Φ and Ψ torsion angles in amides and peptides – Crystalline environment.

1. Introduction

The study of the rotation about the N–C^{α} and C^{α}–C′ bonds in simple amide and peptide systems, corresponding to the classical Φ and Ψ torsion angles (Fig. 1) is fundamental for the understanding of the conformation of polypeptides and proteins (see e.g. [1, 2]). Recently a number of theoretical and experimental studies have been performed on model compounds of the type of acetamide (I), N-methylacetamide (II) and related molecules. Computations carried out with the SCF *ab initio* method using STO 3G basis set [3] and with the PCILO method [4] predict the most stable conformations in these two compounds to be associated with Φ (C′–N–C^{α}–H) = 180° and Ψ (H–C^{α}–C′–N) = 60°. CNDO and EHT methods predict the preferred values of $\Phi = 120°$ and $\Psi = 60°$ [5]. Refined SCF *ab initio* computations using extended 4-31 G basis set [6] confirm the results of the STO 3G

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and PCILO computations with, however, one modification which seems to be a refinement: they reduce the barrier to rotation around Ψ from about 1 kcal/mole in the STO 3G or PCILO computations to the almost negligible value of 0.1–0.2 kcal/mole.

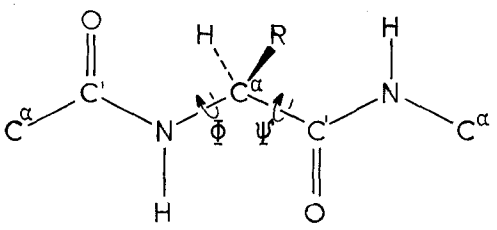
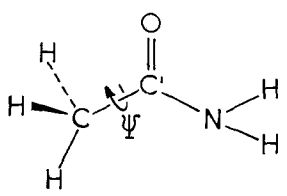
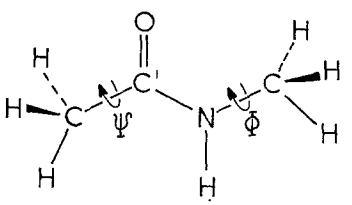


Fig. 1. Φ and Ψ torsion angles in polypeptides



I. Acetamide



II. N-methylacetamide

Fig. 2.

Hagler *et al.* compared recently [6] these theoretical results, representing the intrinsically preferred conformations for the free molecules, with crystallographic data, compiled or established by them for compounds of this type. The experimental results indicate that the most stable observed conformations are associated with Φ in the vicinity of 180° and Ψ comprised between 0° and 30°. The crystallographic results seem thus to agree with the intrinsic preference of the free molecules as concerns Φ, at least as indicated by the *ab initio* and PCILO methods (but not by CNDO or EHT); on the other hand, the observed Ψ values are significantly different from the value of 60° predicted by all theoretical methods, including also empirical computations carried out with potential functions derived from crystal data [6], for the free molecule.

Under these circumstances, Hagler *et al.* [6] supposed that this disagreement could be due to crystal packing forces and performed minimized lattice energy computations for N-methylacetamide. Their results were disappointing. Following their computations, the minimum lattice energy in no case corresponds to the observed structure. When the minimized lattice energies are combined with the different rotational energies as obtained with the different quantum-mechanical or empirical procedures, the disagreement with respect to the value of Ψ (predicted 60°, observed 0°–30°) persists.

It appeared to us that, till the proof of the contrary, there is no particular reason to

doubt the validity of the results obtained for the free molecules by computations at the level of the SCF *ab initio* method using extended (4-31G basis) set and that therefore, $\Phi = 180°$, $\Psi = 60°$ should be considered as representing the intrinsically preferred conformation of small amides and peptides. This leads to the conclusion that the different values of Ψ observed in the crystals must be due to lattice packing forces and that Hagler's *et al.* [6] inability to reproduce the crystalline results could possibly be due to a deficiency in their methodology. The energy differences involved are obviously very small and could actually be difficult to attain. We have recently developed ourselves a procedure for the evaluations of crystal lattice energies [7–9] which has given satisfactory results in the study of a number of delicate problems. It seemed therefore useful to apply this procedure to the present problem. This was done for acetamide and N-methylacetamide. We considered the rhombohedral form of the crystal of acetamide in which $\Psi = 29°$ [10] and the crystal of N-methylacetamide of Ref. [11] in which $\Phi = 180°$, $\Psi = 0°$. The geometrical input data were taken from the two above references.

