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STEREOSPECIFIC AND REGIOSPECIFIC PHOTOREACTIONS INSIDE THE CHANNELS OF THE CHOLEIC ACIDS

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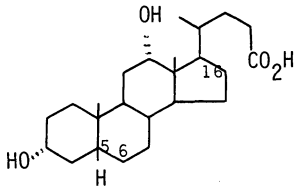
Abstract - The crystalline inclusion complexes of deoxycholic acid *1* (DCA) and apocholic acid *2* ACA (choleic acids) are used as vehicles for the performance of biomimetic reactions between host steroid and included guest. The choleic acids generally appear in three different channel motifs, α, β and γ, in orthorhombic crystals as determined by the size and shape of the guest molecule. Thus the nature of the channel wall can be controlled by the guest. U.V. irradiation of the complexes of DCA with linear aliphatic ketones, crystallized under argon, yields products of addition at sites C5 or C6, depending upon the relative orientation of the ketone to the steroid channel wall. On the other hand, cyclohexanone adds to site C16. The complex between DCA and prochiral acetophenone yields, on irradiation, the addition product at C5, with the formation of a new chiral centre. A comparison of the structure of DCA-acetophenone and the configuration about the new chiral centre indicates a net rotation of 180° by the acetyl group, upon reaction. To gain further insight into the reaction pathway the structure of the partially reacted crystal (these complexes do not disintegrate on reaction) was determined. It proved that during the course of conversion there was minimal motion of the phenyl ring, pronounced rotation of the acetyl group about the exocyclic C-C bond and, displacement of reacted and unreacted molecules. Furthermore the conformation of this photoproduct molecule about the new chiral centre in this partially reacted crystal differs radically from that in the crystal structure of the isolated photoproduct. Other systems which reveal similar photobehaviour are briefly described. Irradiation of several DCA complexes in the presence of molecular oxygen yields 5β hydroxy product of DCA. Possible routes for this reaction, with ketones as well as with other guests serving as oxygen carrier, are discussed.

1. INTRODUCTION

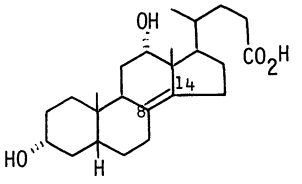
Enzyme-catalysed reactions in nature exhibit the ability to achieve selective reactions on the substrate molecule, primarily due to the proximity and strictly defined orientation between enzyme and substrate. Recently much effort has been directed towards increasing the power of synthetic methods by design and synthesis of molecules that may mimic the methodology of enzymes. We mention in this respect the elegant studies on the remote functionalizations in solution of steroids[1] and of hydrocarbons,[2] and the host-guest chemistry using tailor-made crown ethers[3] and cryptates.[4] An alternative way of imposing geometric constraints on the reaction is by embedding the reactants in ordered matrices such as liquid crystals, micelles, multilayer assemblies or crystals.

Crystalline molecular complexes provide an organized assembly most convenient for this purpose. The number of unactivated sites of both host and guest exposed for reaction are limited, and thus if a chemical reaction will take place between them, one may expect a high degree of both stereo- and regio- specificity. However, in order to exploit these matrices efficiently for such reactions, we must understand the rules that govern the reactivity for a given reagent, and find ways to design host crystals where the potentially reactive guest is occluded in the right position for reaction to occur with the host.

We directed our attention towards the steroids deoxycholic acid (DCA) *1* and apocholic acid (ACA) *2*, which are known on crystallization to incorporate guest molecules such as hydrocarbons, alcohols, esters and acids.[5] In these crystals only certain parts of the steroid molecule are exposed to the guest and so we anticipated that once a potentially reactive



1 DCA



2 ACA

molecule occluded, only the exposed sites of the steroid may react.

2. PACKING PROPERTIES OF CHOLEIC ACIDS

From X-ray analyses of several DCA complexes it became clear that DCA generally crystallizes in one of three different forms, orthorhombic,[6-9] which is the most commonly observed, tetragonal[10,11] and hexagonal.[12,13] The photochemical reactions were performed on complexes of the orthorhombic form. In these structures one observes a two-dimensional bilayer motif, with axial dimensions b = 13.6, c = 7.1 Å. The molecules form chains by translation along the 13.6 Å axis, being interlinked front-to-end by O(hydroxyl)-H...O(carbonyl) hydrogen bonds. These molecules are further joined by hydrogen bonds about 2_1-axes which are parallel to the 13.6Å axis and spaced along the c-axis of 7Å, so generating the bilayer. These bilayers contain grooves parallel to the c-axis which induce DCA to form channel inclusion complexes (Fig. 1). The adjacent bilayers may adjust their relative positions, within limits, to form channels that best fit the guest molecules. There are three degrees

