MOLECULAR ORBITAL STUDIES ON THE CONFORMATION OF PHOSPHOLIPIDS
EHT Calculations on the Polar End

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Recently, semiempirical quantum chemical theories have been used extensively, to study the conformational structure of three major classes of biological molecules: polypeptides, nucleic acids and polysaccharides [1]. In view of the limitations imposed by the computers presently available, such calculations have been performed at a submolecular level but nevertheless have been very successful in predicting stable conformations and metastable structures which may be involved in biological processes. The limitations of the earlier calculations based on classical potential functions as opposed to the quantum chemical calculations, are also well recognised.

The present studies are part of a research program (taken up jointly with Prof. R.K. Mishra) involving quantum mechanical calculations on the constituents of biological membranes with an aim to gain insight into the structure of the component molecules and the intra- and inter-molecular forces responsible for the molecular architecture of membranes. We are aware that a similar study using classical potential functions is in progress in the laboratories of Vanderkooi [2].

The phospholipids (fig. 1) are a major constituent of biological membranes. There are evidences to indicate that in the membrane structures, the molecular forces which orient the polar head groups are different from those orienting the long hydrocarbon chains. Thus, a convenient way to reduce the computer time is to study the structure of α chain separately from that of β and γ chains. Here, we report extended Hückel (EHT) calculations [3] on the fragment enclosed by dotted lines, which enables the study of low energy conformations with respect to the various torsional angles in the α chain.

The primary structure of the α chain (bond lengths and bond angles) is known from X-ray diffraction measurements on glycerol phosphoryl choline (GPC) and related molecules. These results have been reviewed in a recent article by Sundaralingam [4], where he has also suggested a convention for measuring the various angles (α_j) representing rotation about the bond j. Both the geometry, and the convention for measuring angles α_j employed in this paper are identical to those suggested by Sundaralingam [4]. In short, the angles are measured by the clockwise rotation of the bond j+1, relative to the bond j–1, with the *cis* planar configuration defining the 0° torsional angle. The terminal atoms in the fragment represented by the dotted line have been replaced by hydrogen. The parameters used in the EHT calculations are the same as used in the study of the conformation of nucleic acids [5–7].

The results of the calculations are shown in figs. 2 to 5 in terms of isoenergy diagrams drawn in two dimensions conformational hyperspace. As opposed to potential energy curves which involve changes in one rotational angle, such conformational maps take into account the correlation between neighboring bond rotations. Angles which are not varied have been assigned the following values:

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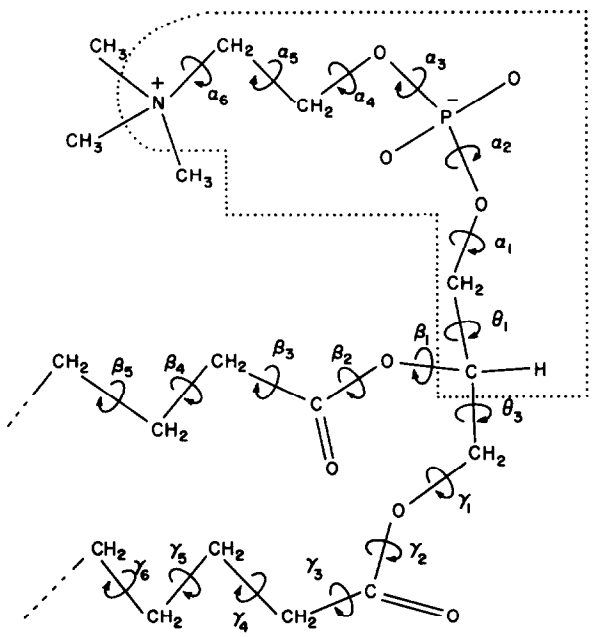

Fig. 1. Notation of the different chains and torsional angles in phospholipids.

$\alpha_1 = 180°; \alpha_2 = 60°; \alpha_3 = 60°; \alpha_4 = 180°; \alpha_5 = 60°; \alpha_6 = 60°$.

The most significant feature of these calculations is that a considerable amount of flexibility is predicted when rotations about the two O–P bonds are considered. This factor may be important in determining the structure and biological functions of membranes. In fact the rotations about these bonds in phospholipids are predicted to be even more flexible than the corresponding rotations (ω,ω^1) in nucleotides [7]. There is a large area on the (α_2,α_3) map where the energy is less than 5 Kcal mole^{-1}. The contours corresponding to 2 Kcal mole^{-1} enclose the areas with combination of α_2 and α_3 values corresponding to 60°, 180° and 300°, with the exception that the regions (60°, 300°) and (300°, 60°) have high energies. The stable regions are interconnected with one another by a low barrier. It would be interesting to compare the theoretical predictions with the experimental measurements on the values of α_2 and α_3 in molecules related to α chain in aqueous solutions. Unfortunately, to the best of our knowledge, no such measurements have yet been made. In the solid state however, the conformation of at least four such molecules are known [4] and fall in two categories: those having (60°, 60°) and those having (300°, 300°) conformations. Thus, a *gauche–gauche* arrangement is stabilised in solid state. While these structures

