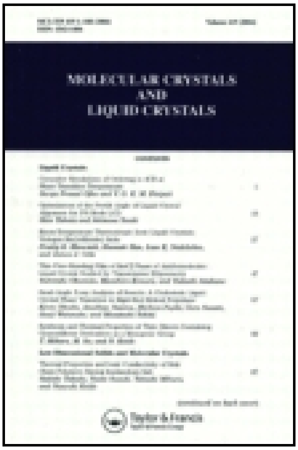

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ASYMMETRIC INDUCTION IN THE PHOTOCHEMISTRY OF CRYSTALLINE SALTS: STRUCTURE-REACTIVITY CORRELATIONS

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ABSTRACT:

The enantioselectivity of the di-π-methane photorearrangement was studied in chiral crystals. Achiral dibenzobarrelene acids **1** and **2** were forced to crystallize as chiral crystals by salt formation with chiral amines. Photolysis of these salts in the solid state yielded photoproducts in > 95% enantiomeric excess. The absolute configurations of the salts and their photoproducts were determined. This allowed the absolute steric course of the di-π-methane reaction to be mapped and the structural features that control the enantioselectivity to be identified. In contrast to the solid state photolyses, irradiations in solutions give only racemic photoproducts, presumably because the salts dissociated.

INTRODUCTION

Non-chiral molecules that crystallize in chiral space groups can undergo solid state reactions that transform the chirality of the crystals into molecular chirality in the products. Only a few such absolute asymmetric syntheses in the crystalline phase have been reported in the literature,[1] since they are usually the result of an accidental discovery of an achiral compound that crystallizes in a chiral space group and undergoes a solid state reaction to give optically active products.

One way to ensure that a chiral space group is adopted is to introduce a resolved chiral handle into the reactant, since such molecules are required to crystallize as chiral crystals. An advantage of performing asymmetric transformations of chiral substances in the solid state rather than in solution is that the chiral center not only ensures chiral crystals but also exerts its own asymmetric influence in the chiral lattice.

Resolved chiral handles can be introduced conveniently by salt formation with an optically active counterion. While the concept of using the solid state as a chiral medium in which to carry out asymmetric synthesis is not new, this and previous reports from our laboratory represent the first time organic salts have been used for such a purpose. Our previous work has shown that the solid state photochemistry of salts of prochiral acids complexed with optically active amines can give photoproducts in high optical yields.[2] The opposite approach, in which the salts of prochiral amines and optically active acids are photolyzed, can also yield photoproducts in good enantiomeric excess.[3]

In this paper we describe the asymmetric induction of salts of dibenzobarrelene acids **1** and **2** with chiral amines. Comparison of the absolute configurations of the starting materials with the absolute configuration of the photoproducts allowed us to map the reaction pathway in the solid state. Furthermore, the crystal structure features of the salts which are responsible for the enantioselectivity have been identified.

RESULTS AND DISCUSSION

Acids **1a** and **2a** (Figure 1), which are readily synthesized by Diels Alder reactions of anthracene, form salts with a wide variety of chiral amines. This paper focuses on the photochemistry of the S-(-)-proline *tert*-butyl ester salt of acid **1a** (salt **1b**) and the S,S-(+)-pseudoephedrine salt of acid **2a** (salt **2b**). These salts were prepared by mixing equimolar quantities of acid and base in diethyl ether and filtering the resulting precipitate. When the products were recrystallized they formed good quality crystals, which were shown to be simple 1:1 salts by IR and ^{1}H-NMR spectroscopy, mass spectrometry and elemental analysis. This salt composition was further confirmed by X-ray structure analysis of the crystals.

Salts **1b** and **2b** were photolyzed in acetone solutions (450 W Hanovia medium pressure mercury lamp), acidified to remove the ionic chiral handle and treated with excess diazomethane to produce the corresponding esters. As expected, these salts underwent the well known[4] di-π-methane rearrangement when irradiated to yield chiral dibenzosemibullvalene derivatives. For salts **1b** and **2b** two regioisomers are possible. Salt

1b yielded the known[5] products **3** and **4** in a 1:1 mixture, whereas salt **2b** afforded only product **5**. The structure of compound **5** was established by an X-ray crystal analysis of a derivative.