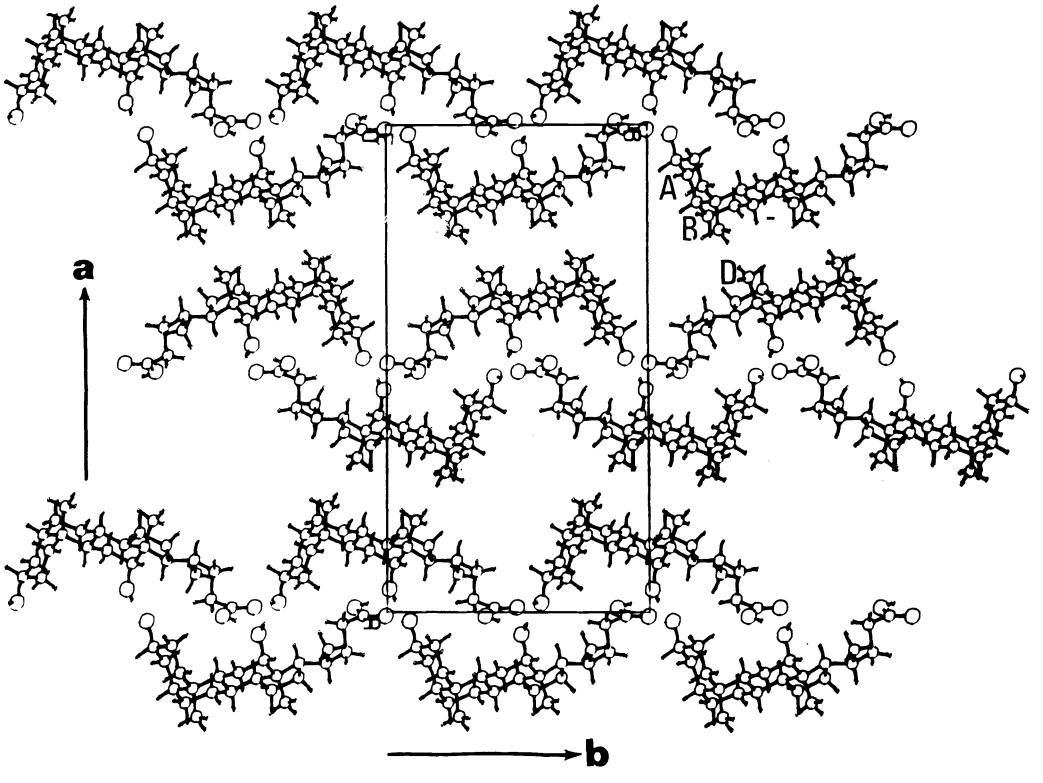


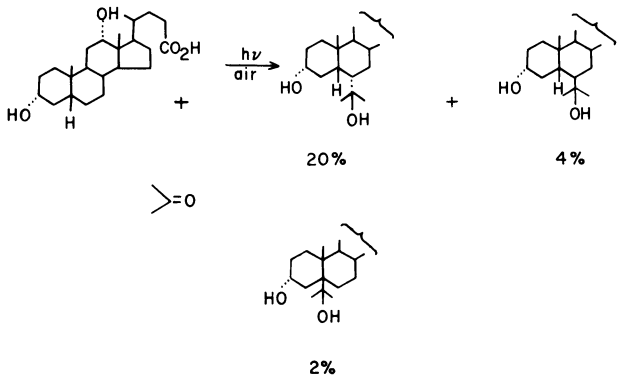
Fig. 1. DCA-acetophenone viewed along channel axis. The guest molecule is not shown. Steroid rings A, B and D are labelled.

of freedom for such adjustment. These are: variation in the bilayer separation along the *a*-axis, change in offset between adjacent bilayers along the *b* direction, and finally, the adjacent bilayers may be related by either a 2_1-axis (the most commonly observed) or a (pseudo) 2-axis parallel to *c*. Consequently three distinctly different channel motifs α, β and γ have been observed. In all three motifs the channel is delineated by what may be simply described as two pairs of parallel walls. One pair comprises steroid ring A and part of ring B, and the other the molecular side chain and ring D (see Fig. 1).

