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IONIC CHIRAL HANDLE-INDUCED SOLID STATE ASYMMETRIC SYNTHESIS: ORIGIN OF THE ASYMMETRIC INDUCTION ELUCIDATED THROUGH ABSOLUTE CONFIGURATION CORRELATION STUDIES

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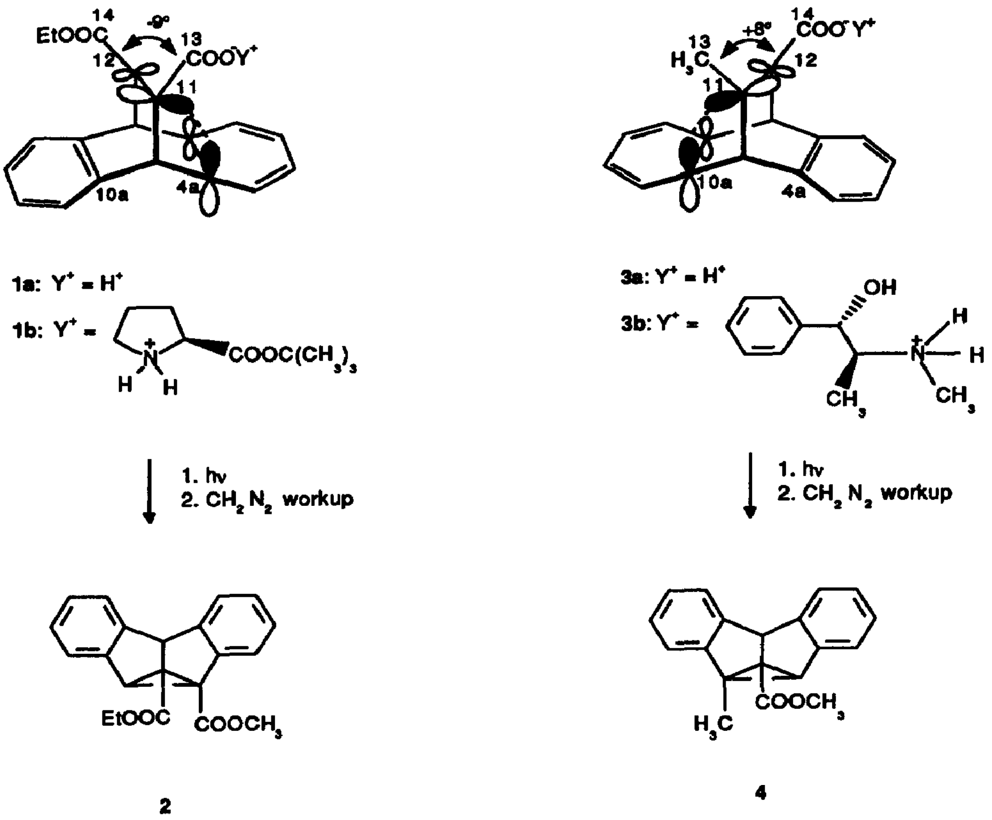
Abstract. Irradiation of crystals of two salts formed between prochiral, photochemically reactive carboxylic acids and non-absorbing, optically active amines is shown to lead to optically active photoproducts in > 95% enantiomeric excess, a process in which the ammonium ion has acted as an "ionic chiral handle." Through a combination of X-ray crystallography and chemical correlations, the absolute configurations of the photoproducts and the salts from which they are derived were determined. This allowed the absolute steric course of the photorearrangements to be charted and the structural factors responsible for the high enantioselectivity to be identified.

The development of new methods of asymmetric synthesis continues to be a major objective of research in organic chemistry, including photochemistry.[1] Consider the photochemical reaction of an achiral carboxylic acid that leads to a chiral product. If we treat the carboxylic acid with an optically active amine and then photolyze the resulting salt, two diastereomeric photoproduct salts can be formed. If one of these is formed in greater amounts than the other, an asymmetric induction has been achieved and the optically active ammonium ion has acted as an "ionic chiral handle." The opposite approach, in which the ammonium ion is the prochiral photoreactant and the carboxylate anion is the ionic chiral handle, is equally feasible.

Previous work from our laboratory[2] has shown that the ionic chiral handle approach to photochemical asymmetric synthesis does not work well in solution, presumably because the optically active ion is too mobile in this medium to exert a definitive asymmetric influence on the photoreaction. If, on the other hand, we immobilize the ionic chiral handle by carrying out the photoreaction in the crystalline state, high enantiomeric excesses can be achieved.[2,3] In the present communication, we report two highly successful applications of the solid state ionic chiral handle methodology as applied to the di-π-methane photoreaction.[6] In both instances, the key structural feature responsible for the asymmetric induction is elucidated through absolute configuration correlations between reactant and photoproduct.

