sistent with the observed tendencies of these molecules to interact with electrophiles.

However the most interesting aspects of this figure are the relatively strong negative regions near the lithiated carbon. These are quite unusual; negative potentials are not normally found associated with carbons.[14] Their occurrence here emphasizes the highly polar nature of the C–Li bond.

The electrostatic potential of 2-lithiocubanecarboxamide, the intermediate formed in the ortho-lithiation approach when the amide group is acting as the directing agent, is given in Figure 2. The presence of the amide group has greatly strengthened the negative region near the lithiated carbon, which now reaches a minimum of −83 kcal/mol. The reason for this is the attractive interaction, mentioned earlier, between the lithium and the amide oxygen. This causes the former to move away from its normal equilibrium position and toward the oxygen; the respective calculated distances are as follows: Li–C; 1.96 Å; Li–O, 1.80 Å. As a result, there is created a channel of strong negative potential, leading to the lithiated carbon (Figure 2).[15] Thus, the molecule is clearly activated for electrophilic attack at the carbon adjacent to the site of the amide group. (A qualitatively similar situation occurs if the amide is rotated 180° so that the lithium is interacting with the nitrogen, but the resulting negative channel is not as strong, its minimum being −73 kcal/mol.) When two methyls were substituted on the nitrogen, producing a tertiary amide group (**3**), the same sort of result was obtained; indeed the attractive channel is even slightly stronger, with a minimum of −85 kcal/mol.

Finally, we investigated the electrostatic potential of 3-lithio-*N*,*N*-dimethylcubanecarboxamide (**4**), in which the sites of the lithium and the amide group are separated by an intervening carbon. As seen in Figure 3, the distribution of negative potential around the lithiated carbon is now quite similar to what it was in lithiocubane (Figure 1). The presence of the amide group at this position no longer serves to activate the lithiated carbon toward electrophilic attack.

IV. Conclusion

The analysis presented in this paper provides a quantitative basis for the interpretation of several aspects of the observed activating and directing tendencies of amide substituents on cubane. First, we have demonstrated that there occurs an enhancement of the acidity of a hydrogen on an adjacent carbon, due to the stabilization of the anion formed by loss of the proton. Thus the hydrogen is susceptible to replacement by Li^+. The 2-lithio ("ortho") derivative is in turn stabilized by an interaction between the lithium and the amide oxygen (at least in the case of cubane carboxamide).

The polar nature of the C–Li bond makes the lithiated carbon a favorable site for electrophilic attack. This tendency is very much strengthened when the amide is situated on an adjacent carbon, because the lithium–amide interaction causes the former to move away from its normal position; this creates a channel of strongly negative electrostatic potential leading to the lithium-bearing carbon, thereby activating it toward electrophilic attack. This does not occur when the two substituted carbons are not adjacent to each other, and the substituents are consequently unable to interact.

By at least these several mechanisms, therefore, the amide group causes a very marked increase in reactivity toward electrophiles at a neighboring ("ortho") site on the cubane framework.

Acknowledgment. We thank Dr. Jane S. Murray and Dr. Gilbert Sollott for very helpful discussions and Dr. Dan Stec and Dr. Reddy Damavarapu for helping to prepare diagrams. We also express appreciation to the U.S. Army Research Office for partial support of this work.

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(14) An exception to this statement is tetraaluminacubane, in which alternate carbons of the cubane framework are replace by aluminum atoms. Strong negative potentials are found near the remaining carbons (Politzer, P.; Zilles, B. A., to be published).

(15) Similar although weaker negative channels have been found to develop when the hydrogens on various hydrocarbons are rotated away from their equilibrium positions. This has been used in interpreting and predicting the reactive behavior of these molecules. See, for example, ref 13a and also: Politzer, P.; Weinstein, H. *Tetrahedron* **1975**, *31*, 915. Chalvet, O.; Decoret, C.; Royer, J. *Tetrahedron* **1976**, *32*, 2927. Bertran, J.; Silla, E.; Carbon, R.; Martin, M. *Chem. Phys. Lett.* **1975**, *31*, 267.

