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A Perturbative Study of Medium and Long Range Interactions between Some Characteristic Fragments of Lipid-Protein Systems

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An intermolecular perturbation theory, originally presented by Murrell and developed by use of the LCAO approximation, was applied to a theoretical study on the interaction of a hydrogen-bonded dimer of formamide with ethane molecule or ammonium ion in order to simulate interaction between characteristic frameworks of proteins and lipids. Ethane has a preferential orientation parallel to the carbonyl bond supported by the prevailing charge-transfer contribution. Ammonium ion has preferential interaction regions dependent on the balance between the charge-transfer and coulombic forces along the NH···OC axis.

Essentially biological membranes are built up from lipid bilayers in which proteins are imbedded. Therefore, to study lipid protein interaction is an interesting task, but hampered by the complexity arising from the size of isolated molecules.[1] One of possible ways to overcome this difficulty is to construct more simplified models describing relevant interactions. From study of these model systems it is possible to get information on the nature of forces and on the spatial preference in interaction between more complex systems. At this stage we examine interaction between fragments of lipids and the polypeptide chain, but for simplicity it is here simulated by using two H-bonded formamide molecules spatially arranged in such a way that the geometry of α-helix may be reproduced. In biological membranes lipids are essentially arranged in such a way that two ranges of interactions are possible to be separated, in one of which the protein interacts with the hydrophobic chain and in the other it interacts with the ionic heads. For the sake of computational economy we selected ethane as a model of the aliphatic chain of lipid and ammonium ion as a simplified model of ionic head. The latter constitutes the simplest model of known lipid heads, *e.g.*, the positive end of phosphatidylethanolamines.

We inspect medium and long range interactions between these fragments along the axis of the H-bonding existing in the pitch of α-helix in order to evaluate i) the entity of interaction energies, ii) the spatial specificity and anisotropy of interactions, and iii) the origin of intermolecular forces.

The energies were evaluated by means of the perturbation theory, following Murrell's approach[2] developed in the LCAO approximation by Fueno *et al.*[3]

Calculations

Interaction energy calculations were performed following the second order perturbation theory put forward by Murrell *et al.*[2] and developed by Fueno *et al.*[3] in the usual LCAO approximation. We adopted the ZDO approximation within single molecules, but retained the overlap integral between interacting molecules. Therefore, coefficients of wave function and transition energies relative to isolated molecules were calculated following the CNDO method.[4] Moreover, intermolecular three- and four-center integrals were approximated by Mulliken's equation:[5]

$$V_{a,rs} \simeq (V_{a,rr} + V_{a,ss}) \frac{S_{rs}}{2},$$

$$(rs|tu) \simeq [(rr|tt) + (rr|uu) + (ss|tt) + (ss|uu)] \frac{S_{rs}S_{tu}}{4}.$$

Following the scheme presented by Fueno *et al.*,[3] the intermolecular interaction energy was divided into five contributions: coulombic (E_Q), exchange (E_k), induction (E_I), dispersion (E_D), and charge-transfer (E_{CT}) energies.

Preliminarily, we have considered several approaches in calculating the electron core attraction and the interelectronic repulsion intermolecular integrals. We first calculated both $V_{a,rr}$ and (rr|ss) integrals theoretically by using an STO basis set, then considered the point charge approximation as suggested by Suzuki and Iguchi,[6] and finally considered the CNDO approximations: $(rr|ss)=\gamma_{ab}$ and $V_{a,rr}=-Z_a\gamma_{ab}$. We have found that, at distances greater than 3.5 Å, all these approximations give convergent values of energy; however, the present figures come from the last approximation. It is to be borne in mind that the present perturbation approach cannot be utilized in calcuating reliable equilibrium distances, many terms being uncorrectly calculated at short distances (*e.g.*, double exchange terms are lacking in the calculation of the exchange energy[7]). However, this method gives good information about preferential approaching pathways at large distances,[3] for which the simplified SCF-MO methods are ineffective.

The geometries of ethane molecule and ammonium ion were taken from the literature.[8] The geometry of the formamide dimer was determined by adopting the standard bond lengths and bond angles,[9] and by choosing the distance and dihedral angle between the two planar molecules so that the standard geometry of the α-helix[9] might be reproduced (see Fig. 1).