Carboxylic acids **1a** and **3a** (Scheme), which are readily prepared through standard Diels-Alder reaction chemistry involving anthracene, form salts with a wide variety of amines. In the present instance, we concern ourselves with the S-(-)-proline *tert*-butyl ester salt **1b** and the S,S-(+)-pseudoephedrine salt **3b**, for which good quality crystals could be grown and whose crystal and molecular structures were determined by X-ray diffraction methods.[7] Upon photolysis,[8] salts **1b** and **3b** react regioselectively in the solid state to afford (after acidification to remove the ionic chiral handles and diazomethane workup) the chiral dibenzosemibullvalene derivatives **2** and **4**, respectively.



The structure of compound **2** was established by comparison with an authentic sample[9] and that of **4** by an X-ray crystal structure of a derivative (vide infra). In both cases, none of the alternative regioisomer could be detected (GC, NMR). The photoproduct structures indicate that the vinyl carbon atom involved in initial benzo-vinyl bridging is C(11) in both cases.[10] These regioselectivities are normal and are in accord with expectations based on the relative radical stabilizing and polar effects of the vinyl substituents on the initially formed 1,4-biradicals.[11]

The enantioselectivity of the solid state photoreactions was established by 400 MHz chiral shift reagent NMR spectroscopy using $Eu(hfc)_3$. This showed that both photoproducts 2 and 4 were formed in over 95% enantiomeric excess.[12] The absolute configuration of photoproduct **2** was determined by polarimetry following acid-catalyzed transesterification to the corresponding diisopropyl diester, whose absolute configuration was established some time ago in our laboratory.[13] The absolute configuration of photoproduct **4** was established by the following sequence of steps: (1) hydrolysis to form the acid, (2) acid chloride formation, (3) reaction of the acid chloride with S-(-)-α-methylbenzylamine to form the amide, (4) determination of the crystal structure of the amide.[14] The correct absolute configurations are those shown in the Scheme.

The absolute configurations of photoproducts **2** and **4** establish that the direction of benzo-vinyl bridging is that shown by the dotted lines in the Scheme. To what can we ascribe the preference for these pathways over what appear to be the equally likely diastereomeric alternatives? While it is possible that intermolecular crystal lattice forces may govern these reactions, such interactions are not apparent from inspection of the packing diagrams, and we attribute the enantioselectivities to an intramolecular effect in which the vinyl substituents seek to remain as far apart from one another as possible during the benzo-vinyl bridging process. The crystal structure of salt **1b** shows that the carboxylate salt and ester substituents are tilted away from one another in the solid state, presumably so as to minimize their mutual steric and electrostatic repulsion (Scheme). The sign and magnitude of this deformation, given by the value of the C(13)-C(11)-C(12)-C(14) torsion angle, is -9°. A similar effect is seen in salt **3b**, where the deformation amounts to +8°. The sign of this torsion angle is, in fact, a convenient measure of the absolute configuration of the anionic component of salts **1b** and **3b** in the solid state.

With this information in hand, it is readily apparent that both salts react in such a way (dotted lines) that the interaction between the vinyl substituents is reduced in the benzo-vinyl bridging transition state rather than increased as it would be if the alternative pathways were followed. Adherence to the alternative pathways would necessarily involve eclipsing of the substituents at some stage. Another factor that may favor the pathways shown by the dotted lines in the Scheme is orbital overlap. Owing to the negative torsion angle in salt **1b**, the p-orbital at C(11) overlaps better with the p-orbital at C(4a) than with the p-orbital at C(10a), thus favoring formation of photoproduct **2**; an exactly opposite situation helps to explain the enantioselectivity in the case of salt **3b**.[15]

We close with a very brief mention of the solution phase photochemistry of salts **1b** and **3b**. Each was photolyzed in acetone solution and found to give only racemic product(s), in agreement with our previous experience with the use of ionic chiral handles in solution.[2] The regioselectivity in the case of **3b** was the same as that observed in the solid state, i.e., exclusive formation of photoproduct **4**. Salt **1b**, on the other hand, gave a 1:1 mixture of photoproduct **2** and its regioisomer. The lack of enantioselectivity in these photoreactions is reasonable given the likelihood that there is an equal distribution of positive and negative torsion angles in solution.

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References and Footnotes

1. Inoue, Y. *Chem. Rev.* **1992**, *92*, 741.
2. (a) Gudmundsdottir, A.D.; Scheffer, J.R. *Tetrahedron Lett.* **1990**, *31*, 6807; (b) Gudmundsdottir, A.D.; Scheffer, J.R. *Photochem. Photobiol.* **1991**, *54*, 535; (c) Jones, R.; Scheffer, J.R.; Trotter, J.; Yang, J. *Tetrahedron Lett.* **1992**, *33*, 5481.
3. While the concept of using the organic solid state as a medium in which to carry out asymmetric synthesis is not new, having been reported for both one component[4] and two component (host-

guest)[5] systems, this and previous reports from our laboratory[2] represent the first use of organic salts for such a purpose.