Photolysis of *meso*- and *d,l*-Hydrobenzoin Carbonate

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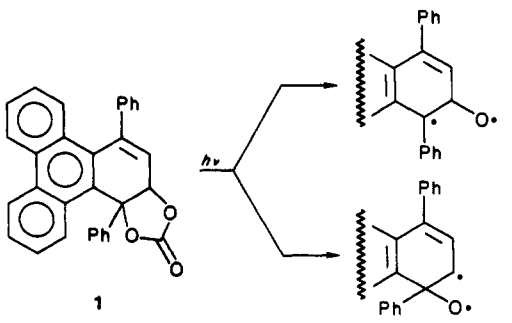
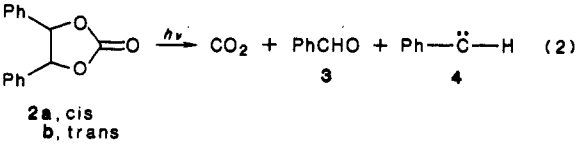
Received January 24, 1986

The photoextrusion of carbon dioxide from esters and lactones that bear radical stabilizing groups in the appropriate position is a well-known and general process.[1] Differing reports have appeared concerning the photolysis of cyclic carbonate esters. The photolysis of carbonate **1** proceeds with loss of carbon dioxide and the formation of two isomeric 1,3-diradicals which undergo further reaction as shown in eq 1.[2]



1 (1)

However, in another study, *meso*- and *d,l*-hydrobenzoin carbonate (**2a** and **2b**, respectively) were reported to yield carbon dioxide, benzaldehyde (**3**), and phenylcarbene (**4**) upon irradiation (254 nm, 14 h) as shown in eq 2.[3] The



2a, cis
b, trans (2)

(1) For a recent review on photoextrusion reactions, see: Givens, R. S. In *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, 1981; Vol. 5, p 227 ff.

(2) Harrison, E. A.; Ammon, H. L. *J. Org. Chem.* **1980**, *45*, 943.

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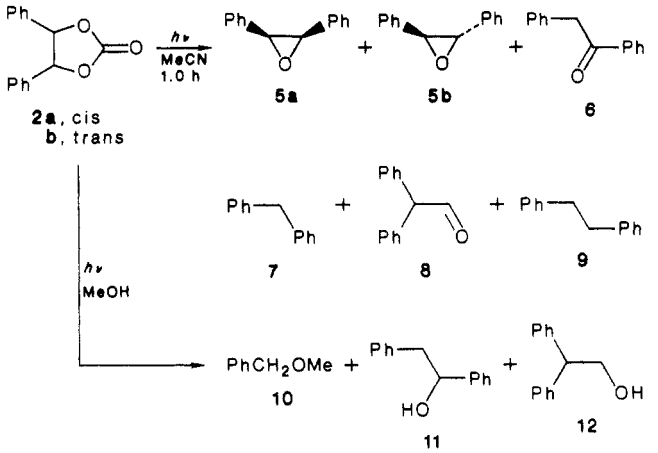
Table I. Direct Photolysis of 2a,b[a,b]

ester	solvent	% conversion	% 5a	5b	6	7	10
2a	MeCN	35	37	4	19	7	
2b	MeCN	44	16	28	32	7	
2a	MeOH	61	29	4	4	6	10
2b	MeOH	65	4	16	5	4	11

[a] Photolyses were carried out for 60 min and analyzed by HPLC employing a reversed-phase C-18 column with 65:35 MeCN/H_2O at 0.8 mL/min. [b] Yields are based upon amounts of starting material consumed during the reaction. In all cases, small amounts of diphenylacetaldehyde were detected. In methanol, 1,2-diphenylethenol and 2,2-diphenylethanol were detected in small amounts.

authors noted the absence of any products which might arise from a 1,3-diradical. In view of these results, we reexamined the photochemistry of **2a** and **2b** to gain further insight into the photochemistry of this functional group.

We found that the direct irradiation of a 2×10^{-3} M solution of **2a** (254 nm, 1.0 h, MeCN) produced *cis*-stilbene oxide (**5a**), *trans*-stilbene oxide (**5b**),[4] deoxybenzoin (**6**), and diphenylmethane (**7**) along with smaller amounts of diphenylacetaldehyde (**8**)[5] and bibenzyl (**9**). The photolysis of the trans isomer **2b** under the same conditions produced the same products except that the trans oxirane **5b** is the major oxirane formed. These results are summarized in Table I.



When the photolysis of **2a** was carried out in methanol, the same products were obtained along with benzyl methyl ether (**10**),[6] 1,2-diphenylethanol (**11**), and 2,2-diphenylethanol (**12**). These results are also summarized in Table I.