In the α-motif (Fig. 1) the channel size in the *ab* plane is approximately 4x6Å. The guest molecules tend to be flat, are less bulky than those which induce the β- and γ- motifs, and lie in the channel with their best planes sandwiched by the channel walls comprising rings A and B. The channel in the β-motif is different in shape and larger in size than in the α-motif. The molecules in these channels are wedged between the steroid side chains. The γ-motif contains bilayers arranged in a similar way to that of the β-motif, the sole difference being that adjacent bilayers are related along the *c* direction by a pseudo 2-axis, rather than by a 2_1-axis. Lattice energy calculations of DCA complexes in the orthorhombic system carried out by De Sanctis and Giglio[14], and independently by us,[15] have demonstrated that the three most stable packing arrangements (excluding guests) are motifs α, β and γ in that order.

3. STEREOSPECIFIC PHOTOADDITION REACTIONS OF KETONES INSIDE THE CHANNELS OF THE CHOLEIC ACIDS

Initially, we studied the photochemistry of occluded aliphatic and aromatic ketones, whose photoexcited species would be capable of hydrogen abstraction from the steroid channel wall. Acetone was the simplest occluded ketone whose photo-behaviour was examined and correlated with the host-guest packing.[8] Irradiation of the 10:6 complex of DCA-acetone led to formation of the addition products of acetone to positions 5, 6eq, and 6ax of the steroid, in the relative yields of 20:4:2 respectively (scheme 1).



Scheme 1

The crystal structure of this complex was first determined at room temperature (∿ 25°C), assuming a 2:1 host-guest ratio and one acetone molecule per asymmetric unit.[8,15] However, the refined thermal motion of the guest molecule was suspect, suggesting incorrect assignment of guest packing. Thus X-ray data were then collected at -170°C. According to the structure refinement the host:guest ratio proved to be 10:6 with three independent acetone molecules per asymmetric unit. The arrangement of the acetone molecules within the channel is shown in Fig. 2.

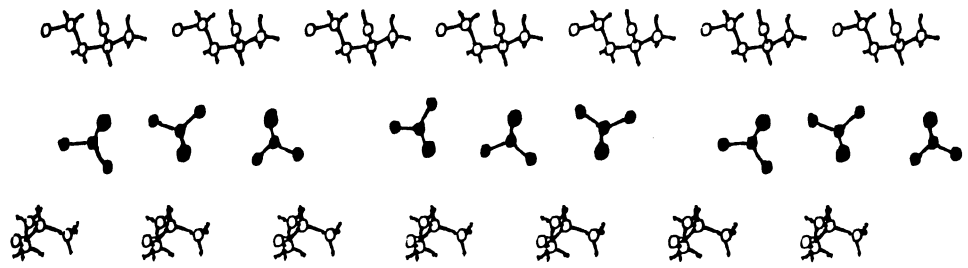


Fig. 2 Packing arrangement of acetone molecules in the channel.

The topochemical nature of this solid-state reaction is evident from comparison with the 1:1 apocholic acid (APA)-acetone complex.[8] The arrangement of the acetone molecules within the channel of APA is radically different to that in DCA because the channel cross-section in the former is larger in size and different in shape. The acetone molecules in the former lie with their molecular planes perpendicular to the channel axis and make plane-to-plane contacts of $\sim$ 3.6Å with each other along this axis *via* 2_1-symmetry (Fig. 3).

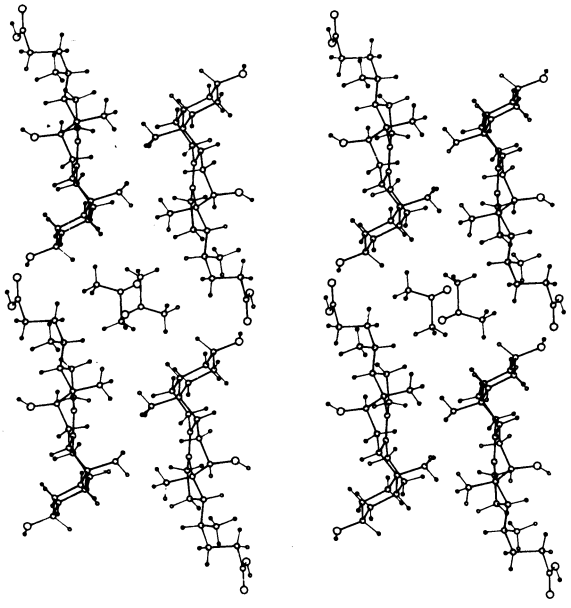
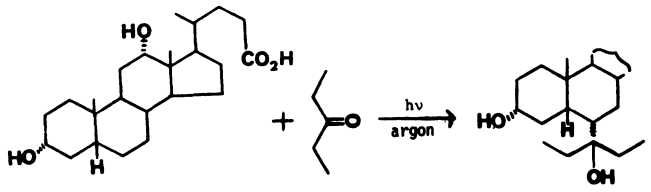


Fig. 3 Stereoscopic view of the packing arrangement of APA-acetone.