4. (a) Vaida, M.; Popovitz-Biro, R.; Leiserowitz, L.; Lahav, M. In *Photochemistry in Organized ana Constrained Media*; Ramamurthy, V., Ed.; VCH Publishers: New York, 1991; Chapter 6; (b) Scheffer, J.R.; Garcia-Garibay, M. In *Photochemistry on Solid Surfaces*; Anpo, M.; Matsuura, T., Eds.; Elsevier: New York, 1989; Chapter 9.3.
5. Ramamurthy, V. In *Photochemistry in Organized and Constrained Media*; Ramamurthy, V., Ed.; VCH Publishers: New York, 1991; Chapter 7.
6. For reviews of the di-π-methane photoreaction in solution, see (a) Zimmerman, H.E. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic: New York, 1980; Chapter 16; (b) Zimmerman, H.E. In *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, 1991; Vol. 11, Chapter 1.
7. Salt **1b**: Needles from acetone, mp 154-169 °C; Anal. Calcd for $C_{29}H_{33}NO_6$: C, 70.86; H, 6.77; N, 2.85. Found: C, 70.99; H, 6.78; N, 2.77; $P2_12_12_1$; a = 9.510(3) Å, b = 31.260(3) Å, c = 9.057(5) Å; Z = 4; R = 5.7%; Salt **3b**: Prisms from acetonitrile, mp 174-183 °C; Anal. Calcd for $C_{28}H_{29}NO_3$: C, 78.66; H, 6.84; N, 3.28. Found: C, 78.94; H, 6.78; N, 3.05; $P2_12_12_1$; a = 8.5165(8) Å, b = 33.201(3) Å, c = 8.1732(8) Å; Z = 4; R = 2.9%.
8. The samples were prepared for solid state photolysis by crushing the crystals between two Pyrex plates and sliding the plates back and forth so as to distribute the crystals over the surface in a thin, even layer. The sample plates were then taped together at the top and bottom ends, placed in polyethylene bags, degassed with nitrogen and sealed under a positive pressure of nitrogen with a heat-sealing device. The bags were immersed in a cooling bath maintained at -40 °C by means of a cryomat and irradiated with the output from a 450 W Hanovia medium pressure mercury lamp. Conversions of 20-40% were possible in the solid state runs without significant sample melting or loss of enantioselectivity. In a typical run, a "sandwich" containing 100 mg of salt required approximately 24 h of photolysis.
9. Garcia-Garibay, M.; Scheffer, J.R.; Trotter, J.; Wireko, F. *Tetrahedron Lett.* **1988**, *29*, 2041.
10. The term benzo-vinyl bridging refers to the first step of the Zimmerman mechanism for the di-π-methane rearrangement of benzo- and dibenzobarrelenes.[6] This step involves formation of a 1,4-cyclopppropyldicarbinyl diradical species via bond formation between one of the vinyl carbon atoms of the ethylene bridge and an adjacent carbon atom in the aromatic ring.
11. (a) Rattray, G.; Yang, J.; Gudmundsdottir, A.D.; Scheffer, J.R. *Tetrahedron Lett.* **1993**, *34*, 35; (b) Scheffer, J.R.; Yang, J. In *Handbook of Organic Photochemistry and Photobiology*; Horspool, W.M.; Song, P-S., Eds.; CRC Press: New York; in press.
12. Photoproduct **2** exhibited $[\alpha]_D = +27°$ (chloroform, C = 0.02) and photoproduct **4** showed $[\alpha]_D = +59°$ (chloroform, C = 0.1). While the magnitudes of the specific rotations are only approximate owing to the small amounts of material involved, the sign of rotation in each case is correct. This was checked in the latter case by photolyzing crystals of the enantiomer of salt **3b** prepared by using R,R,-(-)-pseudoephedrine. This gave photoproduct **4** whose CD spectrum was the exact mirror image of that of (+)-**4** prepared above.
13. Garcia-Garibay, M.; Scheffer, J.R.; Trotter, J.; Wireko, F. *J. Am. Chem. Soc.* **1989**, *111*, 4985.
14. Plates from ethanol, mp 174-175 °C; $P2_12_12_1$; a = 19.741 Å, b = 21.028 Å, c = 10.059 Å; Z = 8; R = 4.0%.
15. Similar orbital overlap and steric effect arguments have been used to rationalize the absolute steric courses of two non-ionic solid state di-π-methane photorearrangements. See reference 13 as well as: Fu, T.Y.; Liu, Z.; Scheffer, J.R.; Trotter, J. *J. Am. Chem. Soc.* in press.

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