Prolonged irradiation **2a** and **2b** at 300 nm in the presence of either benzophenone, acetophenone, or acetone failed to produce any photoproducts, and the starting material was recovered unaltered. Thus, the reaction appears to proceed by a singlet state consistent with the photolysis of other aryl esters.[1]

The stilbene oxides could be produced by a singlet diradical as suggested by Harrison.[2] However, one could not discount the concerted formation of the stilbene oxides followed by secondary photoreactions to produce **6** and **7**. Analysis of the products produced in the photolysis of **2a** in acetonitrile through the first 5 min by HPLC gave the results shown in Figure 1. This shows that **6** and **7** are primary photoproducts formed from **2a** and not secondary products. This is also supported by the observation that irradiation of *cis*-stilbene oxide under the same conditions

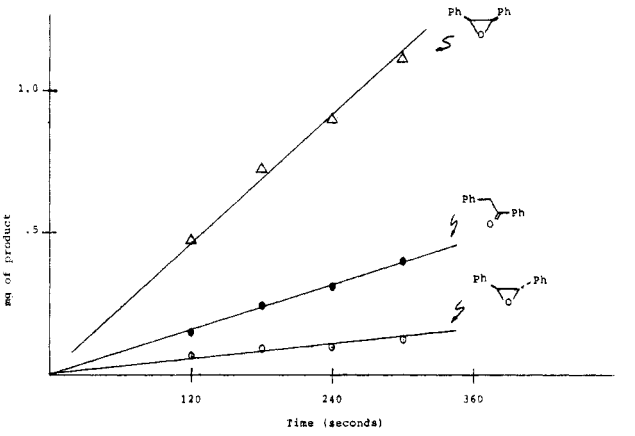
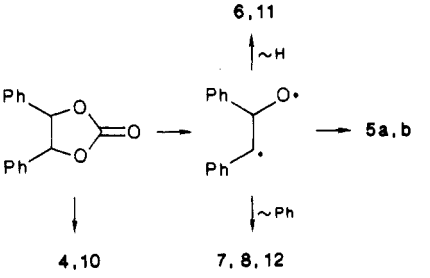


Figure 1. Formation of **5a**, **5b**, and **6** during the initial phases of the photolysis of *meso*-hydrobenzoin carbonate in acetonitrile.

Scheme I. Fragmentation Pathways in the Photolysis of *meso*- and *d,l*-Hydrobenzoin Carbonate



employed for the photolysis of **2a** failed to produce detectable amounts of diphenylmethane.

The observation that diphenylacetaldehyde (**8**) is present in the reaction mixture suggests that **7** is formed by decarbonylation of **8**, consistent with the results obtained in the irradiation of *meso*- and *d,l*-hydrobenzoin sulfite.[5] The bibenzyl is most likely formed by further irradiation of the deoxybenzoin.

In methanol, we find reduction products **11** and **12** as well as benzyl methyl ether (**10**). However, formation of **10** remains a minor pathway for aryl-substituted cyclic carbonate esters. Thus, the major photochemical pathway is loss of carbon dioxide to form a 1,3-diradical followed by ring closure or rearrangement. This is summarized in Scheme I.

Experimental Section

Melting points were determined with a Thomas Hoover capillary melting point apparatus. NMR spectra were obtained with a Varian EM360L spectrometer, and IR spectra were obtained with a Perkin-Elmer Model 1330 spectrophotometer. HPLC measurements were taken with a Tracor Model 880 liquid chromatograph with the UV detector set at 254 nm. Samples were analyzed on a reverse-phase C-19 column (Beckman) with 65:35 acetonitrile/water as the eluent and benzyl disulfide as an internal standard. GC/MS data were obtained with a Hewlett-Packard Model 5992B GC/mass spectrometer equipped with a 3 ft × $^1/_8$

(4) Oxiranes **5a,b** were isolated as a mixture from a preparative-scale photolysis by chromatography over silica gel (hexane) and their spectra compared with those of authentic samples.
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in. glass column of 2% OV-101. The GC parameters were set at 100 °C for 2 min and then rose 6 deg/min until the temperature reached 225 °C. Retention times and mass spectra were compared with those of authentic samples.

Diphenylmethane, deoxybenzoin, diphenylacetaldehyde, and *N,N'*-carbonyldiimidazole were commercially available (Aldrich). Benzyl methyl ether,[5] *cis*- and *trans*-stilbene oxide,[7] *meso*- and *d,l*-hydrobenzoin[3] benzylphenylcarbinol[8] and 1,1-diphenylethanol[8] were prepared by literature procedures.

