

Exact mass measurement by MS gave an M^+ corresponding to C_8H_8OS and indicated the formation of C_4H_4S and C_4H_4O as a major fragmentation process (**5**, m/e 152 (90%), 123 (78%), 107 (63%), 84 (100%), 68 (84%); **6**, m/e 152 (51%), 123 (77%), 107 (43%), 84 (100%), 68 (66%)). In each case the 1H NMR showed four sets of two chemically equivalent protons and the ^{13}C NMR four sets of two identical carbon atoms in agreement with the C_2 symmetry of the structures. The complete NMR data are summarized in Table I. The NMR chemical shifts are entirely consistent with the assigned structures, **5** and **6**. Selective 1H decoupling in the ^{13}C NMR experimentally verified the carbon and hydrogen associations for the assignments of Table I.

Although the symmetry of the molecules gives rise to magnetically nonequivalent protons and renders their 1H NMR spectra higher than first order, selective decouplings in the 1H NMR spectra of **5** and **6** permit their stereochemistry to be determined. An exo configuration of the four-membered ring, as in structure **5**, produces a dihedral angle of nearly 90° between protons H_b and H_c and consequently a very small J_{b-c} coupling constant would be expected. In the alternative endo configuration of the four-membered ring, as in structure **6**, the corresponding dihedral angle is much smaller and therefore the coupling constant should be closer to a normal value. Selective proton-decoupling experiments revealed that the adduct assigned structure **5** had no discernible coupling between its H_b and H_c protons, while in the other adduct a significant J_{b-c} coupling was observed.

For the stereochemistry of the thiirane ring segment there are in each case two possibilities, thereby generating the complete set of four possible stereoisomers that might conceivably be obtained from the Diels-Alder addition between furan and Dewar thiophene. In two stereoisomers, protons H_c and H_d are cis, while in the other two, these protons must be trans. Within each pair of cis or trans isomers the dihedral angle between the H_c and H_d protons is the same; however, the dihedral angle in the trans isomers is much larger as compared with the cis isomers. Examining the H_c - H_d coupling patterns helps in assigning the actual stereochemistry in **5** and **6**. In the two adducts these couplings are very similar, suggesting that protons H_c and H_d bear the same relationship in the two compounds. The adducts where these protons are trans should clearly be, for steric reasons, the favored Diels-Alder products in relation to their counterparts with the opposite stereochemistry at the thiirane ring. On this basis, the isolated adducts were assigned structures **5** and **6**.

In order to ascertain that the trapped species was indeed an intermediate and not a short-lived excited state of thiophene, the photolysis of thiophene was repeated at $-170^\circ C$ in a glassy matrix (10% thiophene in diethyl ether v/v). At the conclusion of irradiation (8 h, Cd resonance lamp), furan was distilled under vacuum and deposited on top of the glass. The mixture was allowed to warm up to $-78^\circ C$ and stirred overnight while slowly warming up to $25^\circ C$. The formation of the two adducts **5** and **6** was established on the basis of capillary GC retention time, coinjection with samples from the liquid phase photolysis, and capillary GC/MS. The ratio of products, **5/6**, was the same as in the liquid-phase photolysis, suggesting that the nature of the intermediate trapped was the same in the two cases.

The combined chemical yield of **5** and **6** in the liquid-phase photolysis was 1.2% of thiophene consumed.¹⁶ The relatively low yield can be explained in terms of the operativeness of primary

steps other than isomerization to the Dewar form, the incomplete trapping of the Dewar thiophene by furan and the destruction of the adducts by free radical attacks and secondary photolysis. That secondary photolysis of **5** and **6** occurs was shown in an auxiliary experiment using the vycor (4 mm) filtered radiation of a Cd resonance lamp $\lambda \geq 235$ nm. Under this condition the effective λ from a Cd resonance lamp is the 326-nm $Cd(^3P_1)$ resonance line. At this wavelength, thiophene does not absorb light, but **5** and **6** do ($\lambda_{max} \approx 287$ nm, onset of absorption is $\lambda \approx 350$ nm). Correcting for secondary photolysis increases the combined primary yield of **5** and **6** to ca. 2.5-3.0%.

