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Conformational Enantiomerism in Chiral Organic Salts Containing Crystallographically Independent Anion−Cation Pairs

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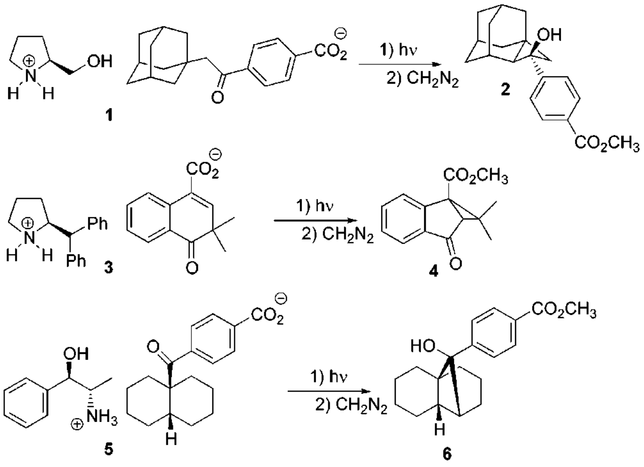
In the course of investigating asymmetric induction via photochemical reactions in the crystalline state, we have had occasion to synthesize and obtain crystal structures of numerous organic salts.[1] For the most part, these consist of an optically pure ammonium ion and a photoreactive, prochiral carboxylate anion. This approach to asymmetric synthesis employs ionic chiral auxiliaries, and exploits the fact that, owing to the presence of an optically pure ion, the resulting salt is required to crystallize in a chiral space group. Consequently, the ion that was achiral in solution adopts a chiral conformation in the solid state. It is the combination of this conformational chirality, coupled with the anisotropy of the crystal lattice, that gives rise to the asymmetric induction observed upon photolysis in the solid state.

We have frequently been able to obtain crystal structures of salts that afford high photoproduct enantiomeric excesses, and to correlate this structural data with the substrate's observed reactivity.[1] Crystals suitable for X-ray analysis have been difficult to obtain for salts that give rise to low ee's. Nevertheless, we have been able to acquire enough data to identify two structural motifs operating in these instances. The first mechanism arises from disorder in the crystals in which two or more conformations of the reactive ion are distributed randomly throughout the crystal (static disorder)[2] or are thermally interconverting (dynamic disorder).[3,4] The second motif, which is the subject of this work, involves the presence of equal amounts of two crystallographically independent ion pairs in the asymmetric unit. Remarkably, the two independent photolabile carboxylate anions are found to exist as *near-perfect conformational enantiomers*, reaction of which gives rise to opposite product enantiomers, thus accounting for the low ee's observed.[5]

One of the most striking examples of this phenomenon involves salt **1**, which can exist as two crystal modifications, needles or plates.[6] The needle dimorph contains one independent ion pair and yields cyclobutanol photoproduct **2** in 97% optical purity after photolysis to low conversion and diazomethane workup (Scheme 1). In this Yang photocyclization reaction,[7] the carbonyl moiety is conformationally poised to react with only one of two enantiotopic γ-hydrogen atoms, thus leading to the high observed stereoselectivity. In the plate dimorph, two independent ammonium-carboxylate ion pairs are present in the asymmetric unit. Figure 1a represents the superposition of the two conformational enantiomers of the reactive anion, one as found in the crystal, and the other as its mirror-image, in order that their relative geometries may be compared. The figure clearly shows the anions to be near-perfect enantiomers. This fact is reflected in a root-mean-square error (RMSE) of 0.12 Å calculated[8] for the overlap of the two species, and is manifested on photolysis, where an ee of 12% is observed at low conversion. A comparison of the reactive conformations in the needle and plate dimorphs reveals their conformational similarity (RMSE = 0.32 Å, Figure 1b), the most noticeable deviation occurring in the carboxyl substituent, which is distant from the site of reactivity. To put these numbers in perspective, the RMSE for the overlap of the anion's two independent conformations in the plate dimorph is 1.60 Å.

Scheme 1. Photochemistry of the Crystalline Salts



In the above example, the presence of a single conformational enantiomer (needles) leads to high ee, and when this conformer and its enantiomer are present in equal proportions (plates), low ee's are observed. All other factors being equal, irradiation of crystals containing equal amounts of two conformational enantiomers would be expected to lead to racemic photoproducts, and the question thus arises as to the source of the 12% ee observed at low conversions in the case of the plate dimorph of salt **1**. We suggest that this stems from a difference in the relative rates of closure of the enantiomeric 1,4-hydroxybiradical intermediates in the chiral crystalline environment. Each of the two conformational enantiomers resides in its own unique crystal lattice reaction cavity that governs its rate of closure relative to reverse hydrogen transfer.[9] To use a lock and key analogy, the crystal contains two lock/key (cavity/conformer) sets, one of which functions more smoothly (i.e., forms cyclobutanol more efficiently) than the other. Thus, ee observed in the reaction of crystals composed of conformational enantiomers is a direct measure of the environmental influence of the chiral crystalline environment and is independent of the reactant's own conformational asymmetry.[10]

A more dramatic illustration of this lattice control is observed with the benzocyclohexadienone salt **3**,[11] which, on irradiation, undergoes a formal oxadi-π-methane rearrangement to furnish

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[1] For examples, see: Leibovitch, M.; Olovsson, G.; Scheffer, J. R.; Trotter, J. *J. Am. Chem. Soc.* **1998**, *120*, 12755 and references therein.