***meso*-Hydrobenzoin Carbonate.** *meso*-Hydrobenzoin (2.0 g, 9.3 mmol) and *N,N'*-carbonyldiimidazole (1.6 g, 9.8 mmol) were dissolved in dry benzene (70 mL) and heated at reflux temperature for 3 h. After cooling, the benzene was washed with water (2 × 40 mL), dried (Na_2SO_4), and then removed by using a rotary evaporator to yield a colorless solid. Two recrystallizations from aqueous methanol gave **2a** (0.9 g, 40%), mp 125–126 °C (lit.[3] mp 126–127 °C).

***d,l*-Hydrobenzoin Carbonate.** This was prepared as above from *d,l*-hydrobenzoin, mp 109–110 °C (lit.[3] mp 110 °C).

Photochemical Reactions. Direct irradiations were carried out with a Rayonet Photochemical Reactor (Southern New England Ultraviolet Co.) equipped with 8 RPR 2537 lamps. An example of the general method is given for the photolysis of **2a**. *meso*-Hydrobenzoin carbonate (**2a**) (52 mg, 0.22 mmol) was dissolved in 6 mL of purified acetonitrile, placed in a quartz phototube, and sealed with a rubber septum. The mixture was sparged for 30 min with deoxygenated nitrogen for 30 min and then photolyzed for 60 min. After GC/MS data was obtained on the photolysate, the solvent was removed, and the residue was examined by NMR. The spectrum revealed singlets at 6.0 (unaltered starting material), 4.32 (**5a**), 4.0 (**7**), 3.92 (**6**) and 3.83 ppm (**5b**). The HPLC measurements were carried out by repeating the photolysis and then adding the internal standard prior to analysis.

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Syntheses of the Enantiomers of Carnitine and 4-Methylcarnitine via the Chromatographic Resolution of γ-(Dimethylamino)-β-hydroxy Ester Precursors

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Received May 27, 1986

It is well-established that L-(−)-carnitine, **1a**, plays a critical role in human energy metabolism via the transport of long-chain fatty acids into mitochondria.[1-3] Considerable recent work has focused on the development of inhibitors of this transport system.[1]

A number of preparations for the enantiomers of carnitine have previously been described. Most of these involved the formation of chiral salts and their sometimes-tedious separations by crystallization.[4] Additionally, the chiral-template approach has yielded several syntheses using chiral carbohydrates as a starting point (e.g., D-mannitol,[5] D- and L-arabinose,[6] or L-ascorbic acid[6,7]), but these provide only a single enantiomer from the natural sugar. More recent reports describe chemomicrobiological syntheses of D- or L-carnitine.[8]

As part of a program to develop carnitine analogues as possible modulators of fatty-acid transport, we recently reported a new synthesis of D,L-carnitine[9] as well as the preparation of several previously unknown racemic methylated analogues.[10] Herein we report the chromatographic resolution of ethyl 4-(dimethylamino)-3-hydroxybutanoate[9,11] (**3**) via the ester formed with (*S*)-(+)-α-methoxyphenylacetic acid.[12] The separated diastereomers are easily and efficiently converted to the enantiomers of carnitine. Furthermore, the utility of this method for obtaining the enantiomers of carnitine analogues is illustrated by the preparation and isolation of all four stereoisomers of 4-methylcarnitine via the chromatographic resolution of ethyl 4-(dimethylamino)-3-hydroxypentanoate.

Results and Discussion

As shown in Scheme I, compound **3** was esterified to (*S*)-(+)-α-methoxyphenylacetic acid by using dicyclohexylcarbodiimide and (dimethylamino)pyridine in CH_2Cl_2[13] to give a 1:1 mixture of diastereomers **5a** and **5b**. The two diastereomers were readily distinguished by ^1H NMR in that the dimethylamino resonances occurred at 2.27 and 2.13 ppm for **5a** and **5b**, respectively. Flash chromatography of this mixture on silica gel using 40:5:1 hexane/ethyl acetate/Et_3N as eluent afforded (after two passes) 76% of pure **5b** and 60% of pure **5a** (isolated chromatographed yields).

The lower yield for **5a** resulted from trailing of the leading band **5b** during chromatography (such that several fractions of **5a** were contaminated with small amounts of **5b**). However, it should be noted that the elution order may be reversed (so that the precursor to **1a** is contained

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