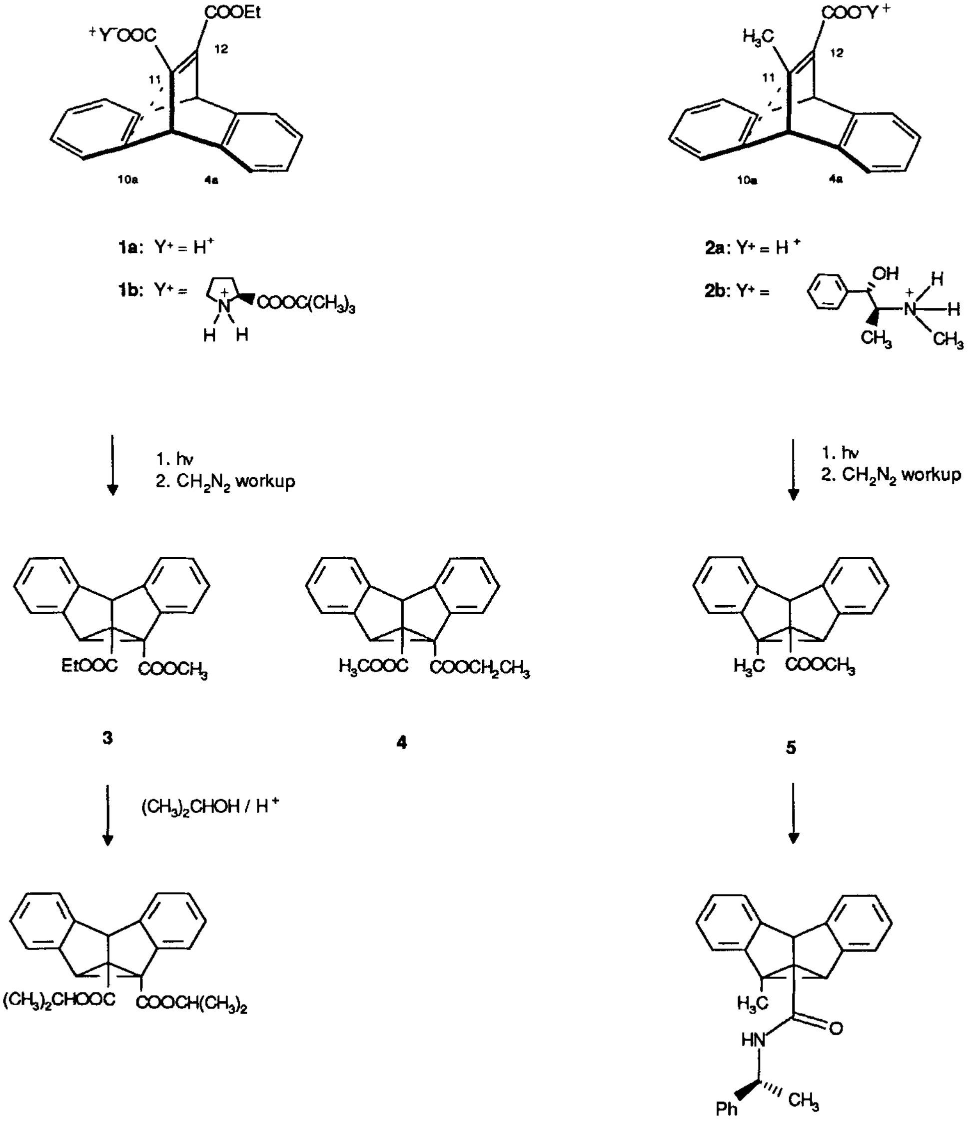

Figure 1. Photolysis of Salts **1b** and **2b**

According to Zimmerman's mechanism for the di-π-methane rearrangement, initial vinyl-benzo bridging is the product determining step.[4] We have therefore explained the lack of preference for either di-π-methane product for close analogs of **1a** by suggesting that the ester and acid groups on the vinyl bond have a similar radical-stabilizing effect.[4] Zimmerman also suggested that the radical terminii of the cyclopropyldicarbinyl diradical become electron rich during the di-π-methane rearrangement, and as a result, both the polar nature and the radical stabilizing ability of the substituents are important in determining the regioselectivity.[4] Consequently, product **4** was formed exclusively when salt **2b** was irradiated owing to the preference of the radical to be formed on the carbon next to the electron withdrawing acid group rather than next to the electron donating methyl group.[6]

The enantiomeric compositions of the photoproducts produced in solution from salts **1b** and **2b** were studied by means ^{1}H-NMR spectroscopy using the chiral shift reagent (+)-Eu(hfc)$_3$ as well as by polarimetry. It was established that the solution photolyses gave only racemic products. The lack of enantioselectivity in these photolyses can be attributed to the dissociation of the salts in solution.