The hydrogen atom bonded to C20 of the steroid side chain makes the sole short contact (of 2.9Å) with the guest oxygen atom O'; the corresponding distance between C20 and C'(carbonyl) is as long as 4.9Å. The C20-H bond is almost parallel to the C'=O' bond and placed 0.6Å from the plane of the carbonyl system >C'=O'. No addition product was isolated from this complex although the O'...H distance is significantly shorter than O'...H distances of the abstractable hydrogen atoms in DCA-acetone. We tentatively conclude that if the neighbouring C-H and C'=O' bonds tend to be collinear no addition reaction takes place.

Further support for the topochemical nature of this reaction was provided by the 2:1 DCA-diethylketone complex.[15] Here the host also crystallizes in the α-form, but the change in the ketone structure, relative to acetone, is sufficient to induce a different host-guest arrangement. Photoirradiation under argon for days under sunlamps yielded only the addition product to 6eq (scheme 2). The room temperature crystal structure (Fig. 4) shows that the ketone oxygen O' is 3.3Å from H6eq, and 3.9Å from H6ax; the corresponding distance from C6 to the ketone C' atom is 3.8Å. We suggest that contacts such as those to H6eq and C6 are required for formation of the addition product. The separation C5...O' is



Scheme 2

3.3Å; however, no addition product to C5 was formed, presumably because of the long C5...C' distance of 4.2Å. Therefore it appears that the latter distance is too long to allow for addition following hydrogen abstraction (we shall return to this point in the section on gas/solid photohydroxylations).

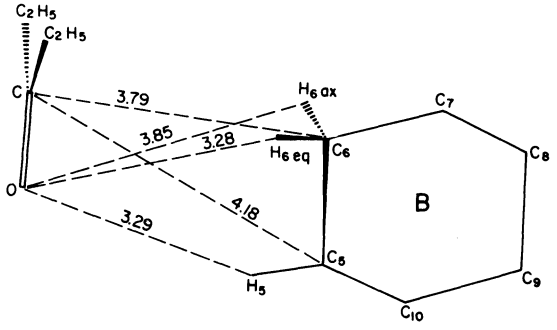


Fig. 4 Orientation and distances between the atoms of the carbonyl group of diethyl ketone and sites C5-H, C6-Heq and C6-Hax.

Linear paraffinic ketone guest molecules will generally induce the α-form packing of the steroid, which will permit hydrogen abstraction only from rings A and B. In order to functionalize rings D or the side chain by a guest ketone it is necessary to generate a channel of the γ-type *via* a bulky guest. Cyclohexanone induces such a channel wall structure, forming a 1:2 complex with DCA (Fig. 5). The channel has dimensions ∿ 7x5Å. Here the guest carbonyl group C'=O' is in close proximity to ring D and the side chain. It is noteworthy that the neighbouring steroid bilayers forming the channel walls are related to each other by a pseudo 2-axis.

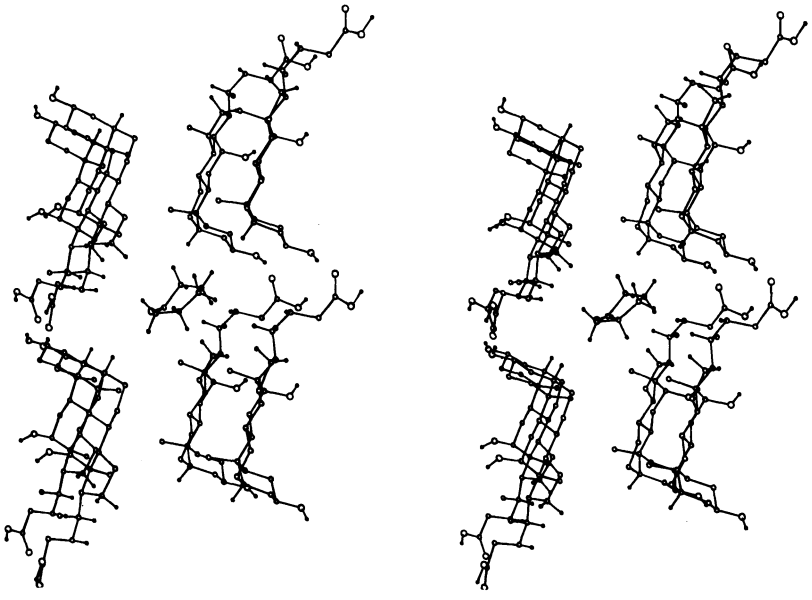
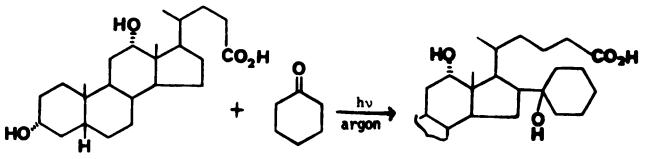


