In the Footsteps of Pasteur: Asymmetric Induction in the Solid-State Photochemistry of Ammonium Carboxylate Salts

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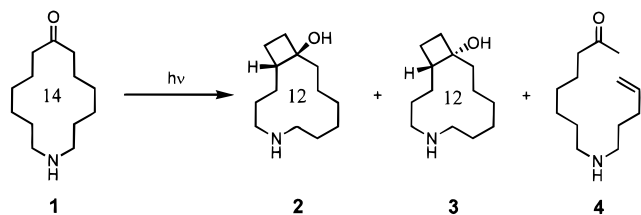John R. Scheffer,* and James Trotter

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In 1853, Louis Pasteur demonstrated that racemic tartaric acid could be separated into its "nonsuperposable right and left bodies" (i.e., its enantiomers) by treatment with an optically active amine (cinchonicine or quinicine) followed by fractional crystallization of the resulting mixture of diastereomeric salts.[1] In the intervening 145 years this procedure has been used countless times to resolve organic acids and bases of all types. An alternative *dynamic* approach to obtaining optically active carboxylic acids (amines) would be to generate them *in situ* from achiral precursors in the presence of optically pure amines (carboxylic acids). Such reactions proceed through ionic transition states that are diastereomerically related (Figure 1), and given a sufficiently large difference in activation energy for a kinetically controlled process,[2] one could in principle obtain near-quantitative yields of a single desired product enantiomer, rather than the 50% one is limited to in the more conventional Pasteur procedure. In the present communication we report the successful realization of this "ionic chiral auxiliary" approach to the synthesis of an optically active amine via the Yang photocyclization reaction, and show that, like the original Pasteur procedure, the key to success lies in utilizing the ionic crystalline state.[3]

The compound chosen for study was the achiral 14-membered ring aminoketone **1** (Scheme 1),[4] which undergoes efficient

Scheme 1

Norrish/Yang type II photochemistry[5] to give the chiral *cis*- and *trans*-cyclobutanols **2** and **3**, as well as the achiral cleavage
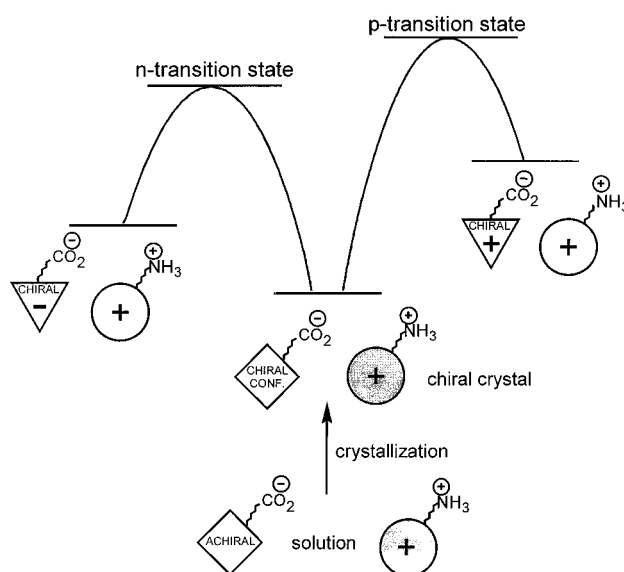
Figure 1. Hypothetical solid-state reaction of the anionic component of a salt of an achiral carboxylic acid with an optically pure amine to give a chiral product. The designation p refers to a salt in which the ions have the same sign of optical rotation; n refers to ions of opposite rotation.

product **4**.[6] Salts **5a−i**, formed between **1** and a number of commercially available, enantiomerically pure carboxylic, sulfonic, and phosphoric acids (Table 1), were prepared, recrystallized, and irradiated in the solid state and in solution (acetonitrile). X-ray crystal structures were obtained for the (S)-(−)-malate salt (**5a**) and the (2R,3R)-(+)-tartrate salt (**5d**).[7]