We turn now to the main focus of this work: the solid state photolyses of salts **1b** and **2b**. Crystals of these salts were irradiated as powders sandwiched between two Pyrex microscope slides and sealed in polyethylene bags. The best results were obtained at -40° C. Conversions of 20-40% were possible without significant sample melting or loss of enantioselectivity. After photolysis, the reaction mixtures were worked-up in the same manner as the solution photolysis products. Salts **1b** and **2b** underwent the di-π-methane rearrangement regioselectivily in the solid state to afford products **3** and **5**, respectively. The increased regioselectivity of the di-π-methane rearrangement of salt **1a** in the solid state compared to solution can be explained in the following manner: the carboxylic acid functional group in salt **1a** is expected to be in its carboxylic anion form, as confirmed by X-ray structure analysis. Consequently, it can be hypothesized that a radical adjacent to an carboxylic anion is not as well stabilized as one next to an ester group and therefore only product **3** is observed. In solution, however more closely resembles the regioselectivity of the photoreaction of acid **1a** in the same solvent, that is both products **3** and **4**.

The enantioselectivity of the solid state reaction was measured in a similar way as for the corresponding solution process. This revealed that both products **3** and **5** were formed in over 95% enantiomeric excess. Both photoproducts **3** and **5** showed positive optical rotations ($[\alpha]_D$= +27° for **3** and $[\alpha]_D$= +59° for **5**, in chloroform). To test the reliability of our system, the R,R-(-)-pseudoephedrine salt of acid **2** (salt **2c**) was prepared. Irradiation of salt **2c** yielded product **5**, but the enantioselectivity was reversed. In other words product **5** was formed in over 95% enantiomeric excess but the optical rotation was negative. As expected, the CD spectrum of the (+)-enantiomer of **5** resulting from photolysis of salt **2b** was the exact mirror image of the spectrum of the (-)-enantiomer of **5** from photolysis of salt **2c**. The fact that the sign of the rotation of the photoproduct was reversed using the optical antipode of the chiral induction agent indicates that the system is well behaved.

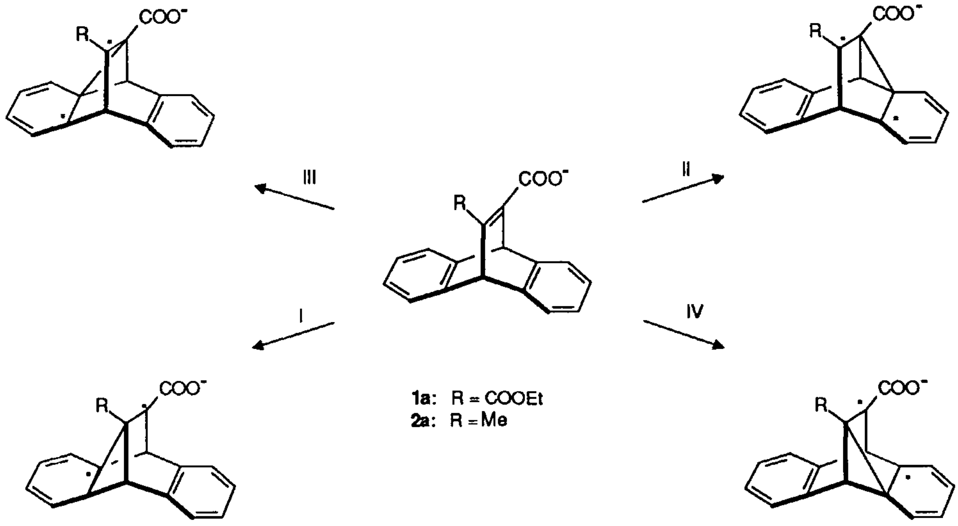

Figure 2: The Four Di-π-methane Systems in Dibenzobarrelene Acids **1a** and **2a**.

There are four potential di-π-methane systems in the dibenzobarrelene derivatives **1a** and **2a**. Each of these systems is associated with a pathway that leads to different products. Two pathways will lead to the same regioisomer whereas the other two give a different regioisomer. However, pathways that lead to the same regioisomer yield opposite enantiomers of the product thus permitting differentiation of the reaction pathways. Since the di-π-methane rearrangements of salts **1b** and **2b** are both regio- and enantioselective in the solid state, only one of these four pathways must be followed in each instance. It is possible to specify which one of these pathways is followed by comparing the absolute configurations of the product with the absolute configurations of the starting materials.