Fig. 5 Stereoscopic view of the DCA-cyclohexanone packing.

Irradiation of crystalline DCA-cyclohexanone under argon yielded the addition product at 16ax with 6% yield (Scheme 3). Position 16ax is the most eligible candidate for addition in terms of both O'...H and C'...C contacts, although the distance of 4.2Å between C16 and C' is unusually long for the reaction to occur.



Scheme 3

In the four complexes discussed above, the distances between the atoms directly involved in abstraction, namely O'(ketone) and H(steroid) and between the atoms to be bonded, namely C'(ketone) and C(steroid) range from 2.9 to 3.9Å, and from 3.7 to 4.2Å, respectively.

4. PATHWAYS OF THE PHOTOADDITION REACTION UTILISING PROCHIRAL KETONES

Prochiral ketones $R_1R_2C'=O'$ are a useful probe for mapping the reaction pathway since their photoaddition to the steroid leads to the formation of a new chiral carbon centre, whose absolute configuration may be compared with the prochiral "configuration" about the guest carbonyl carbon atom. The crystalline complex of ethylmethyl ketone proved to be unsuitable for this purpose because of its packing in the channel. The guest molecules form centrosymmetric pairs (Fig. 6a) in such a way that they lead to the formation of both diastereomers because the reactive centres of the steroid at C5 and C6 are exposed equally well to the two opposite faces of the ketone molecule (Fig. 6b).

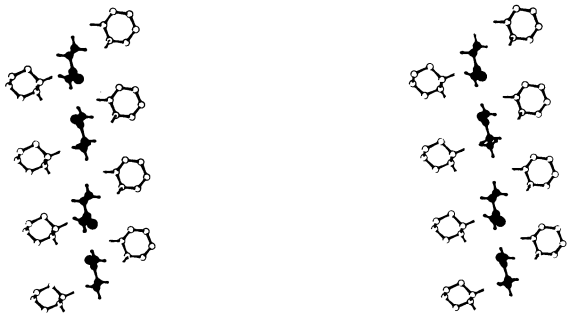


Fig. 6a Stereoscopic view of ethylmethyl ketone molecules in the DCA channel

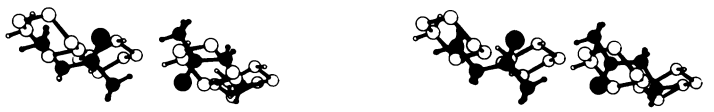


Fig. 6b Stereoscopic view of DCA-ethylmethyl ketone packing leading to photoreaction. The steroid hydrogen atoms attached to C5 and C6 are drawn.

To preclude this type of molecular packing we chose acetophenone whose complex gave, on irradiation, only one product of addition to position 5β. The absolute configuration at the new chiral carbon [H_3C-C*(OH)-C_6H_5] of the isolated 5β addition product of the acetophenone complex was determined from its crystal structure.[15] We shall now correlate the absolute configuration about this carbon atom with the host-guest arrangement about the prochiral carbonyl carbon atom C' of acetophenone prior to reaction.

The crystal structure of 10:4 DCA-acetophenone[16] was determined at -170°C. There are two independent guest molecules, *G* and *G'* which form a chain in the channel as depicted in Fig. 7. The orientation of the acetophenone molecules in proximity to the (abstracted) H5

