Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 8, pp. 1415-1418, 1994

0957-4166/94 $7.00+0.00

0957-4166(94)00195-2

IONIC CHIRAL HANDLE-INDUCED ASYMMETRIC SYNTHESIS IN A SOLID STATE NORRISH TYPE II PHOTOREACTION

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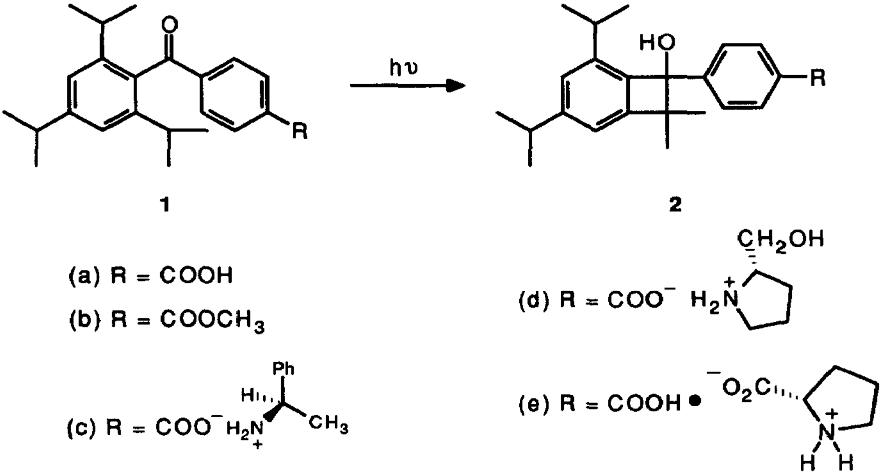
Abstract: Irradiation of crystals of salts formed between 4-(2,4,6-triisopropylbenzoyl)benzoic acid (**1a**) and various optically active amines is shown to lead to optically active Norrish type II photoproducts in low to moderate enantiomeric excesses, a process in which the ammonium ion has acted as an "ionic chiral handle." X-ray crystallography reveals that the salts crystallize with two independent, mirror image-related molecules of the benzophenone moiety in the asymmetric unit, and this is suggested to be the source of the low *ees* observed.

Despite the fact that optically active amines have been used for over a century to resolve carboxylic acids through the formation of diastereomeric salts that can be separated by fractional crystallization, their use as asymmetric induction agents in the *chemical reactions* of carboxylic acids is virtually unknown. This can be attributed to the likelihood that, in solution, the constituent ammonium and carboxylate ions are too loosely coordinated for one to exert a definitive asymmetric influence on the chemical reactivity of the other. In the crystalline state, however, where the ions are held in their lattice positions with fixed intra- and intermolecular geometries, asymmetric induction is much more likely, and several recent publications have documented exactly such an effect.[1-4] The term *ionic chiral handle* has been coined to describe the role of the optically active ammonium (or carboxylate) ions in such processes. In the present communication we describe the use of optically active ammonium ions as ionic chiral handles in the crystalline phase photochemistry of the 4-(2,4,6-triisopropylbenzoyl)benzoate anion.

In order to test the ionic chiral handle approach to asymmetric induction, the reactant should (1) contain an acidic or basic functional group, (2) be achiral, so that salt formation with an optically active amine or acid does not lead to diastereomers, and (3) react efficiently in the solid state to afford, after removal of the chiral handle, a product with one or more newly formed stereogenic centers. The 2,4,6-triisopropylbenzophenone system **1** appeared to offer excellent prospects: compounds of this type, while themselves achiral, have been shown to undergo photochemically-initiated Norrish type II reactions, both in solution and the solid state, to afford chiral benzocyclobutenols of general structure **2**.[5,6] All that was required for the present study, therefore, was to prepare the corresponding carboxylic acid derivative **1a**, and this was readily accomplished through hydrolysis of the corresponding methyl ester **1b**, a known compound.[5]