[2] Cheung, E.; Netherton, M. R.; Scheffer, J. R.; Trotter, J. *J. Am. Chem. Soc.* **1999**, *121*, 2919.

[3] Cheung, E.; Netherton, M. R.; Scheffer, J. R. Unpublished results.

[4] For a nice example in which crystal disorder has been identified as being responsible for altering migratory aptitude in a solid-state photorearrangement, see: Zimmerman, H. E.; Alabugin, I. V.; Chen, W.; Zhu, Z. *J. Am. Chem. Soc.* **1999**, *121*, 11930.

[5] A third scenario, which has the prochiral ion adopting an achiral conformation, has been postulated, but not observed to date.

[6] (a) Jones, R.; Scheffer, J. R.; Trotter, J.; Yang, J. *Acta Crystallogr.* **1994**, *B50*, 601. (b) Jones, R.; Scheffer, J R.; Trotter, J.; Yang, J. *Tetrahedron Lett.* **1992**, *38*, 5481.

[7] Cyclobutanol products in Norrish type II photochemistry were first reported by: Yang, N. C.; Yang, D. H. *J. Am. Chem. Soc.* **1958**, *80*, 2913. For a general review of the Norrish/Yang type II reaction see: Wagner, P.; Park, B.-S. In *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, 1991; Vol. 11, Chapter 4.

[8] Calculations were performed using the HyperChem/ChemPlus software package (versions 5.11/2.0) and reflect the minimized RMS displacement of the non-hydrogen atoms.

[9] A difference between conformational enantiomers in the relative rates of forward or reverse hydrogen-atom abstraction is less likely to be the enantiodifferentiating factor, since the geometry change in this process is minimal, involving only the relocation of a hydrogen atom and slight changes in bond lengths and angles.

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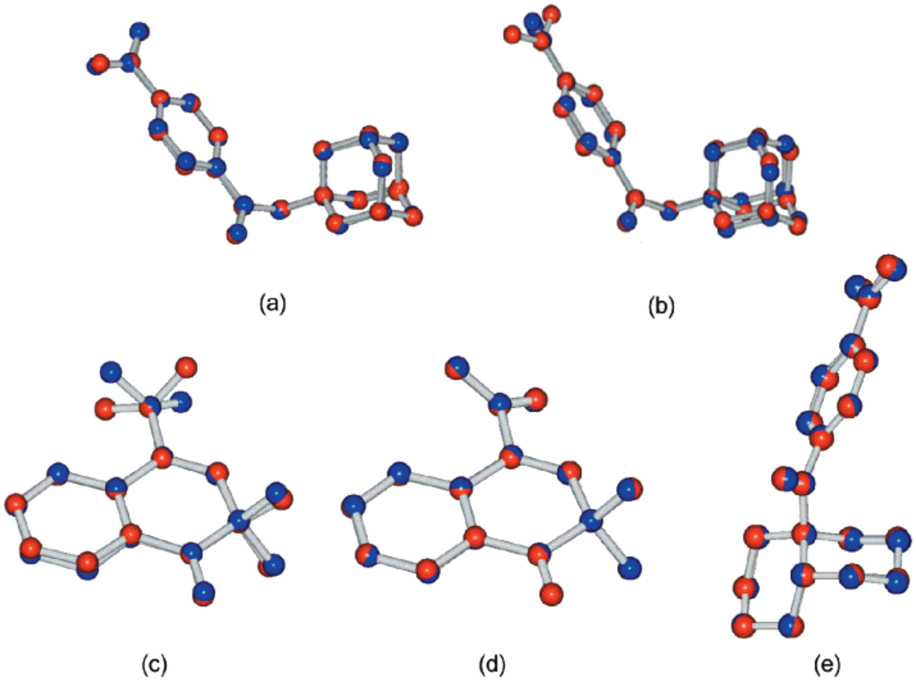

Figure 1. RMS overlays of anions. (a) Plate dimorph of **1** (chirality-matched). (b) Plate (red atoms) and needle (blue atoms) dimorphs of **1**. (c) Native conformations in **3**. (d) Chirality-matched conformations in **3**. (e) Chirality-matched conformations in **5**.

ketoester **4** (Scheme 1).[12] The photolabile anions are rigid; hence, conformationally induced stereocontrol was expected to be limited in salts containing this moiety. Indeed, overlap of the two independent anions (Figure 1c, RMSE = 0.47 Å) reveals that the ring systems are nearly coplanar. The pendant carboxyl groups, however, are related to the ring system with torsional angles of opposite sign (36.0° and −36.9°). Stereochemical inversion of one anion with subsequent superposition onto the other results in a striking picture (Figure 1d). With the near perfect overlap reflected in the negligible RMSE of 0.03 Å, one would expect, as in the case of the needle dimorph of **1**, that the existence of enantiomeric anions in equal proportion should result in racemic **4**. The observed ee at 7% conversion is an astonishing 55%, which underlines the dramatic influence that the reaction cavity can have on the selectivity of reactions carried out in organized media, independent of reactant geometry.