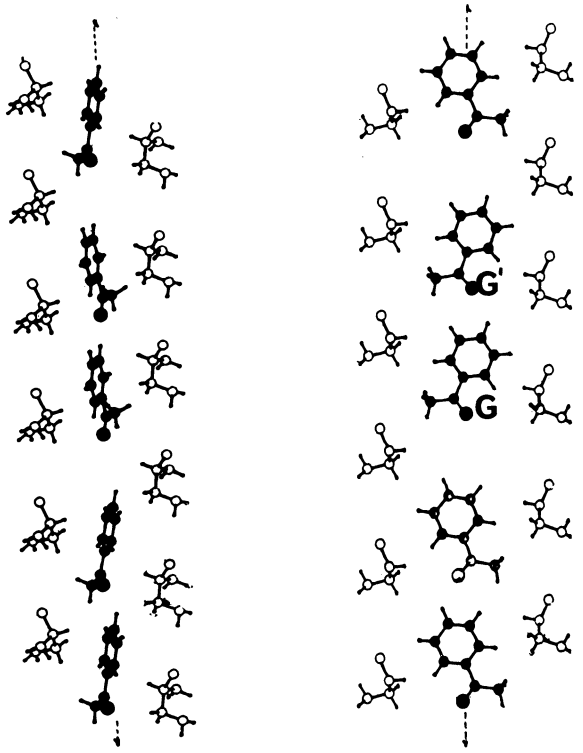
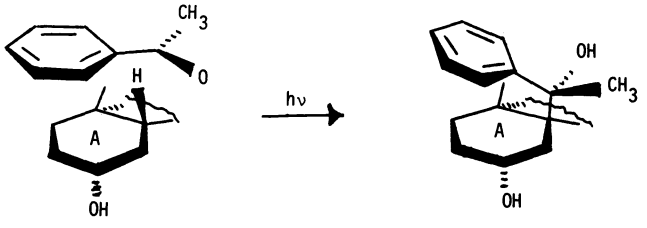


Fig. 7 Packing of acetophenone molecules in channel as viewed:
(a) almost edge-on to plane of guest molecule,
(b) perpendicular to plane of guest molecule.

atom of the steroid is shown in Fig. 8. A comparison of this arrangement with that of the acetophenone addition product as found in its own crystal structure[15] shows that the ketone adds from that face of acetophenone which is the more distant from the steroid in the starting structure. This stereochemical relationship, exemplified in scheme 4, implies the need for unusual motion of the guest acetyl group on reaction



Scheme 4

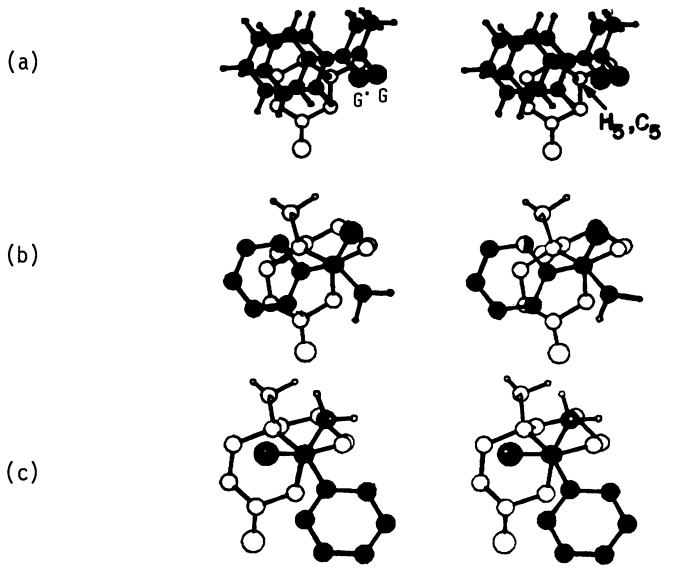


Fig. 8 Stereoscopic views

(a) DCA-acetophenone complex. Host-guest packing seen along the steroid H-C5 bond. The two independent acetophenone molecules *G* and *G'* occupy almost identical sites. Only ring A of the steroid is shown.

(b) The mixed crystal containing DCA host, acetophenone guest and the 5β addition product as seen along the $(C_6H_5)(OH)(CH_3)C^*$-C5 bond.

(c) The photoproduct of DCA-acetophenone in its own crystal structure, as seen along the $(C_6H_5)(OH)(CH_3)C^*$-C5 bond.

This crystalline complex does not disintegrate on formation of the photoproduct. Thus a determination of its crystal structures for different degrees of conversion, *i.e.* a solid solution containing host, guest and photoproduct in various ratios, should further elucidate the reaction course. Such a structure was successfully determined *via* low-temperature X-ray diffraction(at -170°C) with approximately 40% of the guest molecules reacted [16] (Fig.9).