The results of the photochemical studies are reported in Table 1. A general trend is immediately apparent: while irradiation of the free amine in solution leads to products **2** and **3** in an approximately 2:1 ratio,[6] little or none of the *trans*-cyclobutanol **3** is produced when the salts are photolyzed in the crystalline state. Enantiomeric excesses obtained for *cis*-cyclobutanol **2** in the solid state range from excellent (**5a**−**5c**) to negligible (**5g**). As expected, irradiation of salt **5a** and its optical antipode **5b** gives rise to enantiomeric cyclobutanols of similar ee. This result demonstrates that the reacting systems are well-behaved, and can provide access to either enantiomer of **2** with a simple substitution of the chiral ionic auxiliary. As has been observed in other systems,[3] irradiation of these optically active salts in *solution* leads only to racemic cyclobutanols, a fact that serves to highlight the importance of conformational rigidity in controlling the course of the reaction. The observed decrease in enantioselectivity with increasing conversion results from the breakdown of the ordered crystal lattice as photoproducts replace starting material. Nevertheless, enantiomeric excesses of over 80% at 60−70% conversions indicate synthetic viability.

In the crystalline state, where molecular motions are severely restricted, the shape of the reactant as determined by X-ray crystallography has a direct bearing on the initial γ-hydrogen atom

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(1) Pasteur, L. *C. R. Acad. Sci.* **1853**, *37*, 162.

(2) It is to be expected that the conformationally flexible carboxylic acids (amines) that possess average achirality in solution will crystallize in homochiral conformations upon salt formation with optically pure amines (carboxylic acids). This *thermodynamic* component of the process, shown as the first step in Figure 1, may bias the reactant toward one of two possible diastereomeric pathways in the solid state. In the present example, the bias is large, but this need not always be the case. In general, therefore, the preference for formation of one product salt (n or p) over the other is best viewed as a *kinetic* differentiation between diastereomeric transition states of unequal energy.

(3) For previous examples of the utilization of the ionic chiral auxiliary approach to asymmetric synthesis in solid-state organic photochemistry, see: Gamlin, J. N.; Jones, R.; Leibovitch, M.; Patrick, B.; Scheffer, J. R.; Trotter, J. *Acc. Chem. Res.* **1996**, *29*, 203 and references therein.

(4) Macrocycle **1**, an apparently unknown compound, mp 33−34 °C, was synthesized by conventional Dieckmann condensation methodology. All new compounds described in the present paper gave spectroscopic data and elemental analyses completely in accord with their assigned structures. Details will be provided in a subsequent full paper.

(5) Reviews: (a) Wagner, P.; Park, B.-S. In *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York. 1991; Vol. 11, Chapter 4. (b) Wagner, P. J. *Acc. Chem. Res.* **1989**, *22*, 83.

(6) Quantum yields of reaction were measured in solution at 313 nm against a valerophenone actinometer. Benzene: $\Phi_2 = 0.105 \pm 0.009$, $\Phi_3 = 0.048 \pm 0.003$, $\Phi_4 = 0.057 \pm 0.004$; *tert*-butanol/benzene (2:1): $\Phi_2 = 0.218 \pm 0.003$, $\Phi_3 = 0.120 \pm 0.003$, $\Phi_4 = 0.097 \pm 0.003$. Triplet quenching studies with 2,5-dimethyl-2,4-hexadiene gave the following $\Phi_{triplet}/\Phi_{singlet}$ ratios in benzene: 3.1 (**2**), 6.9 (**3**), 2.7 (**4**). Photolysis of the salts in solution leads to product ratios that are essentially anion independent and very similar to those quoted above for the free amine.

(7) Salt **5a**: $P2_1$; $a = 7.3378(8)$ Å, $b = 5.9150(4)$ Å, $c = 21.041(2)$ Å; $\beta = 99.015(8)°$; $Z = 2$; $R = 3.2\%$. Salt **5d**: $P2_1$; $a = 10.209(1)$ Å, $b = 8.6709-(8)$ Å, $c = 10.972(1)$ Å; $\beta = 104.675(9)°$; $Z = 2$; $R = 3.9\%$. This structure is disordered in the macrocycle. X-ray crystallographic refinement of the populations gives a ratio of 72:28 for the two conformers (see text).

