Structure−Reactivity Correlations for Solid-State Enantioselective Photochemical Reactions Established Directly from Powder X-ray Diffraction

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Among the wide-ranging areas of interest in organic solid-state photochemistry[1] the drive to achieve asymmetric synthesis has led, inter alia, to the development of the chiral ionic auxiliary approach for generating chiral products from achiral reactant molecules in crystalline solids.[1e,f] However, in many cases of interest, the reactant material does not form single crystals of appropriate size and quality to allow structural properties to be established using single-crystal X-ray diffraction techniques, thus limiting the opportunity to establish structure−reactivity correlations in such cases.[2] In this paper, we demonstrate the successful application of modern powder X-ray diffraction techniques, using the direct space strategy[3] for structure solution, to establish structure−reactivity correlations for enantioselective reactions carried out within a series of photoreactive crystalline materials, focusing in particular on rationalization of the enantiomeric excesses (ee) observed in these reactions.

We focus on salts containing the carboxylate derivative of *trans*-9-decalyl arylketone (**1**) shown in Scheme 1, which undergoes a Norrish type II reaction under UV irradiation. The molecule **1** contains four γ-hydrogen atoms (H_A, $H_{A'}$, H_B, and $H_{B'}$) that may be potentially abstracted in this reaction, and subsequent Yang cyclization of the 1,4-biradical leads to a cyclobutanol photoproduct.[4] Abstraction of $H_A/H_{A'}$ leads to the two enantiomers of a given chiral cyclobutanol product (as shown in Scheme 1), whereas abstraction of $H_B/H_{B'}$ leads to the two enantiomers of a different chiral cyclobutanol product (not shown).

In this work, crystalline 1:1 salts were formed between **1** and optically pure amines [**a**: (1R,2S)-(−)ephedrine; **b**: (1R,2R)-(−)-pseudoephedrine; **c**: (R)-(+)-α-methylbenzylamine)]. Irradiation of these materials with Pyrex-filtered UV radiation is found[5] to yield the two enantiomers of the chiral cyclobutanol **2** (Scheme 1) via abstraction of $H_A/H_{A'}$. However, the reactions contrast markedly in the values of ee observed, with high ee for **1a** (82.8% ee at 13.7% conversion) and **1b** (84.4% ee at 17.3% conversion), but low ee for **1c** (11.4% ee at 27.9% conversion).

Given the lack of suitable single crystals of **1a**−**c**, the crystal structures were determined directly from powder X-ray diffraction data and provide a basis for rationalization of the observed differences in ee. In each case, powder X-ray diffraction data were recorded,[6] followed by successful unit cell determination[7] and space group assignment (P2₁2₁2₁ for **1a** and **1b**; P2₁ for **1c**). From density considerations, the number of formula units in the asymmetric unit (Z′) is deduced to be Z′ = 1 for **1a** and **1b** and Z′ = 2 for **1c**. Profile parameters for the powder X-ray diffraction patterns were obtained using the Le Bail fitting procedure,[8] and structure solution was carried out using the direct-space genetic algorithm (GA) technique[9,10] implemented in the program EAGER.[11] Following Rietveld refinement[12a] [results for which are shown in Figure 1 (for **1b**) and in Supporting Information (for **1a** and **1c**)] using the

Scheme 1
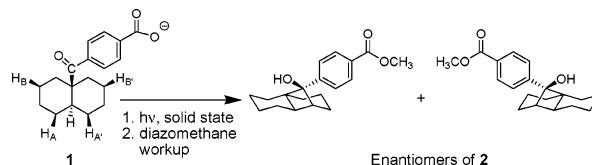
program GSAS,[12b] the crystal structures[13] were used as a basis for establishing structure−reactivity correlations.