One of us (C.R.) has worked out a program in FORTRAN IV for the CDC 6600 computer, such that perturbation energies may be calculated in a step on the basis of the CNDO/2 program. This CNDO/2 program is the Del Bene-Jaffè version[10,11] modified so that it may calculate, for a given geometry, first the electron structure of two isolated molecules, then intermolecular

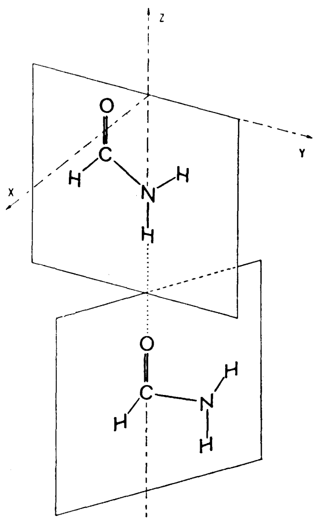

Fig. 1. Spatial conformation of formamide dimer reproducing the framework of protein α-helix.

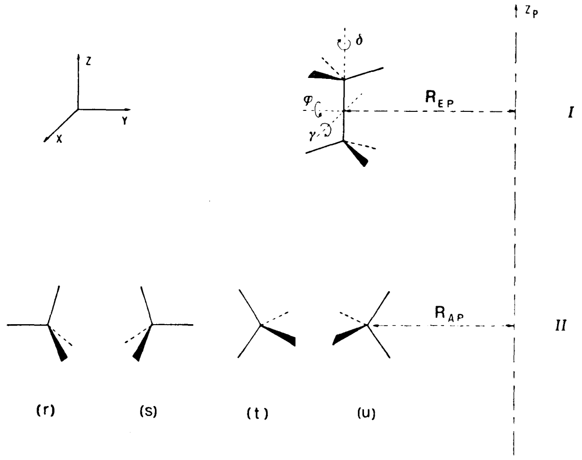

Fig. 2. Approaching pathways for ethane and ammonium ion. Z_P represents the z axis (NH···OC axis) of formamide dimer.

integrals, and finally intermolecular energies.

Figure 2 shows approach pathways between the NH···OC axis and each of ethane (I) and ammonium ion (II, r, s, t, u) and defines the rotation angles (ϕ, γ, and δ) for ethane. Three relative positions were considered for the set of ethane and NH···OC zxis: (1) ethane placed in front of the N–H bond (A_I); (2) ethane placed in front of the C=O (C_I); and (3) ethane placed in an intermediate region (B_I). The ethane–protein axis (R_{EP}) was held perpendicular to the plane of the nearest amide molecule and the intermediate region (B_I) had an averaged orientation imposed.

Five relative positions were considered for ammonium ion in view of its greater specificity for intermolecular interaction. They describe the positioning of the ion in front of atoms N, H, O, and C and in the intermediate (H-bridge) region (A_{II}, B_{II}, D_{II}, E_{II}, and C_{II} regions, respectively). The same criterion as for the ethane–protein axis was adopted also for the orientation of the ammonium–protein axis (R_{AP}).

Results and Discussion

Interaction energies for the set of ethane and formamide dimer, located in the three significant regions along the NH···OC axis, are given in Table 1. Rotation angle ϕ is defined in Fig. 2. The data indicate

