Communications

Cocrystallization with Phosphine Oxide Derivatives as a Means of Modifying Photochemical Reactivity in the Solid State

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Scheme 1

In an important paper published in 1988, Etter and Baures showed that triphenylphosphine oxide, a good hydrogen-bond acceptor, forms large, high-quality crystals when cocrystallized with a variety of hydrogen-bond donors, a procedure that was promoted as a crystallization aid for compounds that do not crystallize well on their own.[1] With our interest in solid-state organic photochemistry,[2] it occurred to us that here was a simple method for growing crystals suitable for investigations of photochemical reactivity in a novel, "cocrystalline" medium—a medium that might lead to results different from those in other ordered as well as isotropic media. Of particular interest was the possibility of utilizing P-chirality to prepare optically active complexes for solid-state asymmetric induction studies.[3] The present communication reports our preliminary results along these lines.

The phosphine oxides chosen for investigation are those given by structures **1a-f** (Scheme 1). Ethanediylbis-(diphenylphosphine oxide) (**1b**)[4] was prepared by oxidation of the corresponding bisphosphine (Aldrich), and its chiral analogue **1c**, together with the new compounds **1d-f**, were prepared in optically pure (*S,S*) form by the procedure of Mislow et al.[5] The 9,10-ethenoanthracene derivative **2** was chosen as the hydrogen-bond-donating photoreactant. Previous work from our laboratory had shown that this material undergoes the di-π-methane photorearrangement in a variety of solid and liquid media to afford (after
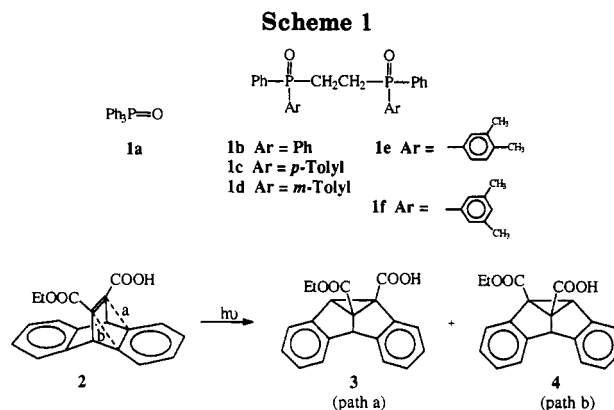
diazomethane workup) diesters of **3** and **4**.[6] The ratio in which these photoproducts are formed along with their optical purity is a sensitive probe of the nature of the reaction medium.

Cocrystals of carboxylic acid **2** with phosphine oxides **1a-f** were grown from mixed xylenes. The cocrystallization attempts were invariably successful, and in every case except **1f**, crystal quality was excellent. The complexes studied along with their melting points are listed in Table 1. The complexes were characterized as having 1:1 stoichiometry in the case of triphenylphosphine oxide (**1a**) and 2:1 stoichiometry in the case of phosphine oxides **1b-f** by ^{1}H NMR spectroscopy and elemental analysis; in addition, the triphenylphosphine oxide complexes prepared by crystallization from toluene and benzene (entries 3 and 4) were found to contain half a molecule of solvent per formula unit. Five of the complexes had their crystal and molecular structures determined by X-ray diffraction (entries 2, 3, 6-8). Of these, the last three were quite highly disordered. A brief summary of the crystallographic data is given in footnote 7. Table 1 also summarizes the results obtained when each of the complexes was irradiated in the crystalline state. For comparison purposes, the table includes the results of photolyzing carboxylic acid **2** in its pure crystalline state (entry 1).

The results outlined in Table 1 show that the solid-state photochemistry of carboxylic acid **2** is profoundly affected by cocrystallization with various phosphine oxides. In terms of regioselectivity, the **3/4** product ratio (which is 100:0 in benzene solution) ranges from 0:100 in crystals of pure **2** to 85:15 in the crystalline complex with ethanediylbis(diphenylphosphine oxide) (**1b**). Such variations are impossible to predict and very difficult to explain after the fact, even with the aid of X-ray crystallography. Owing to problems of disorder in the carboxylic acid substituent and in the ester substituent in the complexes

(1) Etter, M. C.; Baures, P. W. *J. Am. Chem. Soc.* **1988,** *110,* 639.

(2) (a) Scheffer, J. R.; Garcia-Garibay, M.; Nalamasu, O. In *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, 1987; Vol. 8, p 249. (b) Scheffer, J. R.; Pokkuluri, P. R. In *Photochemistry in Organized and Constrained Media*; Ramamurthy, V., Ed.; VCH Publishers: New York, 1991; Chapter 5, p 185.

