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THE PREFERRED CONFORMATION OF THE ESTER GROUP IN RELATION TO SATURATED RING SYSTEMS

by

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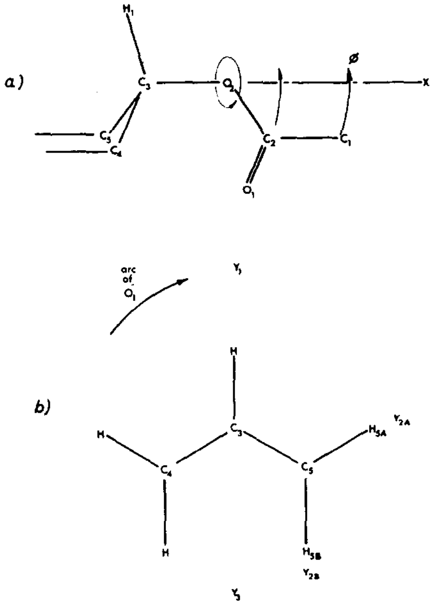
General conclusions regarding the conformations of common chemical groups can assist in the rationalisation of physical observations and in predicting the probable structure and conformation of new compounds. A source of data for such generalisations which has not been fully exploited can be found in X-ray structure analyses, particularly those of natural product molecules. Thus, if a particular conformational pattern is observed consistently in a range of crystal structures involving different packing arrangements and therefore a variety of different intermolecular forces, we may conclude that the intermolecular forces are here of less significance than the intra-molecular forces and hence that the same preferred conformation applies in the case of the isolated molecule. This argument, on the basis of a consistent pattern in crystals, was implicit in the earlier conclusions drawn, for example, about the peptide group (1) and was used by us in deductions regarding the conformation of the lactone and ester groups (2) and of six-membered rings with mono-ene functions (3)

The X-ray evidence for the planarity of the lactone group derived from crystal analyses (2a) has been used by Klyne (4) as a basis for discussion of the optical rotatory dispersion behaviour (in solution) of the lactone chromophore in a wide range of polycyclic lactones. The striking agreement of prediction with observation attained by Klyne, based on this interpretation, encourages the further investigation of crystal structures for indications of the conformations of isolated molecules.

The groups referred to above tend to be regarded as of relatively high stability and therefore the extrapolation from solid to solution is more readily admissible. For groups which involve formal free rotation, the energy difference between their extreme forms *e.g.* ~3 Kcal for ethane, is comparable with values for the *cis-trans* isomerisation of the ester group *e.g.* 2.55 Kcal (5). However, because of the implication of free rotation, the significance of conclusions from X-ray crystal analyses regarding groups which involve free rotation may require a larger number and variety of examples. Nevertheless it would still appear that, when no contradiction in the conformational pattern is noted, for a particular grouping of atoms, a provisional conclusion at least is admissible that the preferred conformation will apply for the isolated molecule.

Arising from a private query from Professor W. Klyne regarding the possibility of a general statement on the conformation of ester groups relative to (saturated) ring systems, we have investigated the available evidence.

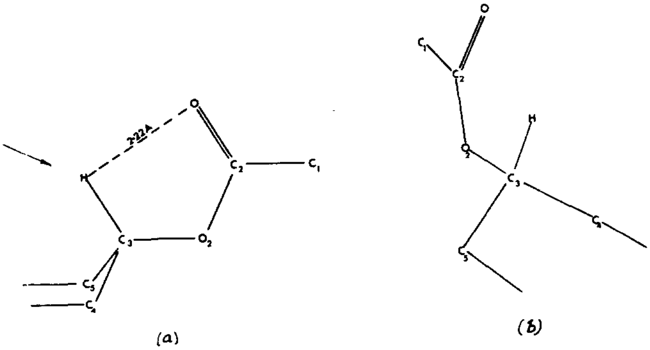
FIG. 1



Consider a typical situation, Fig. 1, in which the ester group is linked equatorially to a six-membered ring in the chair conformation. The co-planar (or peri-planar) condition (2) applies to atoms C(1) C(2) O(1) O(2) and also C(3) and therefore C(1) C(2) is approximately parallel to O(2) C(3). Hence the group C(1) C(2) O(1) can be imagined to rotate about the axis C(3) O(2) X. The conformational problem then reduces to consideration of the potential barrier to rotation, ϕ, of the group C(1) C(2) O(1) around the axis C(3) O(2) X, Fig. 1a.

