(M^+, 3%), 272 (100%), 218 (9%), 175 (3%), 135 (100%), 120 (24%), 107 (33%), 93 (33%). This product was indistinguishable from an independently prepared sample.[3]

Anal. Calcd for $C_{17}H_{31}O_3NS$: C, 61.98; H, 9.49. Found: C, 61.75; H, 9.61.

Enol Ether 20. Copper-catalyzed conjugate addition of ethylmagnesium bromide to crotonate **19**,[10] prepared with crotonyl chloride and silver cyanide,[12] provided the adduct as a ca. 80:20 mixture of diastereomers (by ^{13}C NMR) in 89–97% yield. This adduct had the following properties: mp 53–54 °C; $[\alpha]^{20}_D$ −47.2° (*c* 1.7, chloroform); IR (film) 2950, 2925, 2875, 1725, 1455, 1385, 1375, 1350, 1330, 1280, 1260, 1200, 1180, 1145, 1100, 1050, 1020, 935, 775, 705, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 80 MHz) δ 1.20 (t, J = 7 Hz, 6 H), 0.63–2.50 (m, 24 H), 2.72 (A of ABq, J = 14 Hz, 1 H), 3.25 (B of ABq, J = 14 Hz, 1 H), 3.26 (q, J = 7 Hz, 4 H), 4.81–5.07 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz, resonances of major diastereomer) 11.18, 14.41, 19.15, 19.84, 20.28, 26.92, 29.28, 29.93, 31.91, 39.60, 41.43, 41.71, 44.40, 48.64, 49.13, 49.46, 78.00. Mass spectrum, *m/e* 387 (M^+, 1%), 372 (1%), 323 (2%), 315 (3%), 272 (25%), 252 (11%), 183 (36%), 135 (83%), 115 (100%). Anal. Calcd for $C_{20}H_{37}O_4NS$: C, 61.99; H, 9.62. Found: C, 62.15; H, 9.64. The crude enol phosphate, derived as usual from this adduct, was reduced as described above for phosphate 14 to provide in 55% yield (based on 64% conversion) enol ether **20** (>95% *Z*): $[\alpha]^{20}_D$ −27.3° (*c* 0.8, $CHCl_3$); IR (film) 3025, 2975, 2950, 2875, 1660, 1460, 1380, 1350, 1335, 1250, 1240, 1200, 1150, 1120, 1090, 1020, 940, 770, 710, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 80 MHz) δ 1.19 (t, J = 7 Hz, 6 H), 0.50–2.50 (m, 22 H), 2.68 (A of ABq, J = 14 Hz, 1 H), 3.27–3.66 (q, J = 7 Hz, 4 H; B of ABq, J = 14 Hz, 1 H), 3.94–4.23 (m, 2 H), 5.98 (dd, J = 3 Hz, 6 Hz, 1 H); mass spectrum, *m/e* 371 (M^+, 3%), 272 (47%), 208 (6%), 135 (100%), 120 (23%), 107 (44%), 93 (59%).

Anal. Calcd for $C_{20}H_{37}O_3NS$: M_r, 371.24945. Found: M_r (mass spectrum), 371.24818.

Typical Enol Ether Preparation with Triethylaluminum (Method B): Enol Ether 3. To a stirred solution of 350 mg (1.20 mmol) of phosphate **2** and 42 mg (0.04 mmol) of tetrakis(triphenylphosphine)palladium(0) in 1.5 mL of 1,2-dichloroethane at 0 °C was added over 5 min 3.0 mL (3.0 mmol) of a 1 M solution of triethylaluminum in hexane. Following the addition, the reaction mixture was allowed to warm to room temperature and was then stirred for 30 min, after which it was diluted with ether. After being washed successively with cold 2% aqueous hydrochloric acid, water, and brine, the ethereal solution was dried over potassium carbonate and then concentrated. Filtration of the residue through florisil with ether in pentane provided 88 mg (52%) of enol ether **3**: IR (film) 3025, 3000, 2925, 2850, 2825, 1660, 1445, 1390, 1290, 1260, 1230, 1110, 1085, 975, 935, 885, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 80 MHz) 0.65–2.11 (m, 10 H), 2.11–2.71 (m, 1 H), 3.56 (s, 3 H), 4.22 (dd, J = 6 Hz, 9 Hz, 1 H), 5.77 (dd, J = 1 Hz, 6 Hz, 1 H); mass spectrum, *m/e* 140 (M^+, 38%), 108 (34%), 97 (100%).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.06; H, 11.56.