Table 1. Solid-State Photolysis Results for Chiral Salts of Aminoketone **1**

salt	acid	% conversion	% yield[a] 2	3	4	% ee[b]	α[c]
5a	(S)-(−)-malic acid	10	5	0	4	>98	−
		20	9	0	11	95.3	
		31	13	0	18	92.9	
		50	20	1	29	85.5	
		60	24	2	32	91.3	
5b	(R)-(+)-malic acid	11	6	0	5	>98	+
5c	(R)-(−)-2-hydroxy-	6	6	0	trace	>98	−
	5,5-dimethyl-4-phenyl-	21	17	0	4	>98	
	1,3,2-dioxaphosphorinane-	30	23	0	7	96.0	
	2-oxide	53	35	0	18	88.7	
		69	45	0	24	81.9	
5d	(2R,3R)-(+)-tartaric acid	5	5	0	0	42.9	−
		7	7	0	0	44.6	
		13	13	0	0	44.3	
		24	24	0	0	43.8	
5e	(R)-(+)-Mosher's acid	5	5	0	0	20.9	+
		9	9	0	trace	18.7	
5f	N-Cbz-L-alanine	15	12	1	2	37.8	−
5g	N-Cbz-L-phenylalanine	22	13	1	8	2.4	−
5h	N-Cbz-L-valine	15	10	2	3	30.2	+
5i	(1S)-(+)-10-camphor-	4	4	0	trace	52.8	−
	sulfonic acid	12	10	0	2	44.7	
		24	18	1	5	35.1	

[a] Irradiations were conducted with a Hanovia 450 W medium-pressure mercury vapor lamp through a Pyrex filter (λ > 290 nm). Solid-state irradiations were conducted on samples of 5−10 mg of crushed crystals sandwiched between two Pyrex plates. Yields were determined by GC following basic workup. [b] Enantiomeric excesses are reported for compound **2** and were measured by chiral capillary GC (β-Dex 390 column, 30 m, 0.25 mm i.d., 0.25 μm film thickness, Supelco). [c] Indicates the sign of rotation of the predominant enantiomer of **2** at the sodium D-line.

abstraction process, as well as on the behavior of the resulting 1,4-hydroxybiradical intermediate.[8] Figure 2a shows the solid-state conformation of the macrocycle in salt **5a**. Since the absolute configuration of the (S)-(−)-malate anion is known, the absolute conformation of the reacting macrocycle can be assigned unequivocally. The 14-membered ring adopts a [3434] conformation in which all ring atoms occupy diamond lattice positions.[9] The X-ray crystal structure clearly shows the carbonyl group poised to abstract only *one* γ-hydrogen (H$_a$), the other γ-hydrogens being too far away (>4 Å) and/or unfavorably oriented. At 3.09 Å, the C=O···H$_a$ distance, **d**, is the longest abstraction distance measured to date for a reactive aliphatic ketone.[10] The biradical formed by abstraction of H$_a$ has a pre-*cis* geometry (C−OH and Cγ−H bonds in a *syn* relationship), such that topochemically controlled, least motion cyclization leads to (−)-*cis*-cyclobutanol **2**.[11] Thus, the high enantioselectivity of the reaction is governed by the abstraction of only one of two formally enantiotopic γ-hydrogens,[12] while the product *cis/trans* diastereoselectivity arises from the fixed conformation of the intermediate biradical.

In the solid-state photochemistry of salt **5d**, the moderate ee of cyclobutanol **2** (ca. 44% in favor of the (−)-enantiomer) must
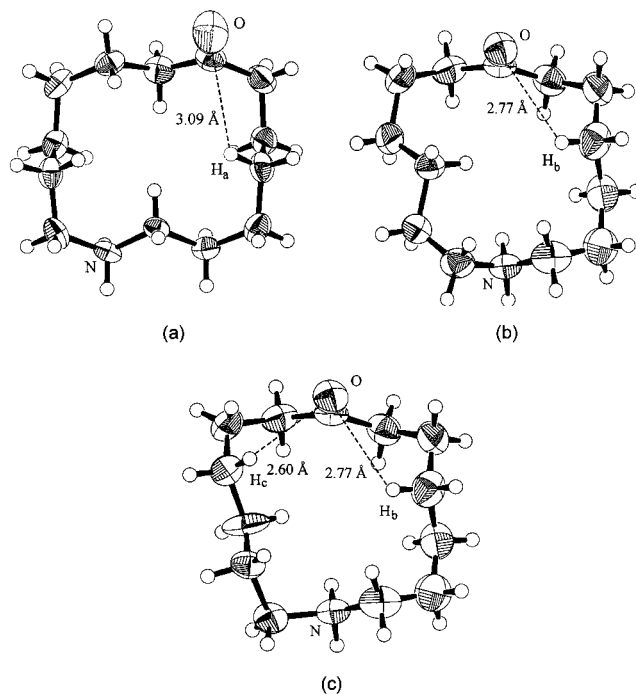
(a)