(3) The concept of using crystal chirality to generate molecular chirality in a solid state chemical reaction is well established and has been approached experimentally in three major ways: (a) utilization of crystal chirality that is spontaneously generated during recrystallization of achiral substances, see: Casewell, L.; Garcia-Garibay, M. A.; Scheffer, J. R.; Trotter, J. *J. Chem. Educ.* **1993,** *70,* 785. (b) Chemical reactions of crystalline complexes formed between optically active host molecules and photoreactive guests, see: Ramamurthy, V. In *Photochemistry in Organized and Constrained Media*; Ramamurthy, V., Ed.; VCH Publishers: New York, 1991; Chapter 7, p 303. (c) Chemical reactions of crystalline salts formed between photoreactive, achiral carboxylic acids and optically active amines (or vice versa), see for example: Jones, R.; Scheffer, J. R.; Trotter, J.; Yang, J. *Tetrahedron Lett.* **1992,** *33,* 5481.

(4) Isslieb, K.; Muller, D. W. *Chem. Ber.* **1959,** *92,* 3175.

(5) Maryanoff, C. A.; Maryanoff, B. E.; Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1973,** *95,* 5839. Experimental details will be published in a later full paper.

(6) Gudmundsdottir, A. D.; Scheffer, J. R.; Trotter, J. *Tetrahedron Lett.* **1994,** *35,* 1397.

(7) Complex 2/**1a** (1:1): $P\bar{1}$; $a = 13.501(1)$ Å, $b = 14.845(1)$ Å, $c = 8.5190(6)$ Å; $\alpha = 102.208(7)°$, $\beta = 98.676(7)°$, $\gamma = 68.697(6)°$; $Z = 2$; $R = 0.039$. Complex 2/**1a**/disordered toluene (2:2:1): $P2_1/n$; $a = 8.546(2)$ Å, $b = 28.164(5)$ Å, $c = 14.368(2)$ Å; $\beta = 98.81(2)°$; $Z = 2$, $R = 0.052$. Complex 2/**1c** (*S,S*) (2:1): $P2_1$; $a = 8.988(4)$ Å, $b = 12.448(3)$ Å, $c = 26.452(4)$ Å; $\beta = 90.74(3)°$; $Z = 2$; $R = 0.053$. Complex 2/**1d** (*S,S*) (2:1): $P2_1$; $a = 9.117(3)$ Å, $b = 12.100(2)$ Å, $c = 26.602(2)$ Å; $\beta = 94.95(1)°$; $Z = 2$; $R = 0.063$. Compound 2/**1e** (*S,S*) (2:1): $P2_1$; $a = 9.184(6)$ Å, $b = 12.515(3)$ Å, $c = 26.567(5)$ Å; $\beta = 91.44(3)°$; $Z = 2$, $R = 0.051$.

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Table 1. Photochemistry of Carboxylic Acid 2 as a Function of Reaction Medium[a]

				% enantiomeric excess[b]	
entry	complex (ratio)	mp (°C)	3/4 ratio (% conversion)	3	4
1	2	220–221	0/100 (20)		
2	2/1a (1:1)	137–139	56/44[c]		
3	2/1a/toluene (2:2:1)	77–79	3/97 (19)		
4	2/1a/benzene (2:2:1)	79–80	1/99 (21)		
5	2/1b (2:1)	209–211	85/15[c]		
6	2/1c (S,S) (2:1)	191–193	65/35 (31)	−20	00
7	2/1d (S,S) (2:1)	188.5–190	18/82 (49)	+21	00
8	2/1e (S,S) (2:1)	173–174	27/73 (25)	−36	38
9	2/1f (S,S) (2:1)	158–159	44/56 (26)	+13	33
10	2/1f (R,R) (2:1)	158–159	46/54 (33)	−09	31

[a] Photolyses were carried out at room temperature on crystals crushed between Pyrex microscope slides; the light source was a Hanovia 450-W medium-pressure mercury lamp. The photolysis mixtures were treated with diazomethane, analyzed by gas chromatography to determine the extent of conversion, chromatographed on silica gel to remove unreacted starting material and the 3/4 ratios and enantiomeric excesses determined by ^{1}H NMR at 400 MHz by using the chiral shift reagent (+)-Eu(hfc)$_3$ (Aldrich). [b] For compound **3**, the sign of rotation of the predominant enantiomer could be assigned on the basis of previous chemical shift-absolute configuration correlations;[6] in the case of compound 4, such information is lacking and the net sign of rotation is unknown. From the NMR spectra, however, it is clear that the enantiomer of photoproduct 4 favored in run 8 is the same as that favored in run 9 and the optical antipode of that favored in run 10. [c] Product ratio constant with extent of conversion.
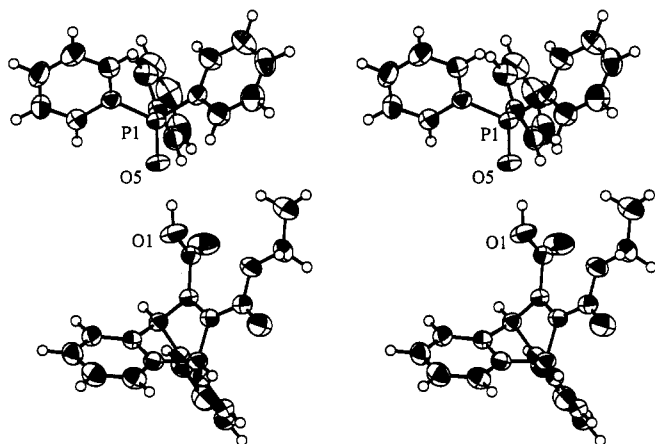