In addition to the Dewar thiophene products we have also observed the formation of several furan dimers.¹⁷

Further studies are in progress.

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Registry No. **5**, 93806-46-3; **6**, 93920-71-9; thiophene, 110-02-1; furan, 110-00-9.

(17) Rendall, W. A.; Torres, M.; Strausz, O. P., to be published.

Systematic Substitution on the Cubane Nucleus. Amide Activation for Metalation of "Saturated" Systems

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Cubane has the highest strain energy (166 kcal/mol) of any stable organic compound available in multigram amounts. The 1,4-dicarboxylic acid from which cubane is made can be prepared easily,¹ and from it various 1,4-disubstituted and monosubstituted cubanes have been synthesized by standard functional group manipulations.^{1,2} Otherwise, and in very much more limited amounts, only 1,3-disubstituted cubanes^{1b,3} and the fully substituted octa(trifluoromethyl)cubane,⁴ octaphenylcubane,⁵ and hexabromo-1,4-dicarboxycubane²⁰ have been reported. The degree of substitution and substitution pattern have always been incident to the synthesis of the skeleton. As we are now interested in differently substituted cubanes for themselves and as precursors for dehydrocubane (cubene), 1,1':3,3'-biscyclobutane, cross-linked cubane polymers, etc., we have developed, and report here, the first method for direct and systematic substitution on the cubane nucleus.

The geometry of cubane requires substantial rehybridization of the component carbons from normal sp^3 bonding (25% s). The 155-Hz ^{13}C -H nuclear coupling constant in cubane translates into 31% s character in that bond and an expectation of enhanced acidity.⁶ Stock and Luh have reported that isotope exchange, H for D, occurs fairly readily from cubane- d_1 using lithium cyclohexylamide in cyclohexylamine at $50^\circ C$.⁷ However, the

(1) (a) Eaton, P. E.; Cole, T. W., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 962, 3157. (b) Barborak, J. C.; Watts, L.; Pettit, R. *Ibid.* **1966**, *88*, 1328. (c) Chapman, N. B.; Key, J. M.; Toyne, K. J. *J. Org. Chem.* **1970**, *35*, 3860. (d) Stock, L. M.; Luh, T.-Y. *Ibid.* **1972**, *37*, 338. (e) Klunder, A. J. H.; Zwanenburg, H. *Tetrahedron* **1972**, *28*, 4131. (f) Della, E. W.; Patney, H. K. *Aust. J. Chem.* **1976**, *29*, 2469.

(2) (a) Cole, T. W., Jr. Ph.D. Thesis, The University of Chicago, 1966. (b) Edward, J. T.; Farrell, P. G.; Langford, G. E. *J. Am. Chem. Soc.* **1976**, *98*, 3075. (c) Eaton, P. E.; Shankar, B. K. R.; Price, G. D.; Pluth, J. J.; Gilbert, E. E.; Alster, J.; Sandus, O. *J. Org. Chem.* **1984**, *49*, 185.

(3) Eaton, P. E.; Cole, T. W., Jr. *J. Chem. Soc., Chem. Commun.* **1970**, 1493.