Table 1. Energies for interaction between ethane and formamide dimer

Conformation		E_Q	E_K	E_I	E_D	E_{CT}	E_{TOTAL}
R_{EP}	φ	kcal mol^{-1}	kcal mol^{-1}	kcal mol^{-1}	kcal mol^{-1}	kcal mol^{-1}	kcal mol^{-1}
			Region A_I				
4.5	0	−0.001	−0.002	−0.002	−0.098	−0.080	−0.184
	45	−0.002	−0.003	−0.003	−0.099	−0.076	−0.183
	90	0.006	−0.003	−0.002	−0.098	−0.070	−0.167
5.5	0	≈0	≈0	−0.001	−0.034	−0.002	−0.038
	45	≈0	≈0	−0.001	−0.035	−0.002	−0.037
	90	0.002	≈0	−0.001	−0.033	−0.002	−0.034
			Region B_I				
4.5	0	0.003	−0.002	−0.002	−0.087	−1.216	−1.305
	45	0.002	−0.003	−0.002	−0.084	−0.681	−0.768
	90	≈0	−0.001	−0.003	−0.085	−0.213	−0.302
5.5	0	≈0	≈0	−0.001	−0.032	−0.026	−0.059
	45	≈0	≈0	−0.001	−0.032	−0.016	−0.048
	90	≈0	≈0	−0.001	−0.033	−0.006	−0.039
			Region C_I				
4.5	0	≈0	−0.002	−0.009	−0.101	−3.208	−3.319
	45	0.001	0.001	−0.010	−0.109	−2.086	−2.203
	90	0.008	0.001	−0.006	−0.092	−1.936	−2.026
5.5	0	≈0	≈0	−0.003	−0.033	−0.072	−0.107
	45	≈0	≈0	−0.003	−0.035	−0.047	−0.085
	90	0.003	≈0	−0.002	−0.031	−0.046	−0.076

that in the proximity of the N–H bond the ethane molecule is isotropic both at $R_{EP}=4.5$ and 5.5 Å. For the other two positions (C=O and H···O), we can note isotropy at 5.5 Å, while at 4.5 Å a preferential orientation of the C–C axis of ethane along the NH···OC axis occurs. In any cases preferred intermolecular binding is in the neighborhood of the C=O bond. This trend is justifiable if we look at the dispersion and charge-transfer contributions to the total energy, the other contributions (E_Q, E_K, and E_I) being nearly zero. Dispersion energy is about −0.03 kcal mol^{-1} at 5.5 Å, independent of the position along the NH···OC axis. Analogously an isotropy appears at 4.5 Å with a value of about −0.1 kcal mol^{-1}. These figures are probably underestimated because of the limited set of excited states; however, since the dispersion results are nearly isotropic along the protein axis (see Table 1), this fact will little affect our future conclusions. The charge-transfer contribution shows a non-isotropic trend. In fact, it is very small in the neighborhood of the N–H bond, so that at 5.5 Å it is nearly zero; a large CT contribution has been evidenced in the H···O region at 4.5 Å, while it is very small at 5.5 Å. The largest CT energy is observed in the proximity of the C=O bond; in fact at 4.5 Å the total interaction energy is due mainly to it, and at 5.5 Å the CT energy appears com-