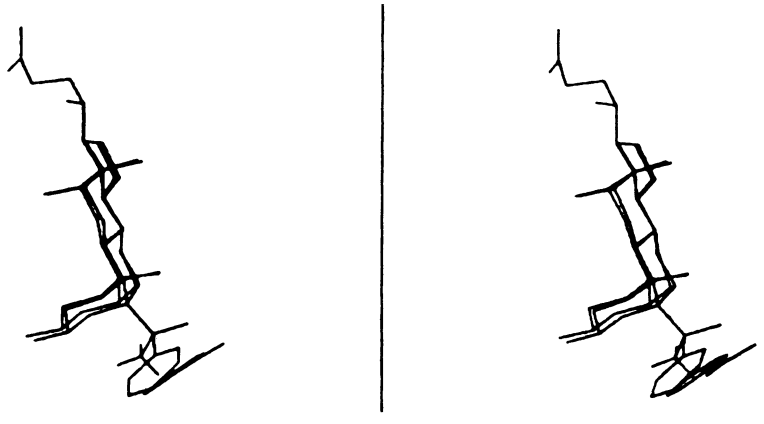
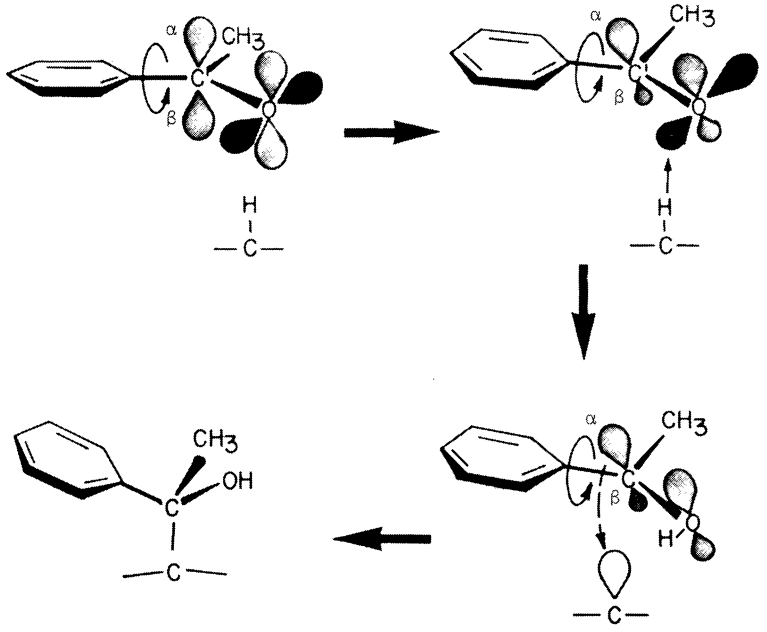


Fig.9 Stereoscopic view along the channel axis of solid solution comprising unreacted DCA steroid, guest acetophenone and photoproduct.

The structure refinement indicates that both guest molecules *G* and *G'* reacted. Furthermore, the overall molecular structure of the photoproduct in this solid-solution was unambiguously established, showing that the phenyl ring underwent minimal positional change on reaction (Fig. 8b and 9). Thus, we may infer that the ketyl function $-C(OH)CH_3$ underwent a net rotation of 180° about the C(phenyl)-$C(OH)CH_3$ bond prior to addition.[3]. Upon isolation and recrystallization the product adopts a conformation different from that found in the partially reacted crystal. (Compare Figs. 8c and 8b).

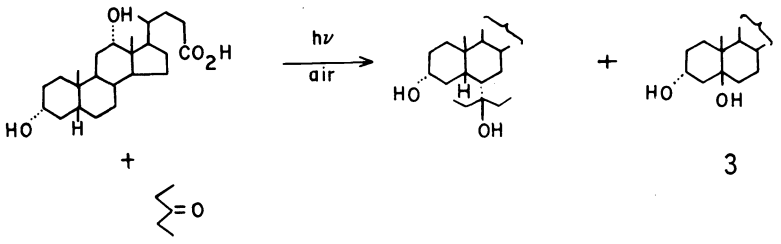
One way to rationalize the stereochemistry of the reaction product of DCA-acetophenone is depicted in Scheme 5. Here we shall invoke the electrophilic nature of the p_y orbital of the excited oxygen. In several studies on hydrogen abstraction by ketones in solution[17,18] and in rigid molecules in the solid[19] it has been reasoned that the ketone abstracts hydrogen through the p_y orbital of the oxygen on n-π^* photoexcitation. We observed that for both guest acetophenone molecules *G* and *G'* (Fig. 7) the p_y orbitals are orthogonal to the C5-H (abstracted) bond. Assuming the above abstraction pathway, and in the light of our experimental results, we propose that the abstraction involves a reorientation of the carbonyl bond to bring its p_y orbital along the line of sight of the C5-H bond (Scheme 5). Furthermore, after abstraction, it is the α-lobe of the π^* orbital on atom C', rather than its β-lobe, which is closer to the steroid atom C5, thus leading to a net rotation of 180° of the ketyl radical prior to coupling to the steroid. However, this proposed route, although attractive, must wait further experimental and theoretical verification.