In a third example, an intermediate enantiomeric excess of 30% is observed in the solid-state Yang photocyclization of salt **5**[13] to cyclobutanol **6**.[14] Here again, the RSME in the overlap of the carboxylate anions drops from 1.39 Å in the native state, to 0.08 Å once the chirality of the anions is matched (Figure 1e). In total, we have encountered seven salts[15] that crystallize in this fashion, providing enantiomeric excesses from 0 to 55%. In each case the two conformers of the prochiral ions exist as near perfect conformational enantiomers.[16,17]

Crystallographically, a pseudo-inversion center relating the two conformers has been identified in each case except one. This motif is reminiscent of the majority of racemate crystals, in which pairs of enantiomers that are related by a center of inversion form a repeating unit.[18] Packing of this type tends to reduce the amount of void space in the crystal and may allow the counterions to approach each other more closely, thereby reducing electrostatic potential and facilitating the formation of more elaborate hydrogen-bonding networks.

In summary, we have identified a recurring and previously undocumented mode of crystal organization. Not only does this unique packing arrangement provide further depth to our studies of asymmetric induction in the solid state, but it also allows the influence of crystal packing on chemical behavior to be measured directly in the absence of conformational bias.

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[10] Visual inspection of the reaction cavity often provides no obvious explanation for reaction selectivity, which is the cumulative result of a large number of small interactions and requires detailed computational analysis. Studies of this type, which were pioneered by Zimmerman and co-workers (Zimmerman, H. E.; Sebek, P.; Zhu, Z. *J. Am. Chem. Soc.* **1998**, *120*, 8549 and references therein) are planned for the compounds described in this work. For a related example of the type of calculations required, see: Garcia-Garibay, M. A.; Houk, K. N.; Keating, A. E.; Cheer, C. J.; Leibovitch, M.; Scheffer, J. R.; Wu, L.-C. *Org. Lett.* **1999**, *1*, 1279.

[11] Salt **3**: $P2_1$; $a = 14.299(1)$ Å; $b = 8.2457(6)$ Å; $c = 21.780(2)$ Å; $\beta = 98.126(2)°$; $Z = 4$; $R = 4.5\%$.

[12] Cheung, E.; Netherton, M. R.; Scheffer, J. R.; Trotter, J. *Tetrahedron Lett.* **1999**, *40*, 8737. Possible mechanistic scenarios are discussed in this reference.

[13] Salt **5**: $P2_1$; $a = 13.959(2)$ Å; $b = 6.396(2)$ Å; $c = 26.705(5)$ Å; $\beta = 97.58(2)°$; $Z = 4$; $R = 4.3\%$.

[14] Cheung, E.; Kang, T.; Raymond, J. R.; Scheffer, J. R.; Trotter, J. *Tetrahedron Lett.* **1999**, *40*, 8729.

[15] In addition to the three salts discussed in this work two are as yet unpublished. For the remaining two see: (a) Cheung, E.; Rademacher, K.; Scheffer, J. R.; Trotter, J. *Tetrahedron Lett.* **1999**, *40*, 8733. (b) Koshima, H.; Maeda, N.; Masuda, N.; Matsuura, T.; Hirotsu, K.; Okada, K.; Mizutani, H.; Ito, Y.; Fu, T. Y.; Scheffer, J. R.; Trotter, J. *Tetrahedron: Asymmetry* **1994**, *5*, 1415.

[16] Although we have observed this unique crystal packing predominantly in organic salts, we have documented this behavior in other systems containing both optically pure and achiral components. See ref 15b (compound **1e**) for an example involving a complex between a zwitterion and a neutral organic molecule, and ref 12 for a crystalline complex of an organic salt with a neutral organic molecule.

[17] The RMS overlap for the two conformers of each cation in salts **1**, **2**, and **3** (0.58, 0.47, and 0.26 Å, respectively) is only slightly decreased by inversion in salt **1** (0.40 Å) and increases for salts **2** and **3** (1.14 and 0.39 Å, respectively).

[18] It has been recognized for many years that inversion centers are favored in the structures of molecular crystals. See: Brock, C. P.; Dunitz, J. D. *Chem. Mater.* **1994**, *6*, 1118 and references therein.