2. Method

2.1. The Computational Procedure

The method being described in detail in Refs. [7, 8], we shall only indicate here its main features.

We evaluate the interaction energy as the sum of three long-range contributions (electrostatic, polarization and dispersion) and a short-range repulsive contribution. At large intermolecular distances (several molecular diameters), the usual simplified formulae (dipole approximation) may be used for the long-range contributions and the short-range one may be neglected. At short distances, however (neighbouring molecules in the crystal), more refined formulae must be used. They are recalled below:

2.1.1. Electrostatic Energy

This energy is given by

$$E_{\rho\rho} = \sum_i^{(1)} \sum_j^{(2)} \frac{\rho_i \rho_j}{R_{ij}} \tag{1}$$

In this formula $\sum_i^{(n)}$ extends to all atoms belonging to the molecule n: ρ_i and ρ_j are atomic net charges obtained from quantum mechanical calculations on the isolated molecule; R_{ij} is the distance between the atom (i) of molecule 1 and the atom (j) of molecule 2.

2.1.2. Polarization Energy

The polarization energy is calculated as a sum of atom polarization contributions

$$\sum_{\text{pol}}^{(1)} = -\frac{1}{2}\sum_i \alpha_i(\mathscr{E}_i)^2 \tag{2}$$

where $\mathscr{E}_i$ is the electric field created at atom i of molecule 1 by all other molecules, and α_i is the mean polarizability attributed to atom i. This last quantity is obtained by sharing the mean polarizability of the bond ij between the atoms i and j, according to the weights attributed to the atoms; these weights are obtained from the number of electrons involved in the bonds and the number of electrons on the atoms (lone pairs) [9].

This mode of calculation of the polarization energy enables us to utilize the atom–atom distances already used in the calculation of the electrostatic energy.

2.1.3. Dispersion and Repulsion Energy

Here we use the Kitaigorodskii-type semi-empirical formula previously described in [7], which also involves atom-atom distances. This formula is a sum of atom-atom terms, each of them being essentially of the Buckingham (6-exp) type:

$$E^{\text{Kit}} = \sum_i^{(1)} \sum_j^{(2)} E(i,j) \tag{3}$$

where the atom-atom contribution $E_{i,j}$ is the sum of a dispersion and a repulsion term:

$$E(i,j) = k_i k_j \left[-\frac{A}{z^6} + (1-\rho_i/N_i^{\text{Val}})(1-\rho_j/N_j^{\text{Val}}) C \exp(-\alpha z) \right] \tag{4}$$

$z = R_{ij}/R_{ij}^{0'}$ with $R_{ij}^{0'} = \sqrt{[(2R_i^w)(2R_j^w)]}$ where R_i^w and R_j^w are the Van der Waals radii of atoms i and j.

The parameters A, α, C are kept independent of the atomic species i and j. Their values are given in Ref. [9]. The factors $(1-\rho_i/N_i^{\text{Val}})$ correspond to the influence of the electronic populations on the repulsion: ρ_i is the net charge already used and N_i^{Val} is the number of valence electrons.

2.1.4. Representation of the Hydrogen Bond

For the interaction between a hydrogen atom and a heavy one (C, O, or N in our case), we use modified parameters A, C, α at short distances. In this way, we are able to reproduce the hydrogen bond interactions when they occur, without introducing any *a priori* information concerning their existence. This modification runs as follows:

We choose two critical distances R_m and R_M ($R_m < R_M$), for $R > R_M$ we use the normal parameters A, C, α; for $R < R_m$ we use the modified parameters A', C', α';

and for $R_m < R < R_m$ we use interpolated values according to the formula

$$K(x) = (K+K')/2 + (0.375x^5 - 1.25x^3 + 1.875x)(K-K')/2 \quad (5)$$

where K stands for A, C or α and $x = [R-(R_M+R_m)/2/[(R_M-R_m)/2]$ the values of R_m, R_M and of the modified parameters A', C', α' are those used previously [7, 9].

2.1.5. Very Short-Range Interaction

When the distance R goes to zero, the dispersion energy (in Eq. (4)) and the polarization energy (Eq. (2)) tend to $-\infty$. Theoretically these contributions should go to finite limits, while the repulsion term should go to $+\infty$ when R goes to zero; it is thus necessary to modify the formulae [7]. A critical value z_c is used, corresponding to the first inflexion point of the curve $-A/z^6 + C \cdot \exp(-\alpha z)$. Thus for $z < z_c$:

$(a_d z^2 + b_d)$ should be used instead of $1/z^6$, with $a_d = -3/z_c^8$, $b_d = 4/z_c^6$ and $(a_r z + b_r)$ should be used instead of $\exp(-\alpha z)$ with $a_r = \alpha z_c^2 \exp(-\alpha z_c)$ and $b_r = (1-\alpha z_c)\exp(-\alpha z_c)$.