We set out to obtain the absolute configurations of salts **1b** and **2b** and their photoproducts. The absolute configurations of salts **1a** and **2a** could be obtained from the X-ray structure analyses, since the absolute configurations of the amine portions of the salts are known. The absolute configuration of photoproduct **3** was determined by acid-catalyzed transesterification to the corresponding di-isopropyl diester, whose absolute configuration was established some time ago in our laboratory.[7] The absolute configuration of product **5** was established by hydrolysis to form the acid followed by acid chloride formation, reaction of the acid chloride with S-(-)-α-methylbenzylamine to form the corresponding amide and finally determination of the crystal structure of the amide. The correct absolute configurations are those shown in Figure 1.

A comparison of the absolute configurations of salts **1b** and **2b** with their respective photoproducts indicates that initial vinyl-benzo bridging occurs as shown by the dotted lines in Figure 1. This leads to the question of what factors control this specificity. The motions associated with the vinyl substituents of the dibenzobarrelene starting material are considered to be the most important in determining the regio- and enantioselectivity of the di-π-methane rearrangement in the solid state.[8] The effects of the crystalline medium on photoreactivity may be divided into two categories. A primary effect controls the conformation of the reacting molecules. In the solid state, flexibility is lost and reaction is generally limited to a single low energy conformation. A secondary effect that restricts the motions responsible for a given reaction is due to intermolecular steric effects, which are dependent on the packing of the crystal.

When the packing diagrams of salts **1b** and **2b** were inspected, no interactions of the vinyl substituents which might control the enantioselectivity of the solid state photoreaction were readily apparent. However when the conformational arrangement of the vinyl substituents in salt **1b** was analyzed, it was seen that the carboxylate salt and the ester substituents are tilted away from one another, presumably so as to minimize their mutual steric and electrostatic repulsion. The torsion angle between C13-C11-C12-C14 is -9°. We would like to suggest that salt **1b** reacts in such a way that the interaction between the vinyl substituents is reduced rather than increased in the benzo- vinyl bridging transition state (Figure 3). Adherence to the alternative pathway would necessarily involve eclipsing of the substituents at some point in the course of the reaction.

For **1b**, the intramolecular distance between C10a and C11 (2.45 Å) is the same as that between C4a and C11 (2.45 Å). However, the torsion angle between the vinyl substituents suggests that the p orbital on C11 overlaps better with the p orbital on C4a than with the p orbital at C10a. This undoubtedly contributes to the observed enantioselectivity.

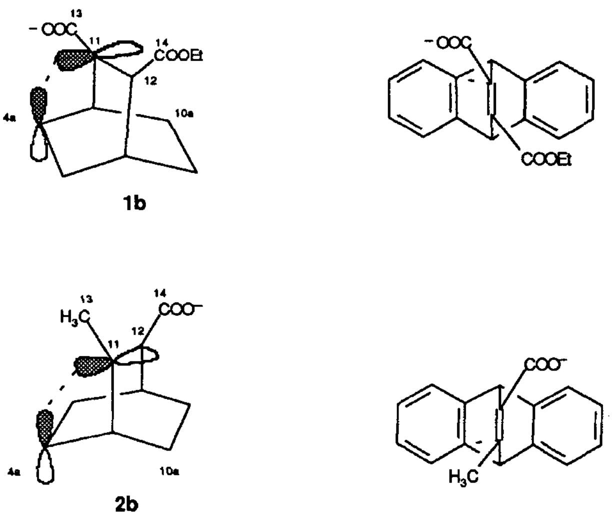

Figure 3. Some Torsion Angles in Salts **1b** and **2b**

This same hypothesis can be used to explain the enantioselectivity of the solid state di-π-methane photorearrangement of salt **2b**. The torsion angle between the vinyl substituents (C13-C11-C12-C14) is +8°. This suggests that initial vinyl-benzo bridging between C11 and C4a is favored, as this does not involve eclipsing of the C11-C13 bond with the C12-C14 bond. It can be suggested, as before, that the p orbital is better aligned for bond formation with C4a than C10a. A similar interpretation served us well in explaining a previous enantioselective solid state di-π-methane photorearrangement.[7]

SUMMARY

The enantioselectivity of the di-π-methane photorearrangement in chiral crystals was studied. Two achiral dibenzobarrelene acids were forced to crystallize in chiral crystals by forming salts with chiral amines. Solid state photolyses of these chiral crystals

resulted in a formation of photoproducts in over 95% enantiomeric excess, whereas the solution photolyses gave only racemic products. The absolute steric course of the photorearrangement in the solid state was determined by comparing the absolute configuration of the starting materials and the photoproducts. This allowed us to propose a general explanation of the factors that control asymmetric induction in the solid state di-π-methane rearrangement of dibenzobarrelene.

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