The crystal structures of **1a** and **1b** are essentially isostructural and contain one formula unit in the asymmetric unit. In each case, the molecular conformation adopted by **1** in the crystal structure is such that the ketone oxygen atom has an unfavorable disposition for abstraction of $H_B/H_{B'}$ but a favorable disposition for abstraction of $H_A/H_{A'}$ (Figure 2a,b). Given the enantiotopic relationship between H_A and $H_{A'}$, abstraction of H_A or $H_{A'}$ leads, respectively, to the two enantiomers of the chiral cyclobutanol photoproduct **2** shown in Scheme 1. Moreover, the conformation of **1** in the crystal structures of **1a** and **1b** (Figure 2a,b) is such that abstraction of the *same* enantiotopic H atom ($H_{A'}$) is favored in each case (on the grounds that it is significantly closer to the carbonyl oxygen atom). These features are consistent with the high values of ee observed for the reactions in **1a** and **1b** and the fact that the *same* enantiomer of the cyclobutanol photoproduct is obtained in excess in each case.[5b]
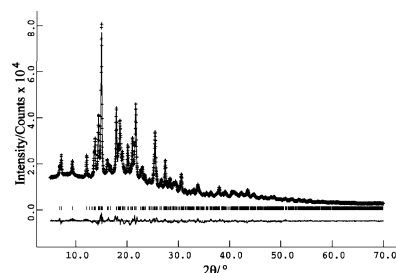

Figure 1. Experimental (+ marks), calculated (solid line), and difference (lower line) powder X-ray diffraction profiles in the final Rietveld refinement for **1b**.
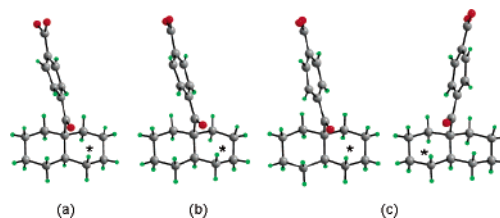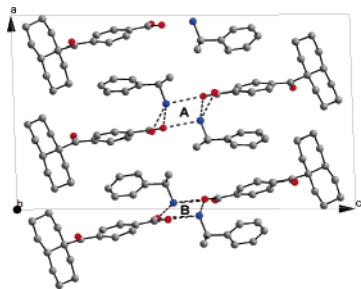

Figure 2. Conformation of **1** in the crystal structures (a) **1a**, (b) **1b**, and (c) **1c**. For **1c**, the two independent molecules (denoted types A and B in the text) are shown. In each case, the H atom implicated in the preferred abstraction reaction pathway is indicated by an asterisk.

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Figure 3. Crystal structure of **1c**. The two independent molecules of **1** and **c**, and their hydrogen-bonding networks, are denoted A and B. Hydrogen atoms are omitted for clarity.

The low ee for **1c** is also rationalized directly from the crystal structure. In this structure, the asymmetric unit contains two independent molecules of **1** (denoted types A and B) and two independent molecules of **c**. The crystal structure (Figure 3) has hydrogen-bonded chains running along the *b*-axis, with molecules of **1** and **c** alternating along these chains; there are two crystallographically independent chains, one containing only type A molecules of **1** and the other containing only type B molecules of **1**, and each chain forms hydrogen-bonded cross-linkages to an equivalent chain. Crucially, the molecules of types A and B differ in molecular conformation (see Figure 2c) and represent chiral conformations of opposite chirality [there is a near-mirror relationship (rms deviation 0.1 Å) between the conformations of types A and B]. Clearly, the conformation is predisposed toward abstraction of H_A in one case and abstraction of $H_{A'}$ in the other, leading to preferential formation of cyclobutanol photoproducts of *opposite* chirality. We therefore infer from the crystal structure that both enantiomers of **2** will be obtained in significant yield, although, as the relationship between the environments of molecule types A and B in the structure is diastereoisomeric, the rates of reaction to produce the two enantiomers of **2** are not necessarily identical, and the product may be expected to be richer in one enantiomer. Thus, on the basis of the crystal structure, a relatively low (but nonzero) ee is anticipated, as indeed observed experimentally. It is clear that "conformational enantiomerism"[14] (rather than crystallographic disorder,[15] which has been found to reduce ee in other solid-state photochemical reactions) is responsible for the relatively low ee observed for **1c**.