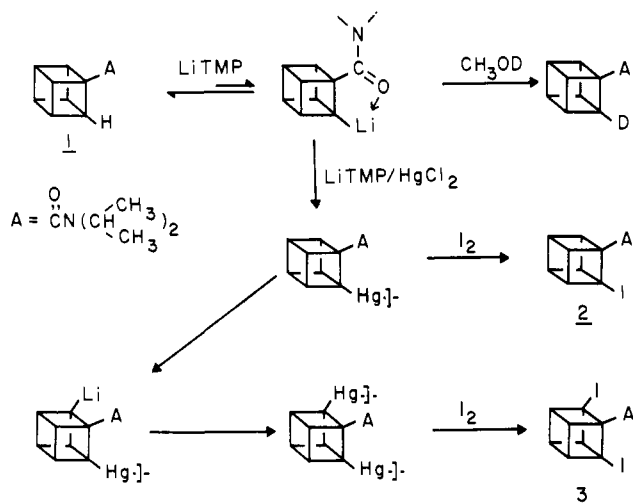
(4) Miller, W. T.; Pelosi, L. F. *J. Am. Chem. Soc.* **1976**, *98*, 4311.

(5) Slobodin, Y. M.; Aleksandrov, I. V.; Khitrov, A. P. *Zh. Org. Khim.* **1977**, *13*, 1377.

(6) Muller, N.; Pritchard, D. E. *J. Chem. Phys.* **1959**, *31*, 768, 1471.

(16) The quantum yield in the photolysis of hexafluorobenzene for the formation of the corresponding Dewar benzene has been reported to lie in the range 0.01-0.04. Haller, I. *J. Chem. Phys.* **1967**, *47*, 1117-1125.

Scheme I



instantaneous concentration of the cubyl anion is presumably very low (*vide infra*). The problem then is how to make cubyl anions in a way synthetically useful for the preparation of new substituted cubanes.⁸

In aromatic systems, there are many substituents that encourage lithiation at an adjacent ortho position.⁹ The tertiary amide is one of the best. We reasoned that a similar substituent effect might pertain in the cubane system. The C-H bond s character in cubane is not unlike that of benzene, and the planar arrangement of ortho groups is fixed similarly in both systems (albeit the distance between them is larger in cubane). Whether such reasoning is correct or specious is a moot point for little is known about the details of ortho-lithiation.¹⁰ Nonetheless, the idea proved very fruitful. We report now direct demonstrations of anion formation on the cubane nucleus mediated by an adjacent amide group.

Cubane *N,N*-diisopropylcarboxamide (**1**) was reacted with a large excess of lithium tetramethylpiperide (LiTMP) in THF at 0 °C. After 10 min the reaction was quenched with CH₃OD. Mass spectroscopic analysis (CI⁺, isobutane) showed nearly 3% monodeuteriation in recovered **1**. The deuteriation is taken to have occurred adjacent (ortho) to the amide group in accord with the results reported below. There was little if any dideuteriation. *With cubane itself, there was no significant substitution (<0.5%) of D for H under equivalent conditions even after much longer reaction times.* To our knowledge, these results constitute the first evidence that amide activation for ortho-metalation can be extended beyond unsaturated systems. As in the common aromatic cases, other substituents should show this activating effect, and we are now comparing variously substituted aromatic and cubane systems with reference to the mechanism of activation.

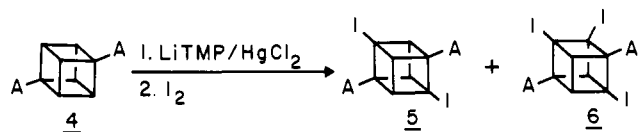
The preparation of "ortho" anions from activated cubanes opens the door to the synthesis of many new cubanes, in particular 1,2-disubstituted examples which are otherwise unknown. To do this productively, a way must be found to make use of the small amount of anion in equilibrium with the starting material. Most interesting, at least at the moment, is the generation of cubyl anions in the presence of mercury salts as trapping electrophiles. Addition of monoamide **1** (50 mg, 0.216 mmol) in THF (1 mL) to a freshly made mixture of LiTMP (1.73 mmol, from 1.08 mL of 1.6 M *n*-BuLi in hexane and 0.269 g of TMP) and HgCl₂ (59 mg, 0.217 mmol) in THF (9 mL) gave, after 5 min at room temperature and aqueous workup, a mixture of ortho-mercurated cubanes

(Scheme I). Only very little starting material remained unreacted. Thus, the mercury salt acted as an effective anion trap, and the mercury-for-lithium transmetalation resulted in nearly complete conversion of the starting material by drawing the lithiation equilibrium to the right. The activating substituent is essential for this transformation. When cubane was subjected to such reaction conditions, even for longer times, it was recovered (>90%) unchanged.