Enol Ether 6. Treatment of 114 mg (0.29 mmol) of phosphate **5** in 0.7 mL of dichloroethane with 16 mg (0.01 mmol) of the palladium catalyst and 1.2 mL (1.2 mmol) of the triethylaluminum solution gave 63 mg (89%) of enol ether **6**: $[\alpha]^{23}_D$ 64.7° (*c* 1.2, cyclohexane); IR (film) 3050, 3025, 2950, 2925, 2860, 2840, 1660, 1465, 1445, 1380, 1250, 1120, 1090, 1070, 745, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 80 MHz) δ 0.50–1.59 (m, 9 H), 0.82 (d, J = 7 Hz, 3 H), 0.99 (d, J = 7 Hz, 3 H), 1.59–2.35 (m, 3 H), 4.23 (d, J = 6 Hz, 1 H), 4.28 (pseudo q, J = 7 Hz, 1 H), 5.84 (dt, J = 1 Hz, 6 Hz, 1 H), 7.26 (s, 5 H); mass spectrum, *m/e* 246 (M^+, 3%), 205 (18%), 133 (100%), 132 (34%), 105 (9%).

Anal. Calcd for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 82.93; H, 11.06.

Enol Ether 18. Treatment of 136 mg (0.34 mmol) of phosphate **17** in 1 mL of dichloroethane with 20 mg (0.02 mmol) of the palladium catalyst and 0.69 mL (0.69 mmol) of the triethylaluminum solution for 15 h afforded 61 mg (73%) of enol ethers **18**: IR (film) 3075, 3050, 3025, 2925, 2850, 1650, 1600, 1490, 1440, 1390, 1370, 1280, 1190, 1170, 1140, 1070, 1025, 755, 595 cm^{-1}; ^{1}H NMR ($CDCl_3$, 80 MHz) δ 0.50–2.00 (m, 13 H), 1.93 (d, J = 1 Hz, *Z*-CH_3), 2.00 (d, J = 1 Hz, *E*-CH_3), 3.90 (t, J = 7 Hz, *Z*-CH_2O), 3.95 (t, J = 7 Hz, *E*-CH_2O), 6.26 (q, J = 1 Hz, *Z*-HC=), 6.57 (q, J = 1 Hz, *E*-HC=), 7.00–7.50 (m, 5 H). ^{1}H NMR at 300 MHz indicated a 4:1 mixture of *E* and *Z* isomers (assigned by NOE studies). Mass spectrum, *m/e* 244 (M^+, 100%), 134 (100%), 111 (26%), 105 (38%), 69 (100%).

Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.41; H, 9.74.

Acknowledgment. We thank Dr. Luche for his interest in our work and the CNRS (UA 332) for financial support. A.M. is grateful to NATO for a postdoctoral fellowship.

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A Computational Investigation of the "Ortho"-Directing Effect in Cubanecarboxamide

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I. Introduction

A very useful route for the regiospecific synthesis of a variety of polysubstituted aromatic systems makes use of the fact that certain functional groups X promote lithiation of an ortho position on the ring, which is subsequently susceptible to electrophilic attack (Scheme I).[1]

A number of different groups have this directing ability, with tertiary amides being the most effective.[1,2] Other very useful ones include oxazines[3] and oxazolines;[4] these have the advantage of being readily hydrolyzable (to carboxylic acids) once their ortho directing function has been performed. The directing group X is believed to exert its effect via several different mechanisms, including enhancement of the acidity of the neighboring hydrogen (to permit its replacement by Li^+) and also interactions between X and first the lithiating agent and then the lithium after it is in the ortho position.[1b,5]