Salts of carboxylic acid **1a** were formed with the optically active amines (R)-(+)-α-methylbenzylamine (**1c**) and (S)-(+)-pyrollidinemethanol (**1d**). In addition, a crystalline, hydrogen-bonded complex (**1e**) could be obtained by allowing the solvent to evaporate slowly from a methanol/ether solution of an equimolar mixture of carboxylic acid **1a** and the amino acid (S)-(+)-proline. The new materials were fully characterized by IR, NMR, MS, elemental analysis and, in the case of **1d** and **1e**, by single crystal X-ray diffraction studies.[7]

Scheme 1



Finely divided samples of crystalline materials **1c** and **1e** were placed between Pyrex glass plates and photolyzed under argon in heat-sealed polyethylene bags. A similar procedure was followed in the case of salt **1d**, except that a specially designed photolysis apparatus was employed.[8] After photolyzing the samples to various conversions at various temperatures (see Table 1 for details), the reaction mixtures were acidified and extracted with ether. The ether extracts were washed with water to remove the ionic chiral handles and treated with excess diazomethane to form benzocyclobutenol methyl ester derivative **2b** along with **1b**, the methyl ester of unreacted starting material. The extent of conversion was estimated by GC, and the enantiomeric excess in which photoproduct **2b** was formed in each case was determined by chiral HPLC (Chiralcel OD and AD columns).

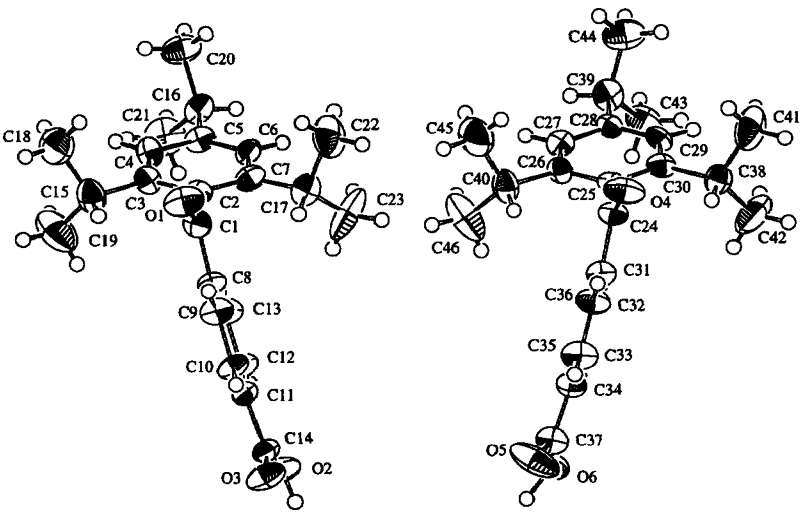
Table 1. Solid State Photolysis Results

Reactant	Photolysis Temp	Conversion	**2b** ee[a]
1c	–40 °C	2%	(+)-66%
1c	20 °C	10%	(+)-17%
1d	10 °C	26%	(–)-29%
1d	10 °C	77%	(–)-30%
1d	10 °C	99%	(–)-29%
1e	–40 °C	6%	(–)-26%
1e	20 °C	16%	nil

[a] Sign of rotation of major enantiomer shown in parentheses. Photolyses in ethanol gave racemic product only.

The results compiled in Table 1 indicate that lower photolysis temperatures increase the enantiomeric excesses and that *ee* is unaffected by increasing conversion, at least in the case of salt **1d**. The disappointing *ees* realized in the present work for reactants **1d** and **1e** have a clear origin in their solid state conformations as deduced from their X-ray crystal structures. Both salt **1d** and complex **1e** crystallize with two independent conformational isomers of the benzophenone moiety in the asymmetric unit. In each case, the independent conformers, which are chiral owing to their non-planarity, have a near mirror image relationship. This is illustrated in Figure 1 for complex **1e**. A convenient measure of the absolute configuration of the benzophenone units in this complex is the sign of the dihedral angle between the triisopropylphenyl group and the carbonyl group: O1-C1-C2-C3 = −77.7° and O4-C24-C25-C30 = +71.6°. An analogous situation obtains in the case of salt **1d**, but here the dihedral angles are much closer to 90°: half the benzophenone units deviate from planarity by −87.1° and the other half by +90.8°.