TABLE 2. ENERGIES FOR INTERACTION BETWEEN AMMONIUM ION AND FORMAMIDE DIMER

Conformation		E_Q	E_K	E_I	E_D	E_{CT}	E_{TOTAL}
R_{AP}	Path	kcal mol^{-1}	kcal mol^{-1}	kcal mol^{-1}	kcal mol^{-1}	kcal mol^{-1}	kcal mol^{-1}
Region A$_{II}$							
4.5	r	−2.173	0.020	−0.341	−0.033	−0.051	−2.582
	s	−2.129	0.011	−0.335	−0.032	−0.022	−2.507
	t	−2.132	0.031	−0.350	−0.037	−0.070	−2.558
	u	−2.174	0.007	−0.334	−0.037	−0.017	−2.555
5.5	r	−1.730	≈0	−0.173	−0.011	−0.002	−1.916
	s	−1.711	≈0	−0.171	−0.011	≈0	−1.894
	t	−1.715	≈0	−0.176	−0.012	−0.002	−1.905
	u	−1.725	≈0	−0.171	−0.013	≈0	−1.910
Region B$_{II}$							
4.5	r	−1.678	0.016	−0.490	−0.035	−0.059	−2.245
	s	−1.644	0.007	−0.480	−0.032	−0.024	−2.173
	t	−1.670	0.018	−0.502	−0.046	−0.096	−2.296
	u	−1.690	0.005	−0.476	−0.031	−0.023	−2.215
5.5	r	−1.826	≈0	−0 229	−0.012	−0.002	−1.529
	s	−1.273	≈0	−0.226	−0.012	≈0	−1.511
	t	−1.286	≈0	−0.225	−0.016	−0.003	−1.537
	u	−1.288	≈0	−0.233	−0.012	≈0	−1.525
Region C$_{II}$							
4.5	r	−1.053	0.004	−0.535	−0.039	−0.214	−1.837
	s	−1.059	0.002	−0.532	−0.037	−0.170	−1.796
	t	−1.137	0.004	−0.550	−0.049	−0.503	−2.235
	u	−1.029	0.002	−0.521	−0.026	−0.202	−1.775
5.5	r	−0.560	≈0	−0.241	−0.014	−0.005	−0.820
	s	−0.561	≈0	−0.240	−0.014	−0.004	−0.819
	t	−0.588	≈0	−0.245	−0.017	−0.012	−0.862
	u	−0.548	≈0	−0.236	−0.010	−0.004	−0.798
Region D$_{II}$							
4.5	r	0.208	0.004	−0.327	−0.035	−0.731	−0.881
	s	0.107	0.012	−0.341	−0.041	−2.439	−2.702
	t	0.135	0.007	−0.333	−0.033	−1.639	−1.863
	u	0.215	0.007	−0.331	−0.039	−0.985	−1.133
5.5	r	0.440	≈0	−0.162	−0.013	−0.015	0.250
	s	0.406	≈0	−0.166	−0.014	−0.051	0.176
	t	0.416	≈0	−0.163	−0.012	−0.034	0.207
	u	0.441	≈0	−0.163	−0.013	−0.021	0.243
Region E$_{II}$							
4.5	r	1.722	0.009	−0.196	−0.037	−1.390	0.108
	s	1.758	0.027	−0.202	−0.034	−3.996	−2.447
	t	1.751	0.018	−0.198	−0.029	−3.215	−1.673
	u	1.725	0.008	−0.201	−0.045	−1.695	−0.208
5.5	r	1.363	≈0	−0.109	−0.012	−0.029	1.212
	s	1.370	≈0	−0.111	−0.011	−0.090	1.158
	t	1.372	≈0	−0.109	−0.010	−0.068	1.186
	u	1.363	≈0	−0.111	−0.015	−0.030	1.208

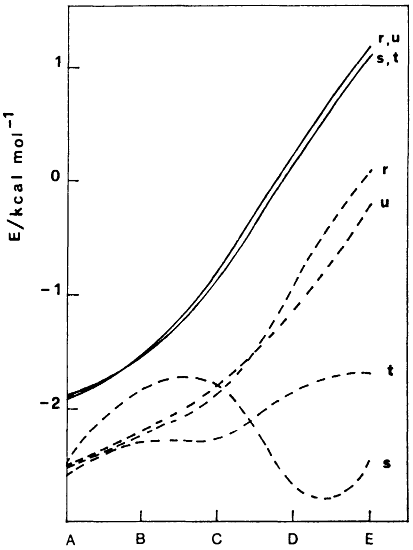

Fig. 3. Interaction energy curves for approaching pathways of ammonium ion in various regions of the NH··· OC axis. r, s, t, and u are defined in Fig. 2.
A, B, D, and E correspond to z coordinates of atoms N, H, O, and C, respectively. C corresponds to the intermediate region. ······ : $R_{AP}=4.5$ Å, ——— : $R_{AP}=5.5$ Å.

parable with the dispersion term. This behaviour is well justified if we bear in mind that the HOMO of formamide dimer is essentially located on the carbonyl group. Calculations were also undertaken for various angles of rotation (δ) around the C–C axis of ethane. The results indicate a small anisotropy, of about 0.5 kcal mol^{-1}, at 4.5 Å and in the proximity of the carbonyl group. Further calculations were carried out at 3.5 Å. The results are not reliable because of the large overlap which limits the validity of the present perturbation approach. However, even if the results are numerically unacceptable (essentially the CT contribution is overestimated at short distances), the figures are sure to follow the same trend.