In recent years, the ortho-lithiation technique has been extended to the synthesis of other types of compounds, including nonaromatic systems.[5,6] In particular, it has been shown that this approach can be used to achieve the functionalization of cubane.[7] *N,N*-Diisopropylcubanecarboxamide was treated with lithium tetramethylpiperidide and, after formation of a mercurated intermediate, eventually yielded both the 2-iodo and the 2,6-diiodo derivatives of the starting amide. It was suggested that the initial lithiated system is stabilized by an interaction

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[1] This general approach has been reviewed by: (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* (*N.Y.*) **1979**, *26*, 1. (b) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306.

[2] (a) Beak, P.; Brown, R. A. *J. Org. Chem.* **1977**, *42*, 1823. (b) Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34.

[3] Meyers, A. I.; Politzer, I. R.; Bandlish, B. K.; Malone, G. R. *J. Am. Chem. Soc.* **1969**, *91*, 5886.

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[5] Klumpp, G. W. *Recl. Trav. Chim.* **1986**, *105*, 1.

[6] (a) Klumpp, G. W.; Kool, M.; Schakel, M.; Schmitz, R. F.; Boutkan, C. *J. Am.* Chem. *Soc.* **1979**, *101*, 7065. (b) Marsais, F.; Queguiner, G. *Tetrahedron Lett.* **1983**, *39*, 2009.

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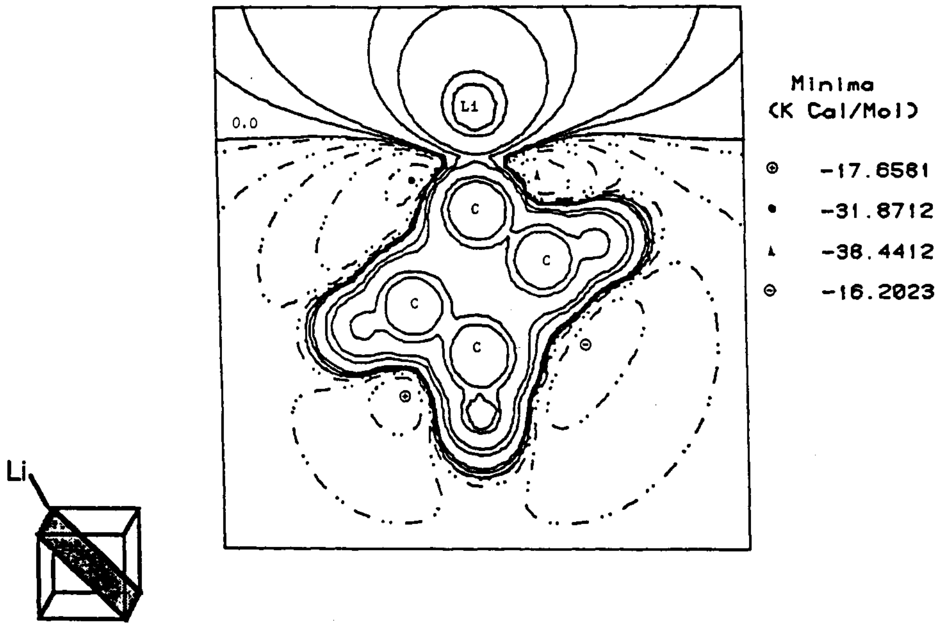


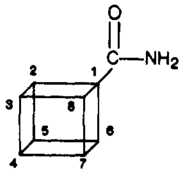
Figure 1. Calculated electrostatic potential of lithiocubane (**2**) in a diagonal plane, as shown. Dashed contours correspond to negative potentials; The zero contour is shown. The magnitudes of the other contours are in kcal/mol: −25.01, −12.5, −6.3, −3.1, −0.6, 3.1, 6.3, 31.4, 62.7, 313.7, 627.5. The locations and values of the minima are indicated.

between the lithium and the oxygen of the adjacent amide group.[7]

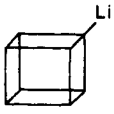
Our objective in this work has been to investigate the manner in which an amide group activates cubane for lithiation. Since this activation is believed to involve enhancement of the acidity of a neighboring hydrogen, our study has included a comparison of the amidocubane anions formed by loss of a proton at each possible position on the cubane framework, as well as an examination of the interaction between the amide and an adjacent lithium substituent. One of our aims is to be able to predict the likely sites for lithiation of polysubstituted cubanes.