The atomic environment as viewed down X C(3) from O(2) is shown in Fig. 1b. The relation of O(1) with the ring hydrogen atoms as ∅ changes are as follows. At Y_1, O(1) is ~ 2.2Å from H(1). At sites Y_{2A} and Y_{2B}, O(1) would lie about 1.5Å from H(5A) and H(5B) respectively whereas when it is equidistant from the two H(5B) at site Y_3, the approach distances are again ~2.2Å. On this basis, region Y_{2A} to Y_{2B} would involve repulsive forces *e.g.* (6) and regions Y_1 and Y_3 thereby constitute broad minima slightly differing in depth.

FIG. 2



(a) (b)

A survey was made of a number of crystal structure analyses involving ester groups, mainly acetate and haloacetate, in equatorial relation to six-membered rings in the chair conformation, a selection of which is given in (7). The survey revealed that, in such an environment, the atom O(1) is located without exception in the region of Y_1, Fig. 1b. The preferred conformation is therefore as shown in Fig. 2, (b) representing the view as indicated by the arrow in (a). We may note that although not defined by the X-ray evidence, H(1) is fixed since C(3) is tertiary.

With the probable dimensions for bond lengths and angles from X-ray studies (2b), the distance H(1) - - - O(1), Fig. 2a, was assessed as 2.22Å. This does not imply normal hydrogen bonding since the distance is too great (for a normal hydrogen bond of $\sim$2.8Å (say), the H - - - O distance would be $\sim$1.7Å) and the atoms concerned, C(3), H(1) and O(1), are not co-linear (see *e.g.* (1)). Although the distance is akin to that of the weaker bonding of CH - - - O pointed out by Sutor (8), again angular conditions preclude classification in this group. Stabilisation of this conformation may be partly ascribed either to an interaction between a partial negative charge on O(1) (arising from the "resonance" structure of the ester group) and a partial positive charge on H(1) (and/or O(2)), or as due to a more diffuse interaction of H(1) with the p electron distribution* of the group O(1) C(2) O(2). However this proposal cannot provide a complete explanation for the conformation selected. When the crystallographic evidence for esters involving primary alcohols *e.g.* (2) (6) is considered, in this case the stable position of the two hydrogens of the alcohol α-carbon is in a staggered relation to O(1), Fig. 3. The combined evidence would suggest that the principal factor is

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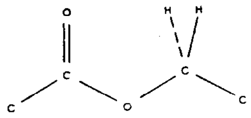
*Footnote:- In support of this viewpoint, we may note that the distances of H(1) to O(1) C(2) and O(2) are 2.22, 2.42 and 2.11Å respectively, Fig. 2, so that a generalised interaction between H and the mobile electron cloud of the three atoms is not inconsistent with this interpretation. Only in site Y_2, Fig. 1b, is H(1) in a position to interact in this manner with the whole group. In other sites, Y_2 and Y_3, the corresponding hydrogens approach only O(1), see Fig. 1b or alternatively test on a Dreiding model.

the repulsive forces which determine the location in a given potential minimum region and that subsidiary local forces play their part in determining more specifically the final location.

FIG. 3



This interpretation of the conformational pattern for the ester group by reference solely to intra-molecular forces is valid because O(2) appears to be effectively "non-reactive" with respect to specific inter-molecular interactions and hence is not involved with adjacent molecules (or solvent molecules in solution). Evidence for the "non-reactive" nature of O(2) has been noted in the course of a comparison of the crystal structures of the two epimers of iridomyrmecin (10) which showed that there was no evidence for any specific interaction with adjacent molecules.* Interpretation of optical rotatory dispersion

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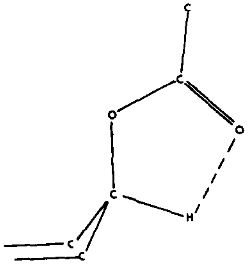
*Footnote:-
(a) Indirect chemical evidence may also be presented in that the oxygen atom in ethers appears capable of forming donor-acceptor compounds whereas there appears to be no evidence for a corresponding activity on the part of the ester oxygen, O(2).
(b) By contrast with the ester group, the peptide group, in which O(2) is replaced by NH, is involved in H-bonding with adjacent molecules and hence rotation of the whole peptide group is readily produced by this type of intermolecular interaction. For the ester group, a simpler interpretation on the basis of the isolated molecule is permitted.

studies of steroidal acetates (in solution) on the basis of the conformational restriction outlined above will be given separately by Klyne (11).

FIG. 4



For esters attached to rings by a polar oxygen, structure analyses are somewhat more limited but, from the few examples available *e.g.* (12) there appears to be a corresponding tendency to a preferred location of O(1) adjacent to H(1), Fig. 4, again in accord with the interaction with hydrogen atoms outlined above.

Acknowledgment:- We wish to express our appreciation of correspondence with Professor W. Klyne which stimulated the survey of the available crystallographic data and of valuable discussion with Dr. C. C. J. Culvenor.

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