As far as the charged molecule NH_4^+ is concerned, a large anisotropy is evidenced in the neighborhood of the C=O group at 4.5 Å, as we can see from Fig. 3 (region E) and Table 2, which summarizes results for the five positions of the ion located at 4.5 and 5.5 Å in front of the NH···OC axis. Moreover, a complete isotropy is found in correspondence with the N–H bond, and only a little preference for *t* conformation is found in the intermediate region. At 5.5 Å the four orientations (r, s, t, and u) of the ion are isoenergetic; the minimum potential is found in correspondence with the N–H bond. Even if the energy scale is not so accurate owing to the underestimation of dispersion forces, the trend may be considered reliable since the dispersion term is isotropic as observed for ethane. The overall trend is dependent essentially on the balance between the electrostatic and CT contributions since the other terms are almost constant or zero. At 4.5 Å the total energy curves have such trends as are highly differentiated for the various orientations of ammonium ion with respect to the protein z axis (see Fig. 2) as a consequence of the trend of the CT contribution, which, in the neighborhood of the carbonyl group, can be predominant when an optimum overlap is attained (pathways s and t). At 5.5 Å the curves for the total energy nearly match the trend of the electrostatic term.

From the present results we can argue that an aliphatic chain prefers to locate itself in the proximity of, and parallel to the carbonyl group of the polypeptide chain. The ammonium ion at 5.5 Å shows a preference for the N atom lone pair, while at shorter distances (in the range of experimental equilibrium distances) a competitive attraction of the N atom and of the C=O bond appears. From a study on formamide interacting with metal ions, a preferential binding of the ion along the C=O bond axis was found.[12] In our case, even if the C=O group is bound to the N–H bond by an H-bridge, we are still to find this tendency of the carbonyl group to attract the positive ion. However, it is to be pointed out that energies in balance are so small that the steric and/or solvent effects may also be competitive.

The present results, which may be considered as a good description of lipid systems with poly-L-glycine, suggest that in proteins with nonpolar side residues, the field experienced by the molecules adjacent to the polyamidic α-helix is nearly isotropic. Consequently, we may conclude that, for proteic systems without ionic or highly polar side residues, the approximation which simulates the protein as a dielectric cylinder[13] is reasonably applicable. However, effects of hydrophobic and/or polar residues and of the solvent on lipid–protein interactions are a matter of further investigation.

References

1) D. F. Bocian and S. I. Chan, *Ann. Rev. Phys. Chem*, **29**, 307 (1978) and references cited.

2) J. N. Murrell, M. Randic, and D. R. Williams, *Proc. R. Soc. London, Ser. A*, **284**, 566 (1965).

3) T. Fueno, S. Nagase, K. Tatsumi, and K. Yamaguchi, *Theor. Chim. Acta (Berl.)*, **26**, 43 (1972).

4) J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory," McGraw-Hill, New York (1970).

5) R. S. Mulliken, *J. Chim. Phys.*, **46**, 497 (1949).

6) K. Suzuki and K. Iguchi, *J. Chim. Phys.*, **75**, 779 (1978).

7) P. Hobza and R. Zahradnik, "Weak Intermolecular Interactions in Chemistry and Biology," Elsevier, Amsterdam (1980).

8) L. E. Sutton, "Intermolecular Distances," The Chem. Soc., Spec. Publ., London (1965).

9) G. E. Schulz and R. H. Schirmer, "Principles of Protein Structure," Springer-Verlag, New York (1979).

10) a) J. DelBene and H. H. Jaffé, *J. Chem. Phys.*, **48**, 1807 (1968); b) G. Kuehnlenz and H. H. Jaffé, *ibid.*, **58**, 2238 (1973).

11) J. DelBene, H. H. Jaffé, R. L. Ellis and G. Kuehnlenz, "CNDOS-CI Molecular Orbital Calculations with the Complete Neglect of Differential Overlap and Configuration Interaction," Program No. 174, Quantum Chemistry Program Exchange, Indiana University, Bloomington, IN.

12) R. Fussenegger and B. M. Rode, *Chem. Phys. Lett.*, **44**, 95 (1976).

13) J. Mahanty and B. W. Ninham, "Dispersion Forces," Academic Press, London (1976).