Although distance-based γ-hydrogen atom abstraction parameters[16] can provide quantitative rationalization of observed values of ee in solid-state reactions, we have not attempted to derive such parameters in the present case as the results may be biased by the geometric restraints applied in the Rietveld refinement.[17] Nevertheless, it is clear that the crystal structures determined here from powder X-ray diffraction data allow a direct and unequivocal understanding of the significant differences in ee observed for **1a** and **1b** in comparison with **1c**. Importantly, this work reiterates that structural problems in solid-state chemistry, which have traditionally been tackled using single-crystal X-ray diffraction, can also be directly amenable to rationalization by exploiting modern techniques for structure determination from powder X-ray diffraction data.

Supporting Information Available: Crystallographic data and results from Rietveld refinements. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Thomas, J. M. *Philos. Trans. R. Soc.* **1974**, *277*, 251. (b) Cohen, M. D. *Tetrahedron* **1987**, *43*, 1211. (c) Ramamurthy, V.; Venkatesan, K. *Chem. Rev.* **1987**, *87*, 433. (d) Toda, F. *Acc. Chem. Res.* **1995**, *28*, 480. (e) Gamlin, J. N.; Jones, R.; Leibovitch, M.; Patrick, B.; Scheffer, J. R.; Trotter, J. *Acc. Chem. Res.* **1996**, *29*, 203. (f) Scheffer, J. R.; Xia, W. J. *Top. Curr. Chem.* **2005**, *254*, 233.

(2) (a) Cheung, E.; Rademacher, K.; Scheffer, J. R.; Trotter, J. *Tetrahedron* **2000**, *56*, 6739. (b) Cheung, E.; Kang, T.; Raymond, J. R.; Scheffer, J. R.; Trotter, J. *Tetrahedron Lett.* **1999**, *40*, 8729. (c) Gudmundsdottir, A.; Scheffer, J. R.; Trotter, J. *Tetrahedron Lett.* **1994**, *35*, 1397.

(3) (a) Harris, K. D. M.; Tremayne, M.; Lightfoot, P.; Bruce, P. G. *J. Am. Chem. Soc.* **1994**, *116*, 3543. (b) Harris, K. D. M.; Tremayne, M.; Kariuki, B. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1626. (c) Chernyshev, V. V. *Russ. Chem. Bull.* **2001**, *50*, 2273. (d) David, W. I. F., Shankland, K., McCusker, L. B., Baerlocher, C., Eds. *Structure Determination from Powder Diffraction Data*; Oxford University Press: Oxford, U.K., 2002. (e) Harris, K. D. M.; Cheung, E. Y. *Chem. Soc. Rev.* **2004**, *33*, 526.

(4) (a) Wagner, P. In *Rearrangements in Ground and Excited States*; Mayo, P. D., Ed.; Academic Press: New York, 1980; Vol. 3, pp 381−444. (b) Yang, N. C. *J. Am. Chem. Soc.* **1958**, *80*, 2913.

(5) (a) Reaction products were characterized by liquid state ¹H and ¹³C NMR, MS, IR, and elemental analysis, giving spectroscopic and elemental analyses in accord with their assigned structures. (b) Values of ee were measured (for the methyl esters; see Scheme 1) on a Chiracel OD column; the sign of rotation was determined at 675 nm.

(6) Powder X-ray diffraction data were recorded at ambient temperature in transmission mode on a Siemens D5000 diffractometer (Cu Kα1; Ge monochromated; linear position-sensitive detector covering 8° in 2θ; 2θ range = 5−65° (**1a**, **1c**) and 5−70° (**1b**); step size = 0.019°; data collection time = 10 h).

(7) Using the program DICVOL: Boultif, A.; Louër, D. *J. Appl. Crystallogr.* **1991**, *24*, 987.

(8) Le Bail, A.; Duroy, H.; Fourquet, J. L. *Mater. Res. Bull.* **1988**, *23*, 447.