Scheme 5

5. COOPERATIVE PHOTOHYDROXYLATIONS

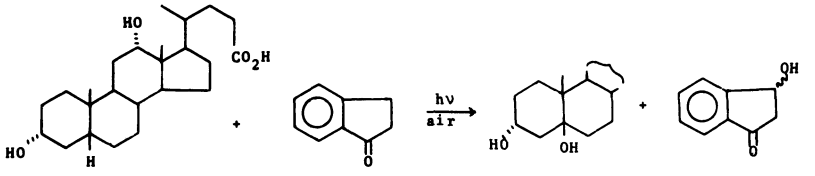
In the previous section we discussed the photochemical behaviour of various DCA-ketone complexes crystallized and irradiated under argon atmosphere. We now consider the effect of the presence of molecular oxygen on the photochemical behaviour of the DCA-complexes. Thus, complexes such as those of ethylmethyl ketone, diethyl ketone, cyclohexanone, ethylpropyl ketone and propiophenone gave, on irradiation in air 5β-hydroxy DCA *3* in yields ranging from 10-30%, as well as their original addition products. This process depicted in Scheme 6 for diethyl ketone.[20]



Scheme 6

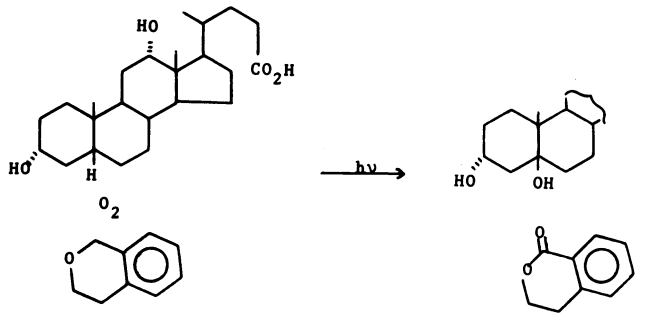
The important role played by the guests in inducing formation of product *3* is established by the fact that complexes which contain acetone, acetophenone, *p*-fluoro, *p*-or *m*-chloro-acetophenone do not yield this oxidation product.

We have pointed out above the unique arrangement of diethyl ketone and the steroid, where there is a short distance of 3.3 Å between H5 and the carbonyl oxygen O', apparently sufficient for an abstraction, but too long a separation of 4.3A between C5 and C' for bond formation to occur between them. Similar C5...C'=O' contacts have been found for cyclohexanone and ethylmethyl ketone. Thus one attractive rationalization of this hydroxylation process is that the hydrogen attached to C5 is abstracted by the oxygen of the ketone, generating an C' radical, which is trapped by molecular oxygen available in the steroid channels. However the expected hydroperoxide-DCA could not be isolated. Nevertheless, the fate of the second oxygen has been directly established by recent photochemical experiments on DCA-indanone. Irradiation of this complex in the presence of O_2 yields 3-hydroxy indanone (Scheme 7). C.D. measurements indicated that this molecule is optically active. A clear understanding of the pathway of this reaction must wait the determination of the crystal structure of the complex and the absolute configuration of the 3 hydroxy indanone.



Scheme 7

As mentioned above the hydroxylation has been found only for ketones that contain an activated α methylene group CH_2-C=O. Thus the question arose as to the role, if any, played by an activated methylene, particularly in the absence of a keto-group. Consequently we examined the photochemistry of DCA with guests such as isochromane, fluorene and indane. In all these systems the 5β hydroxylation product was obtained in yields ranging from 5-30%. Furthermore the guests underwent oxidation in the allylic position to form ketones. These reactions may be accounted for by the train of events proposed in Scheme 8 for isochromane. Here the activated methylene reacts with molecular oxygen to form a peroxy radical, which reacts with C5-H. The decomposition of the hydroperoxide terminates with formation of the hydroxylation product.



Scheme 8

All these results suggest that hydroxylation may occur via alternative routes. We hope that once we understand the rules which govern these reactions we will be able to design a variety of new guests which may serve as oxygen carriers for the purpose of oxidizing desired sites on both host and guest. Finally we hope that these kindsof experiments can be extended to other crystalline steroids.

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