The complex ortho-mercurated product mixture obtained from reaction of **1** with LiTMP/HgCl₂ was simplified by treatment with elemental iodine (methylene chloride, room temperature, overnight). Iodine cleavage of the carbon-mercury bonds^{11,12} gave the 2-iodo (**2**) and the 2,6-diiodo (**3**) derivatives of the starting amide in 72% and 15% isolated yields, respectively. Each was identified by high-resolution mass spectroscopy, by high-field proton NMR (which permits unambiguous assignment of substituent positions),¹³ and by reduction with sodium *tert*-butyl alcohol/THF back to the starting amide, the last demonstrating that the cubane skeleton remained intact. Similar results were realized on reaction of the mercurated products with bromine rather than iodine. The formation of diiodo and dibromo compounds along with the monohalo compounds is particularly interesting. As there was little indication of dideuteriation of the monoamide in the earlier quenching experiment, the dihalo compounds probably have their origin in the sequence shown in Scheme I: ortho anion formation (lithiation) on the cubane nucleus, transmetalation (mercuration), anion formation at another ortho position, second mercuration. The possibility of a third lithiation/mercuration occurring at the remaining amide-activated ortho site is under investigation.

We next considered the reactions of cubane 1,4-bis(*N,N*-diisopropyl)carboxamide (**4**). Here each hydrogen atom on the cubane nucleus is ortho to one or the other of the two amide groups. Treatment of **4** with a large excess of LiTMP in THF at 0 °C for 10 min followed by quenching with CH₃OD gave nearly 80% monodeuteriation.¹⁴ There was little (≤1%) dideuteriation;¹⁵ apparently, once one strongly anionic center is on the cubane nucleus, electrostatics dictates against a second. The much greater degree of monodeuteriation of bisamide **4** relative to monoamide **1** after similar treatment is due in part to a statistical effect but mostly seems a consequence of inductive stabilization of the intermediate anion by the remote second amide group.¹⁶ We shall discuss this in detail when more quantitative data are available and we know the effects of other remote substituents.

Treatment of bisamide **4** with LiTMP/HgCl₂, as in the reaction of monoamide **1**, gave rapid mercuration. Iodine cleavage of the organomercurials so formed led principally to **5**, the centrosymmetric 2,5-diiodo derivative of **4**, identified spectroscopically¹³ and by reduction back to starting material. The isolated yield was usually 70–90%; from one run **6**, the 2,3,5-triiodo derivative of



4, was also isolated. We do not as yet know all the variables that

(11) Cf.: Jensen, F. R.; Rickborn, B. "Electrophilic Substitution of Organomercurials"; McGraw-Hill: New York, 1968; p 203.

(12) In the absence of strong base, **1** and **4** do not react with iodine, mercuric halides, or combinations thereof.

(13) ¹H NMR (500 MHz, CDCl₃) in the cubyl region δ (integral), **2**, 4.10 (1), 4.14 (1), 4.31 (2), 4.44 (2); **3**, 4.22 (1), 4.37 (2), 4.43 (1), 4.59 (1); **5**, 4.59; **6**, 4.63 (1), 4.68 (1), 4.71 (1).

(14) Reaction of deuteriated **4** with methyl lithium gave the corresponding 1,4-bis(methyl ketone) also substantially deuteriated. This established that the deuterium atom was on the cubane nucleus rather than on an amide substituent.

(15) The lack of dideuteriation incidentally (and importantly) established that D-for-H exchange had not occurred at a significant level during the quenching with CH₃OD.