For the electric field $(\boldsymbol{R}/R)/R^2$, we put $1/R^2 = 1/(R_{ij}^{0\prime} z)^2$ and $a_p z^2 + b_p$ instead of $1/z^2$, with $a_p = -1/z_c^4$, $b_p = 2/z_c^2$.

2.2. *Choice of Minimization Procedure*

In principle, for a set of angles Ψ and Φ (actually, in the present work, only Ψ will vary), the lattice energy is minimized with respect to the degrees of freedom of the crystal, namely cell and molecular position (rotation and translation) parameters. Then, the lattice energy thus obtained is added to the intrinsic conformational energy (corresponding to the Ψ and Φ values considered), and the total energy is studied as a function of Ψ (and eventually Φ) in order to find the angles for which the overall minimum is reached.

In practice several possibilities appear for minimizing the lattice energy:

1) We may choose as lattice energy the sum of the electrostatic, dispersion, repulsion and polarization terms (let us denote it E_{lat}); we may also include the non-additivity correction (essentially 3-body effects beyond the second order of perturbation), which, in a previous work [9], we proposed to evaluate as -7% of the dispersion energy. We shall denote $E_{\text{lat}}^{(3)}$ the total energy thus modified. It was indicated in Ref. [9] that this evaluation is somewhat uncertain, because it is based on results concerning small non-polar molecules, while new many-body terms exist for polar molecules. Moreover, when dealing with medium- or large-size molecules, most distances between the atoms of a triplet (one atom in each molecule) will be large, even for neighbouring molecules, and it is conceivable that the ratio between the 3-body (or many-body) terms and the 2-body ones will finally be smaller than in the case of small molecules. Actually, minimization procedures bearing upon $E_{\text{lat}}^{(3)}$ did not lead to any significant improvement with respect to those bearing upon E_{lat}, and we therefore give here the results obtained

by minimizing E_{lat}. As an extra information we also give in our tables the values of $E_{lat}^{(3)}$ corresponding to these positions (but these values do not correspond exactly, of course, to the exact minimum of $E_{lat}^{(3)}$).

2) A more difficult question arises concerning the symmetry of the crystal. Since the symmetry group of the experimental crystal is known, we may use this information in order to reduce the number of degrees of freedom in our minimization procedure: beyond the cell parameters (lengths and angles), we may introduce the position parameters of one molecule only, and then generate the other molecules of the cell through the symmetry transformations. We followed this procedure in all our previous works [7–9]. Nevertheless a fully *ab initio* procedure is in principle possible, in which the position parameters of *all* molecules in the central cell are allowed to vary independently. More precisely, since translations of all molecules as a whole are irrelevant (because they obviously lead to the same crystal), three translational parameters must be suppressed. The solution that we chose was to allow *rotations* only for *one* among the molecules of the central cell. Hagler *et al.* [2] chose the second way (where the crystal symmetry is not explicitly maintained), which is obviously more cumbersome owing to the substantial increase of the number of degrees of freedom. We therefore also considered this procedure ("without symmetry maintained"). But a second cause of increase of the computation time appears there: when symmetry is maintained, it is sufficient to evaluate the interaction energy between only *one* of the molecules of the central cell and the surrounding ones, but when symmetry is not kept it is necessary to evaluate this energy for *all* molecules of the central cell (and to minimize their mean value), in order to recover a final configuration with some symmetry. If only one molecule of the central cell is considered (without maintaining symmetry), important displacements of the central molecules occur, accompanied by too large energy decreases. Clearly, this procedure leads to a strongly deformed microcrystal (it must be mentioned that the summation over the surrounding molecules was limited to the first shell of cells around the central one in order to avoid large computing time). Maintaining the symmetry elements of the central cell avoids all these difficulties. Of course, it is theoretically possible to calculate the interactions for *all* molecules of the central cell, instead of doing this for a single one, and to extend the summation to a large number of shells, but this would need much longer computation times, and such a procedure could not be used as a routine one; it would be justified for checking purposes only. Thus, in the present study, we continued to use essentially the "symmetry maintained" approach, and all results displayed in the tables correspond to it.