II. Methods

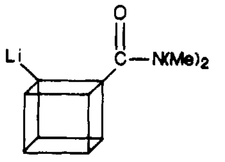
The systems that we have studied are cubanecarboxamide (**1**), its three isomeric anions formed by loss of a proton at positions 2, 3, or 4, its 2-, 3-, and 4-lithio derivatives, lithiocubane (**2**), and 2- and 3-lithio-*N*,*N*-dimethylcubanecarboxamide (**3** and **4**). Our approach is a computational one, involving ab initio self-consistent field (SCF) molecular orbital calculations at the STO-3G level with the GAUSSIAN 82 program.[8] The initial phase of the study of each system was the determination of its optimized geometry.



1



2



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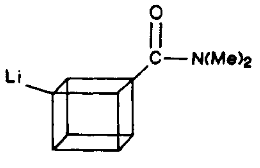
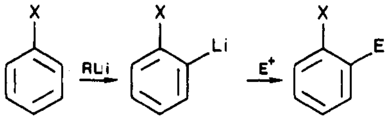


4

Scheme I



One of the key elements of our investigation is the analysis of the electrostatic potential of each molecule of interest. This is the potential $V(\vec{r})$ that is created at any point $\vec{r}$ in the surrounding space by the nuclei and electrons of the molecule; it is given rigorously by eq 1.

$$V(\vec{r}) = \sum_{A} \frac{Z_A}{|\vec{R}_A - \vec{r}|} - \int \frac{\rho(\vec{r}\,')\,d\vec{r}\,'}{|\vec{r}\,' - \vec{r}|} \qquad (1)$$

Z_a is the charge on nucleus A, located at $\vec{R}_A$, and p($\vec{r}$) is the electronic density function of the molecule, which we obtain from an SCF wave function at the STO-5G level.

The first term on the right side of eq 1 represents the contributions of the nuclei to the electrostatic potential, while the second gives that of the electrons. Thus an approaching electrophile will initially tend to go to those regions in which $V(\vec{r})$ is negative, indicating that the effects of the electrons predominate. The electrostatic potential is now well established as a means for interpreting and prediciting the reactive behavior of molecules.[9-11] One of its very important features is that it is a real physical property, which can be determined experimentally as well as computationally.[11]

III. Results and Discussion

1. Structures and Energies. Of the three isomeric anions of cubane carboxamide, the "ortho" or 2-anion is the most stable, by 5.5 and 5.3 kcal/mol relative to the 3- and 4-anions, respectively. This indicates that the hydrogens adjacent to the amide group are the most acidic, which may reflect stabilization of the anion by delocalization of its charge, with the inductive effect of the amide

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(8) Binkley, J. S.; Frisch, M.; Raghavachari, K.; DeFrees, D.; Schlegel, H. B.; Whiteside, R.; Fluder, E.; Pople, J. A. GAUSSIAN 82, Release H, Carnegie-Mellon University.

(9) Scrocco, E.; Tomasi, J. *Adv. Quantum Chem.* **1978**, *11*, 116.

(10) Politzer, P.; Daiker, K. C. In *The Force Concept in Chemistry*; Deb, B. M., Ed.; Van Nonstrand-Reinhold: New York, 1981; Chapter 6.

(11) Politzer, P., Truhlar, D. G., Eds. *Chemical Applications of Atomic and Molecular Electrostatic Potentials*; Plenum: New York, 1981.