(16) Cf.: Cole, T. W., Jr.; Mayers, C. W.; Stock, L. M. *J. Am. Chem. Soc.* **1973**, *96*, 4555.

(7) Stock, L. M.; Luh, T.-Y. *J. Am. Chem. Soc.* **1974**, *96*, 3712.

(8) Cf.: Della, E. W.; Pigou, P. E. *J. Am. Chem. Soc.* **1984**, *106*, 1085.

(9) For reviews, see: (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.

(10) For example, an amide may activate in a multitude of ways, see: Al-Aseer, M.; Beak, P.; Hay, D.; Kempf, D. J.; Mills, S.; Smith, S. G. *J. Am. Chem. Soc.* **1983**, *105*, 2080. Beak, P.; Hunter, J. E.; Jun, Y. M. *Ibid.* **1983**, *105*, 6350.

influence product distribution.¹² It is clear, however, that sequential anion formation/mercuration similar to that of Scheme I is required to account for the products as the deuteration experiment established that a dianion of **4** was not formed under the reaction conditions.

The LiTMP/HgCl₂ system has potential beyond the cubane case given here. Survey experiments have already demonstrated that the combination rapidly ortho-mercurates *N,N*-diethylbenzamide and other activated aromatics.¹⁷ The *N,N*-diisopropylamine of 1-methylcyclopropanecarboxylic acid can also be mercurated in this way.¹⁸ However, the corresponding cyclobutane derivative is inert, an observation appropriate to the significantly lower *s* character in cyclobutane C-H bonds. Perhaps using stronger bases,¹⁹ we can substitute even such systems.

We are working on the use of other electrophiles and the salts of other metals to trap the ortho anions of suitably activated cubanes. We shall report soon on this, extensions of these reactions, and elaboration of cubylmetallics into new substituted cubanes of substantial interest.

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Registry No. **1**, 94138-16-6; **1** monodeuterated, 94138-21-3; **2**, 94138-17-7; **3**, 94138-18-8; **4**, 94161-36-1; **4** monodeuterated, 94138-22-4; **5**, 94138-19-9; **6**, 94138-20-2; LiTMP, 38227-87-1; TMP, 768-66-1.

(17) The combination is not unlike that of LiTMP/Me₃SiCl in its reactivity toward activated aromatics [Martin, J. C.; Krizan, T. D. *J. Am. Chem. Soc.* **1983**, *105*, 6155]. However, this reagent is not at all effective in substituting cubane amides.

(18) Cf.: Klumpp, G. W.; Kool, M.; Veeffkind, A. H.; Schakel, M.; Schmitz, R. F. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 542 and references therein.

(19) Fraser, R. R.; Mansour, T. S. *J. Org. Chem.* **1984**, *49*, 3442.

(20) Griffin, G., private communication.

Use of the Pyroelectric Effect To Determine the Absolute Orientation of the Polar Axis in Molecular Crystals

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The presence of a polar axis in a molecular crystal has chemical implications that have only recently begun to be recognized. Thus, the reaction of crystalline *p*-bromobenzoic anhydride with ammonia gas occurs preferentially in one direction along the polar axis of the crystal.^{1,2}

The absolute direction of a polar axis in a polar crystal has thus far been difficult to determine except by the classic method of X-ray anomalous scattering,¹⁻⁵ the method employed in the determination of the absolute configuration of chiral crystals. Indeed,

(1) Curtin, D. Y.; Paul, I. C. *Chem. Rev.* **1981**, *81*, 525-541.

(2) Duesler, E. N.; Kress, R. B.; Lin, C.-T.; Shiau, W.-I.; Paul, I. C.; Curtin, D. Y. *J. Am. Chem. Soc.* **1981**, *103*, 875-879.

(3) Buerger, M. J. "Elementary Crystallography"; Wiley: New York, 1956; pp 186-189.

(4) Bunn, C. W. "Chemical Crystallography", 2nd ed.; Oxford University Press: London, 1961; pp 321 ff.