3. Results and Discussion

3.1. Variation of the Ψ Angle in Acetamide

We recall that the values of the torsion angle Ψ are defined so that 0° corresponds to a conformation where a methyl C–H bond is eclipsed by the C′–N bond. The

value of 30° then corresponds to a conformation in which a methyl C–H bond is *gauche* to the C′–N bond.

We give in Table 1 the minima of the lattice energy for the three conformations with $\Psi = 0°$, 30°, 60°, obtained without the non-additivity correction and including this correction (between brackets). These values are obtained by keeping the symmetry of the experimental crystal. In these three minimizations, the displacements with respect to the initial positions, corresponding to the experimental crystal, remain quite small. The values of Table 1 show that differences between the lattice energy minima corresponding to the various conformations are small, as they are also in the work of Hagler *et al.* [6]. But in the present work the best value corresponds to $\Psi = 0°$, with a very close value for $\Psi = 30°$ in contrast to Hagler *et al.* who always obtain their energy minima for $\Psi = 60°$.

Ψ_{deg}	E_{lat} (kcal/mole)
0	−12.36 (−11.53)
30	−12.30 (−11.39)
60	−11.51 (−10.62)

Table 1. Minimum lattice energy of acetamide as a function of methyl rotations (the bracketed values correspond to the 7% reduction of the dispersion energy aiming to represent the non-additivity effect)

In order to obtain the total conformational energy in the crystal we have to combine the lattice energy with the rotational potential energy. The torsion energy of the methyl group in the molecule may be represented by $V_\Psi = V_0 (1 + \cos 3\Psi)/2$. Thus for $\Psi = 0°$, $V_\Psi = V_0$, for $\Psi = 30°$, $V_\Psi = V_0/2$, and for $\Psi = 60°$, $V_\Psi = 0$.

Thus, the two parts of the total energy exhibit opposite behaviours: the intrinsic torsion energy favours the starred configuration ($\Psi = 60°$), while the lattice energy favours the eclipsed ($\Psi = 0°$) and intermediate ($\Psi = 30°$) configurations. The overall result will therefore depend on the values of these contributions. As indicated in the introductory part of this paper, recent SCF *ab initio* computation using extended basis set [6] indicate that the rotational barrier for Ψ is very small, of the order of 0.1–0.2 kcal/mole. The total energy (lattice + rotational) obtained with the upper limit (0.2 kcal/mole) adopted for the rotational barrier is indicated in Table 2. As previously, the bracketed values correspond to the 7% reduction of the dispersion energy. The results of Table 2 indicate the preference of the crystal for a conformation with $\Psi = 0°$ or 30° in comparison with $\Psi = 60°$. The results for $\Psi = 0°$ and 30° are very close together and it would be risky to distinguish between them. The situation accounts very satisfactorily for the observed crystallographic results: while Ψ is equal to 29° in the rhombohedral form of acetamide [10], taken as

Ψ_{deg}	V_Ψ (barrier)	E_{tot}
0	0.2	−12.16 (−11.33)
30	0.1	−12.20 (−11.29)
60	0	−11.51 (−10.62)

Table 2. Total energy (lattice + rotational) for the acetamide crystal

input in our computations, its value is equal to 15° in the acetamide-oxalic acid complex [6], to 0° in the acetamide-allenedicarboxylic acid complex [6] and to 5° in the acetamide-5,5′-diethylbarbituric acid complex [12]. There is thus obviously the possibility for this angle to be distributed within the range of 0°–30° but not beyond.

3.2. *Variation of the Ψ Torsion Angle in N-methylacetamide*

In this molecule the two angles Φ and Ψ are susceptible to vary. Theory and experiment agreeing as to the preference of Φ for 180°, we have for reasons of economy kept this angle fixed in this value and minimized the lattice energy for different Ψ angles ($\Psi = 0°$, 30°, 60°). The results are given in Table 3. As in the case of acetamide, these minimizations were obtained by maintaining the symmetry of the crystal, and the bracketed values correspond to the 7% reduction of the dispersion energy. Here, too, the displacements with respect to the initial (experimental) positions are small (rotations of at most 3°).