Figure 1. Stereodiagram of the complex formed between triphenylphosphine oxide and ethenoanthracene derivative **2** (entry 2, Table 1).

with bisphosphines **1c–e**, plus the fact that each contains two independent molecules of compound **2** in the asymmetric unit, only the crystal structures for the triphenylphosphine oxide complexes of entries 2 and 3 were of much use in analyzing the solid-state photoreactivity. A stereodiagram of the crystal structure corresponding to entry 2 is shown in Figure 1. Here we see that the carboxylic acid group is twisted 71° out of conjugation with the double bond, whereas the ester group is fully conjugated. This favors formation of photoproduct **3** as observed since, in the likely reaction mechanism,[8] initial bond formation will be preferred at the carbon atom of the double bond to which the COOH group is attached in order to place the resulting radical next to the fully conjugated ester substituent (path a, Scheme 1). An analogous argument rationalizes the reversed regioselectivity observed for the toluene-containing complex of entry 3. In this case, it is the ester substituent that is out of conjugation (by 69°) in the solid state, while the carboxylic acid group is nearly fully conjugated (14°). This would

favor formation of photoproduct **4** via path b as observed experimentally.[9]

In terms of enantioselectivity, the optically active bisphosphine oxides **1c–f** have relatively low powers of solid-state asymmetric induction. Phosphine oxide **1e** is best, but even there only modest enantiomeric excesses are achieved. Interestingly, even though phosphine oxides **1c–f** have identical (S,S) absolute configurations, two of the four lead to a preponderance of (+)-**3** and the other two give an excess of (−)-**3**. The ees reported in Table 1 are reproducible from run to run, both in sign and in magnitude, and our faith in them is bolstered by the fact that the enantiomers of phosphine oxide **1f** lead to mixtures enriched in enantiomeric forms of photoproduct **3** (entries 9 and 10). Unfortunately, for the reasons discussed above, the crystal structures of the complexes of compound **2** with phosphine oxides **1c–f** do not permit firm conclusions to be drawn regarding the source of the solid-state enantioselectivities which, in any event, are small. One conclusion that can be drawn from the asymmetric induction studies is that, contrary to what one might infer from the literature on the subject,[3] not all photoreactions of crystals in chiral space groups lead to high ees. Low ees probably just do not get submitted for publication.

In summary, the results of the present study indicate that phosphine oxides can be used as photochemically inert crystallization aids to provide new supramolecular media that alter solid state photochemical behavior and facilitate X-ray crystallographic investigations of structure–reactivity relationships. Work is continuing in our laboratory on the design, synthesis, and application of new phosphine oxide derivatives for this purpose.

(8) Zimmerman, H. E.; Sulzbach, H. M.; Tollefson, M. B. *J. Am. Chem. Soc.* **1993**, *115*, 6548.

(9) A correlation between extent of conjugation and regioselectivity is not always found in the solid-state photochemistry of 11,12-disubstituted ethenoanthracenes.[10] Because benzo–vinyl bridging requires substantial movement of the attached vinyl substituent, a second factor that must be considered is the free volume around each substituent in the crystal lattice. Visual inspection of the packing diagrams for the complexes of entries 2 and 3 reveals that, in both cases, the ester substituent of compound **2** is in a crowded environment. The strong hydrogen bond that exists between the COOH group of 2 and triphenylphosphine oxide (entries 2 and 3) very likely plays a role in these transformations as well.[11] Initial bridging that involves movement of the COOH group (path a) is disfavored because it disrupts hydrogen bonding. This effect would reinforce the conjugation effect in entry 3 but oppose it in entry 2, thus accounting for the lowered regioselectivity in the latter case. Except for high conversion runs with the relatively low melting complexes of entries 3 and 4, crystallinity is maintained throughout the photoreactions reported in Table 1. Although they were not determined, it seems unlikely that the crystal structures of the photoproducts play a role in determining regioselectivity, since product crystallization occurs only after its solubility in the reactant lattice is exceeded.

(10) Chen, J.; Scheffer, J. R.; Trotter, J. *Tetrahedron* **1992**, *48*, 3251.

(11) Garcia-Garibay, M. A.; Scheffer, J. R.; Watson, D. G. *J. Org. Chem.* **1992**, *57*, 241.