(b)

(c)

Figure 2. (a) Solid-state conformation of the ammonium ion in salt **5a**. (b) Solid-state conformation of the major component of salt **5d**. (c) Solid-state conformation of the minor component of salt **5d**.

be rationalized. Analysis of the X-ray data revealed disorder in the macrocycle. Two conformations were found (occupancy ratio 72:28), which differ only in the placement of four methylene groups. The major component adopts a nondiamond lattice twist [34′3′4′] conformation[9] (Figure 2b), while the minor component exists in a different nondiamond lattice conformation (Figure 2c). The major conformer contains only one abstractable γ-hydrogen (H$_b$, **d** = 2.77 Å), and the absolute conformation of the ring is similar to that of **5a**, such that formation of the (−)-enantiomer of cyclobutanol **2** is expected from reaction at this site. For the minor solid-state conformer, however, the stereoelectronically favored γ-hydrogen is H$_c$ (**d**$_c$ = 2.60 Å; **d**$_b$ = 2.77 Å), which predicts formation of the (+)-enantiomer of cyclobutanol **2**.[13] It is tempting, therefore, to equate the 44% enantiomeric excess favoring (−)-**2** with the 72% − 28% = 44% difference in conformer population, and this seems to be the most straightforward explanation of the reduced enantioselectivity in this case.[14]

In summary, the solid-state ionic chiral auxiliary approach promises to become one of the most general and powerful techniques for asymmetric synthesis in organic photochemistry,[15] and we are continuing our studies in this fascinating area.

(8) While crystallographic data obviously do not provide exact information on the situation in the excited state or in the biradical, there is every reason to believe that crystal structure−solid-state reactivity correlations for the Norrish/Yang reaction are approximately correct and can be used in a predictive sense. See: (a) Scheffer, J. R. In *Organic Solid State Chemistry*; Desiraju, G. R., Ed.; Elsevier: New York, 1987; Chapter 1. (b) Ihmels, H.; Scheffer, J. R. *Tetrahedron* **1999**, *55*, 885.

(9) For a discussion of the conformational analysis of 14-membered ring containing compounds, see: Keller, T. H.; Neeland, E. G.; Rettig, S.; Trotter, J.; Weiler, L. *J. Am. Chem. Soc.* **1988**, *110*, 7858.

(10) In previous work on the crystalline state photochemistry of a series of medium-sized and large-ring aliphatic diketones, the average value of **d**, the C=O···H$_γ$ abstraction distance, was found to be 2.74 ± 0.04 Å. See: Gudmundsdottir, A. D.; Lewis, T. J.; Randall, L. H.; Scheffer, J. R.; Rettig, S. J.; Trotter, J.; Wu, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 6167.

(11) For related examples of topochemically controlled cyclizations of photochemically generated pre-*cis* and pre-*trans* 1,4-biradicals, see ref 10.

(12) In terms of Figure 1, the result of crystallizing amine **1** as its malate salt is to render the abstraction of γ-hydrogens other than H$_a$ energetically prohibitive.

(13) For an example of complete discrimination in the type II abstraction of the nearer of two γ-hydrogen atoms whose **d** values differ by 0.27 Å, see ref 10.

(14) This explanation requires that the two conformers react with equal quantum efficiencies, and that the minor conformer reacts exclusively by abstraction of H$_c$. An alternative scenario is one in which the 44% ee is the accidental result of the minor conformer reacting more efficiently (more favorable abstraction parameters) than the major one, but with less than 100% enantioselectivity. Regardless of the details, it is clear that competing reactions from independent conformers are responsible for the low ee.

(15) For reviews on methods of asymmetric induction in organic photochemistry, see: (a) Inoue, Y. *Chem. Rev.* **1992**, *92*, 741. (b) Rau, H. *Chem. Rev.* **1983**, *83*, 535.