Figure 1. Independent Benzophenone Moieties in Complex **1e**.



The low *ees* in the case of complex **1e** can be ascribed to competing reactions in which half the molecules afford primarily one stereoisomer of **2b** while the other half lead mainly to its enantiomer. Because the reactions occur in a chiral environment, the competing processes have diastereomeric transition states of unequal energy, thus accounting for the non-racemic nature of the photoproduct mixture. This is not the first time such an explanation has been advanced. Jones et al.[3] observed an identical situation in the solid state photochemistry of the (S)-(+)-prolinol salt of α-adamantylacetophenone-p-carboxylate. Here, too, low *ees* were obtained (12%), and the crystal structure showed that, as above, there were two independent, mirror image conformers of the carboxylate moiety in the asymmetric unit. Lending credence to the argument in this case was the finding that photolysis of a dimorph of this material in which the carboxylate unit exists in a single, homochiral conformation afforded a photoproduct that was nearly enantiopure.[3] In the case of salt **1d**, the low *ees* obtained are probably more a reflection of the fact that the benzophenone units, with a carbonyl-aryl angle of essentially 90°, are poised to react non-stereoselectively. Which of these models (competing stereospecific reactions versus non-stereospecific reaction) applies to salt **1c** could not be determined crystallographically, as crystals of this material were not suitable for X-ray diffraction study.

The nature of complex **1e** deserves some comment. Proline should not be sufficiently basic to form a salt with carboxylic acid **1a**, and in agreement with this, crystals of complex **1e** are made up of molecules of compound **1a** in which the hydroxyl group is hydrogen bonded to the COO$^-$ group of one independent proline zwitterion and the carbonyl oxygen atom of the carboxylic acid group is hydrogen bonded to the NH_2^+ moiety of a second independent zwitterion. Gudmundsdottir and Scheffer[1] have reported other carboxylic acid/amino acid complexes that may be similar.

We close with a brief mention of the geometric parameters associated with the solid state γ-hydrogen abstraction processes in salt **1d** and complex **1e**. The data are summarized in Table 2 for the lowest values of d, the C=O···H distance, in each case; ω is the angle by which the γ-hydrogen atom lies outside the mean plane of the carbonyl group, Δ is the C=O···H angle, and θ is the C-H···O angle. The values in parentheses refer to the second molecule in the asymmetric unit. Overall, the data are similar to those associated with other Norrish type II systems that have been investigated by the crystal structure-reactivity correlation method,[9] although the values of Δ are somewhat lower than usual. Such geometric data, which are readily available through the use of force field calculations, now permit *predictions* to be made regarding Norrish type II photoreactivity.

Table 2. Hydrogen Atom Abstraction Geometry

Compound	d (Å)	ω (°)	Δ (°)	θ (°)
1d	2.74 (2.81)	58 (60)	58 (59)	119 (111)
1e	2.58 (2.59)	63 (62)	69 (69)	126 (125)

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. Financial support by the Natural Sciences and Engineering Research Council of Canada is also gratefully acknowledged.

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7. Salt **1d**: colorless prisms from ethanol, mp 212 °C; Anal. Calcd for $C_{28}H_{39}NO_4$: C, 71.30; H, 8.76; N, 2.97. Found: C, 71.28; H, 8.28; N, 2.88; $P2_12_12_1$; a = 51.70(2) Å, b = 11.743(7) Å, c = 9.045(3) Å; Z = 8; R = 6.8%. Complex **1e**: colorless needles from methanol/ether, mp 208-209 °C; Anal. Calcd for $C_{28}H_{37}NO_5$: C, 71.92; H, 7.98; N, 3.00. Found: C, 71.83; H, 8.00; N, 2.94.; $P2_1$; a = 11.650(3) Å, b = 8.530(8) Å, c = 26.837(3) Å, β = 97.60(1)°; Z = 4; R = 5.8%.
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(*Received in USA* 10 *May* 1994)