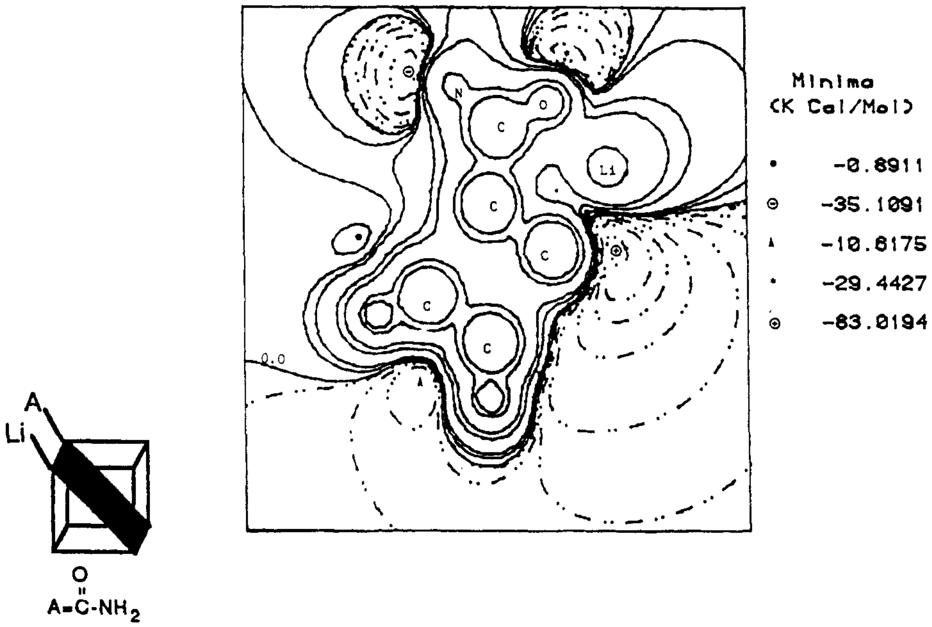

Figure 2. Calculated electrostatic potential of 2-lithiocubanecarboxamide in a diagonal plane, as shown. Dashed contours correspond to negative potentials; The zero contour is shown. The magnitudes of the other contours are in kcal/mol: −50.2, −37.65, −25.01, −12.5, −6.3, −3.1, −0.6, 3.1, 6.3, 31.4, 62.7, 313.7, 627.5. The locations and values of the minima are indicated.