(5) "International Tables for Crystallography"; Kynoch Press: Birmingham, England, 1983; Vol. A, pp 782-785.

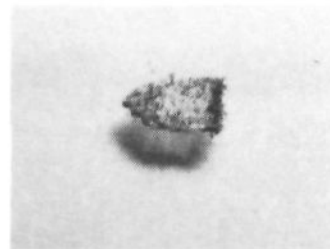


Figure 1. Crystal of *p*-bromobenzoic anhydride that had been heated, allowed to cool to room temperature, and then sprayed with a jet of a mixture of sulfur, carmine, and lycopodium powder. The polar *b* axis is right to left with the carbonyl oxygen atoms pointing to the left side of the page. The positively charged lycopodium powder can be seen at the pointed (carbonyl oxygen) end of the crystal and the negatively charged sulfur and carmine at the opposite end, the middle of the crystal being relatively free from the applied powder.

it has been pointed out that the determination of the absolute direction of the polar axis of a chiral crystal provides, in addition, the absolute configuration of the crystal.^{1,2,6} We have thus been encouraged to search for other methods, easier to apply, which might provide such information.

A technique making use of the pyroelectric effect^{3,4,7} and attributed³ to Kundt, has long ago been employed as an aid in X-ray structure determination to ascertain whether or not crystalline substances were centrosymmetric. The method consists of blowing through a muslin sieve particles of a mixture of differently colored powders onto a single crystal that has just been heated or cooled. The powders are substances whose particles, as they separate from each other, become electrically charged. (The crystal must be subjected to a change in temperature since the electric dipole of a static polar crystal is likely to have become masked by the accumulation of stray electrostatic charges on its surface.) The positive particles of one substance are attracted to the negative end of the crystal and the negative particles to the positive end. The method seems not to have been employed to determine the absolute direction of the polar axis of a crystal (or even as a device for marking the plus and minus ends once the absolute direction has been determined by some other method).⁸ In this paper we describe the application to single crystals of *p*-bromobenzoic anhydride (whose absolute configuration was previously determined^{1,2} by X-ray diffraction employing anomalous scattering) and to some other related compounds and correlate the results with the direction of the reaction with ammonia gas.

Although the powders originally employed were a mixture of sulfur and red lead, we have used a refinement introduced by Hull⁹ to analyze the distribution of static electric charge on paper during the manufacturing process. This treatment employs (yellow) flowers of sulfur and (red) carmine as the negatively charged particles and lycopodium powder which had been dyed with methyl violet as those positively charged.¹⁰ This mixture was applied

(6) In Dunitz's words, "Polarity is just one-dimensional chirality" (Dunitz, J. D. "X-ray Analysis and the Structure of Organic Molecules"; Cornell University Press: Ithaca, NY, 1979; pp 129-147).

(7) It has been pointed out³ that the effect measured in any particular case may not be a pure pyroelectric effect but may contain a contribution from a piezoelectric effect.

(8) We would like to express our indebtedness to researchers at the Central Research Departments of both E. I. du Pont de Nemours and Co. and also at the 3M Co. who a number of years ago provided samples of powders and encouragement to attempt this method. We obtained successful results, however, only much later and with powders prepared as described in this paper.

(9) Hull, H. H. *J. Appl. Phys.* **1949**, *20*, 1157-1159.

(10) A mixture of five parts (by volume) of flowers of sulfur ground and sieved to a particle size of less than 0.063 mm with one part of carmine (Aldrich Chemical Co.) was ground and then mixed with three parts of lycopodium powder (Sargent-Welch Scientific Co.) dyed blue with methyl violet. The crystal to be investigated was heated on a glass slide to 100 °C in an oven and after being allowed to cool was treated with a stream of the powder mixture blown with an atomizer bulb through a muslin sieve. The success of the method depends on sieving the flowers of sulfur to obtain particles of sufficiently small size.