The results of Table 3 show a distinct preference of the lattice for $\Psi = 0°$, followed by $\Psi = 30°$. It is interesting to note that there is in this case a preference of about 0.3 kcal/mole for the former with respect to the latter, i.e. a significantly larger difference between the two than in the case of acetamide. This result is worth stressing in view of the value $\Psi = 0°$ observed in the crystal of N-methylacetamide [11]. The conformation with $\Psi = 60°$ comes out at about 1.5 kcal/mole above the preferred one with $\Psi = 0°$. Our results are thus in appreciable variance with those of Hagler *et al.* [6].

Ψ_{deg}	E_{lat}	$(E_{lat}^{(3)})$
0	−16.98	(−15.52)
30	−16.64	(−15.17)
60	−15.43	(−14.44)

Table 3. Minimum lattice energy (kcal/mole) of N-methylacetamide as a function of methyl rotations

When the lattice energies are combined, as in the case of acetamide with the methyl torsional energies, in order to obtain the total conformational energies, the results presented in Table 4 are obtained. They confirm the overall preference of the crystal for $\Psi = 0°$ and account thus satisfactorily for the experimental situation.

Ψ_{deg}	V_{Ψ} (barrier)	E_{tot}	
0	0.2	−16.78	(−15.32)
30	0.1	−16.54	(−15.07)
60	0	−15.43	(−14.44)

Table 4. Total energy (lattice + rotational energies) for the N-methylacetamide crystal (all energies in kcal/mole). (Bracketed values are obtained with $E_{lat}^{(3)} = E_{lat} - 7\%$ dispersion energy, instead of E_{lat})

4. Conclusion

Two types of conclusions may be drawn from this work, one of a technical nature and the other relevant to the very problem investigated.

Concerning the technical aspect of the treatment of the problems involving minimizations of the lattice energy it is seen that no decisive advantage is gained by minimizing $E_{lat}^{(3)}$ (involving a 3-body non-additivity correction) instead of E_{lat} (which does not involve this correction: see formula (15) in Ref. [9]). Thus, in the present study, we chose to minimize E_{lat} and to evaluate also $E_{lat}^{(3)}$ for the final lattice conformation thus obtained.

As concerns the problem of maintaining, or not, the symmetry of the crystal during the minimization process, it seems that the first choice (the conservation of the symmetry elements) is quite satisfactory from the practical point of view. Indeed, the second choice, which could appear more appealing from some theoretical point of view requires substantially longer computing times, for three cumulative reasons: 1) the number of degrees of freedom is increased, since all molecules of the central cell are allowed to move independently, instead of a single one when symmetry is maintained (this means a dramatic increase in the case of acetamide, where the cell contains 18 molecules). 2) Since the molecules of the central cell are no more automatically geometrically equivalent, it is necessary to compute the interaction energy of *all* of them with the surrounding shells of molecules (in order to evaluate the lattice energy as the mean value of these energies); otherwise, there is no reason for recovering a final configuration with some symmetry. By contrast, when the symmetry is maintained, computing the interaction energy for a *single* molecule of the central cell is sufficient. 3) In order to have a correct evaluation of the interaction energy between all molecules of the central cell and the surrounding ones, it will be necessary to consider a large enough number of shells around the central cell, in order to reach a similar degree of convergence (of the summation over the surrounding molecules) for all molecules of the central cell. By contrast, when a single molecule of this cell needs to be considered, taking into account only one shell of surrounding cells may already give representative results.

Under these circumstances and in view of the results obtained the conservation of the symmetries is a justified approach.

We now turn to the specific problem dealt with in this paper, namely the influence of the crystal environment upon the rotational conformation of methyl groups in acetamide and N-methylacetamide. We have seen that while the intrinsically preferred value of the azimutal angle Ψ is 60°, our method for intermolecular crystal interactions indicates that the minimum lattice energy is obtained for low values of Ψ (between 0° and 30°). This result combined with the indication of *ab initio* computation with extended basis set of a low barrier for methyl rotations (0.1–0.2 kcal/mole) results in the minimum of the total energy (lattice energy plus intrinsic rotational energy) also occurring for values of Ψ in the range 0° to 30°, in an overall satisfactory agreement with experimental data.

We could wonder about the reasons for the difference between our results and those

of Hagler *et al.* [6]. Two main differences between the two treatments may be responsible for it: a) the basic atom-atom potentials are different in the two procedures. In particular, we use an exponential formula for the short-range repulsion instead of the R^{-9} or R^{-12} formulas of Hagler *et al.*; b) we performed the minimization procedure with the crystal symmetry maintained, while Hagler *et al.* relaxed this requirement. Hopefully future work will clear up the relative importance of these factors in explaining the differences between the results of the various methods.

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