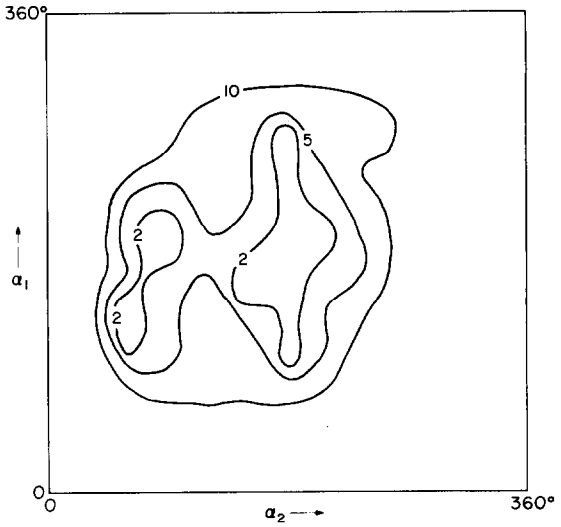

Fig. 2. Isoenergy contours in the (α_1,α_2) hyperspace. The energies are in Kcal mole^{-1} relative to the value for the most stable conformation (−29900.8 Kcal mole^{-1}).

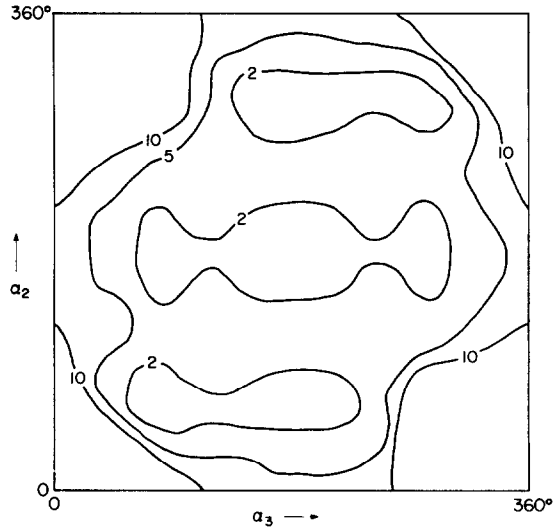

Fig. 3. Energy contours in the (α_2,α_3) hyperspace.

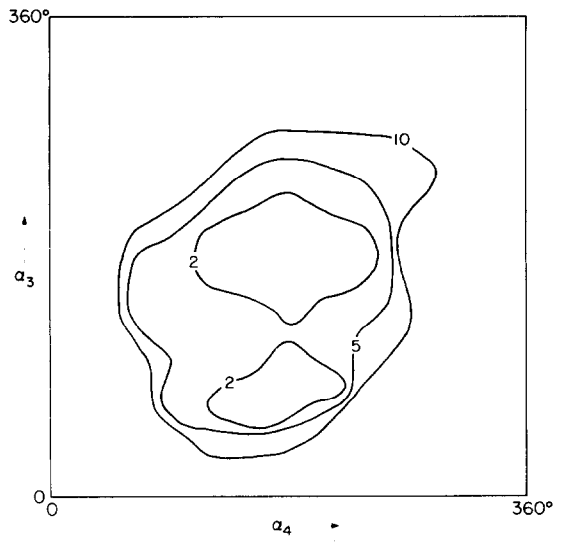

Fig. 4. Energy contours in the (α_3 ,α_4) hyperspace.

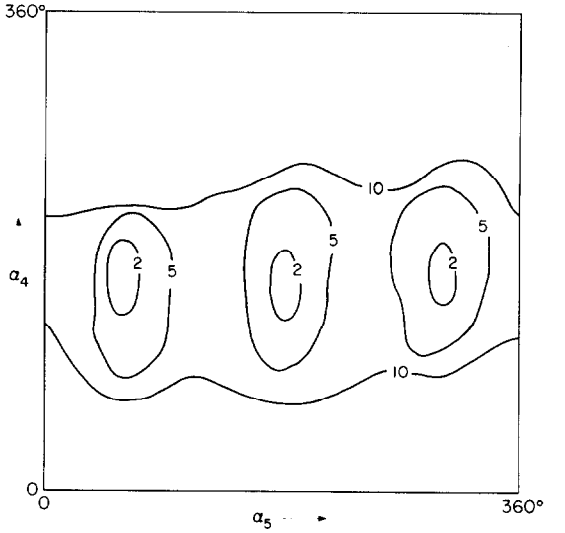

Fig. 5. Energy contours in the (α_4 ,α_5) hyperspace.

correspond to minimum energy regions in the theoretical conformational map, the theory does not predict any specific preference for such structures over extended structures (*gauche–trans, trans–gauche* or *trans–trans*).

From fig. 2 it is seen that the low energy regions with respect to α_1 fall around values of 180°. This value is in good agreement with experiments. Similarly, an extended structure is predicted, with respect to rotation about the other O–C bond (α_4), which is again in agreement with the results in solid state.

The angles α_5 and α_6 show preferences for 60, 180 and 300° regions. With respect to α_6, the three regions are equivalent. However the α_5 values are experimentally found to correspond to a *gauche* configuration, both in the structure of muscarinic and cholinergic systems as well as in GPC and related molecules [4].

It is clear from these studies that the possible conformations for α chain in phospholipids are somewhat limited, even in the absence of packing and intermolecular interaction, which may possibly force the molecules in a better defined three dimensional structure. We hope that the theoretical studies when completed, will help in understanding the complete conformational space spanned by the various rotational angles and help in proving or disproving conclusions drawn from rather limited numbers of experimental points obtained in solid state.

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References

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