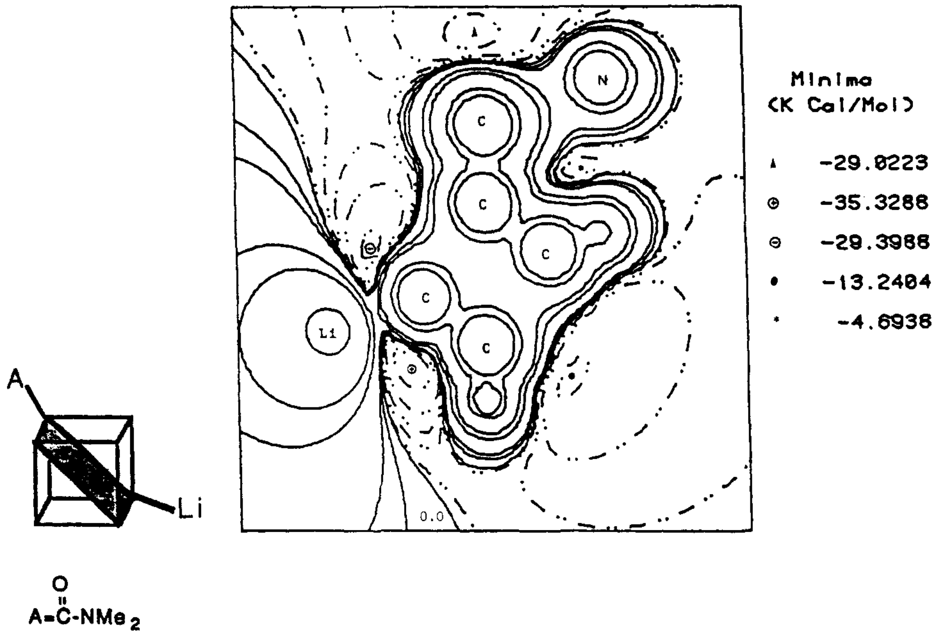

Figure 3. Calculated electrostatic potential of 3-lithio-*N*,*N*-dimethylcubanecarboxamide (4) in a diagonal plane, as shown. Dashed contours correspond to negative potentials; The zero contour is shown. The magnitudes of the other contours are in kcal/mol: −50.2, −37.65, −25.01, −12.5, −6.3, −3.1, −0.6, 3.1, 6.3, 31.4, 62.7, 313.7, 627.5. The locations and values of the minima are indicated.

playing a key role. Such stabilization presumably occurs to a lesser extent for more distant anionic sites. Consistent with these findings and with the interpretation that the lithiation of cubane carboxamide involves an acidic hydrogen, the ortho-lithiated system was calculated to be the most stable of the three-lithiocubane carboxamides; the 3- and 4-substituted isomers are respectively 49.0 and 49.6 kcal/mol higher in energy.

In our most stable conformation for the 2-lithiocubane carboxamide, the lithium is near the amide oxygen, the separation being 1.80 Å. Since the sum of the lithium and oxygen van der Waals radii is 3.3 Å,[12] it can be inferred that an attractive interaction is occurring. If the amide group is made to rotate by 180° around its bond to the cubane framework, then the nitrogen is in the vicinity of the lithium (the separation is 1.96 Å), and there is again an interaction (sum of van der Waals radii is 3.4 Å). However, this rotation increases the energy of the molecule by a calculated 18 kcal/mol. Thus our results support the concept that there occurs a stabilizing interaction between the directing group and the substituted lithium and that in the present instance it involves the amide oxygen, as was suggested by Eaton and Castaldi.[7]

2. Electrostatic Potential. The calculated electrostatic potential in a diagonal plane of lithiocubane (2) is presented in Figure 1. An interesting feature is the negative potential near the middle of the unsubstituted C–C bond. Similar (but usually weaker) negative regions have been found to be characteristic of the C–C bonds in many strained hydrocarbons (e.g., cyclopropane, tripismane, bicyclobutane, cubane, etc.)[13] and are fully con-

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[12] Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.

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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[13] (a) Politzer, P.; Domelsmith, L. N.; Sjoberg, P.; Alster, J. *Chem. Phys. Lett.* **1982**, *92*, 366. (b) Politzer, P.; Domelsmith, L. N.; Abrahmsen, L. *J. Phys. Chem.* **1984**, *88*, 1752. (c) Politzer, P.; Jayasuriya, K.; Zilles, B. A. *J. Am. Chem. Soc.* **1985**, *107*, 121. (d) Politzer, P.; Jayasuriya, K. *THEOCHEM* **1986**, *135*, 245.

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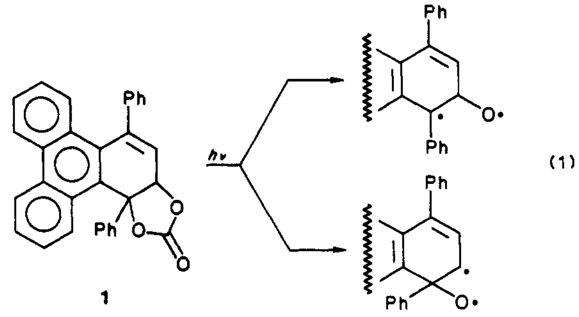
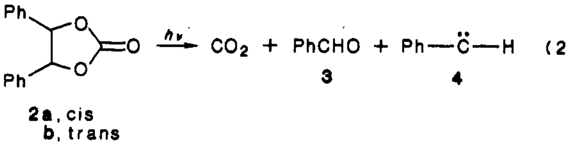
The photoextrusion of carbon dioxide from esters and lactones that bear radical stabilizing groups in the appropriate position is a well-known and general process.[1] Differing reports have appeared concerning the photolysis of cyclic carbonate esters. The photolysis of carbonate **1** proceeds with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



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



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

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