(9) (a) Kariuki, B. M.; Serrano-González, H.; Johnston, R. L.; Harris, K. D. M. *Chem. Phys. Lett.* **1997**, *280*, 189. (b) Harris, K. D. M.; Johnston, R. L.; Kariuki, B. M. *Acta Crystallogr., Sect. A: Found Crystallogr.* **1998**, *54*, 632. (c) Turner, G. W.; Tedesco, E.; Harris, K. D. M.; Johnston, R. L.; Kariuki, B. M. *Chem. Phys. Lett.* **2000**, *321*, 183. (d) Habershon, S.; Harris, K. D. M.; Johnston, R. L. *J. Comp. Chem.* **2003**, *24*, 1766. (e) Cheung, E. Y.; McCabe, E. E.; Harris, K. D. M.; Johnston, R. L.; Tedesco, E.; Raja, K. M. P.; Balaram, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 494.

(10) The GA technique carries out global optimization on a multidimensional R_{wp} hypersurface by mimicking the evolutionary processes that occur in biological systems. Each independent molecule in the asymmetric unit is defined by the following structural variables: the position (*x*, *y*, *z*) and orientation (θ, ψ, φ) of the molecule in the unit cell and *n* variable torsion angles (τ₁, ..., τ_n) defining the molecular conformation [**1a**: 2 molecules, 16 variables. **1b**: 2 molecules, 16 variables. **1c**: 4 molecules, 27 variables]. In each GA calculation, the population comprised 100 trial structures, with 50 mating and 20 mutation operations carried out per generation. In each case, the correct structure solution was obtained in less than 100 generations and was used as the starting structural model for Rietveld refinement.

(11) Habershon, S.; Turner, G. W.; Zhou, Z.; Kariuki, B. M.; Cheung, E. Y.; Hanson, A. J.; Tedesco, E.; Albesa-Jové, D.; Chao, M.-H.; Lanning, O. J.; Johnston, R. L.; Harris, K. D. M. *EAGER − A Computer Program for Direct-Space Structure Solution from Powder X-ray Diffraction Data*; University of Birmingham: Birmingham, U.K.

(12) (a) Rietveld, H. M. *J. Appl. Crystallogr.* **1969**, *2*, 65. (b) Larson, A. C.; Von Dreele, R. B. *General Structure Analysis System*, Los Alamos National Laboratory Report LAUR 86−748; Los Alamos National Laboratory, Los Alamos, NM, 2000.

(13) Final Rietveld refinement for **1a**: *a* = 6.74156(28) Å, *b* = 13.9904(6) Å, *c* = 25.7097(9) Å, *V* = 2424.8(4) Å³; R_{wp} = 0.0474, R_p = 0.0336 [100 variables, 3094 profile points]. **1b**: *a* = 6.73624(34) Å, *b* = 13.9700(11) Å, *c* = 25.6874(13) Å, *V* = 2417.3(2) Å³; R_{wp} = 0.0377, R_p = 0.0286 [100 variables, 3429 profile points]. **1c**: *a* = 14.1919(8) Å, *b* = 6.4486-(4) Å, *c* = 24.432(2) Å, β = 91.697(4)°, *V* = 2235.0(4) Å³; R_{wp} = 0.0465, R_p = 0.0346 [187 variables, 3094 profile points].

(14) Cheung, E.; Kang, T.; Netherton, M. R.; Scheffer, J. R.; Trotter, J. *J. Am. Chem. Soc.* **2000**, *122*, 11753.

(15) Cheung, E.; Netherton, M. R.; Scheffer, J. R.; Trotter, J. *J. Am. Chem. Soc.* **1999**, *121*, 2919.

(16) Ihmels, H.; Scheffer, J. R. *Tetrahedron* **1999**, *55*, 885.

(17) Standard restraints on bond lengths and bond angles were applied during Rietveld refinement, with these restraints gradually relaxed as the refinement progressed. Hydrogen atoms were omitted during structure solution and included at idealized positions during refinement.

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