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Dicubyl Disulfide

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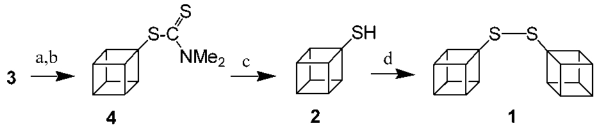
Since its initial synthesis by Eaton and Cole in 1964,[1] cubane and its derivatives have generated a great deal of interest as both a preparative template and a theoretical theme.[2] The highly strained cage structure has proven to be remarkably stable, allowing numerous synthetic transformations to be carried out at the exocyclic centers without fracturing the cubical core.[3] Consequently, it has been possible to prepare derivatives with a wide range of properties related to the internal strain, molecular symmetry, and hydrophobicity of the molecule: nonplanar carbocations, an extraordinarily pyramidalized olefin (cubene),[2] the most powerful nonnuclear explosive (octanitrocubane),[4] propellants,[5] antivirals,[2,6] receptor ligands,[7] controlled release agents,[8] and a novel, superdense allotrope of carbon (supercubane).[9]

Classes of compounds for which little work has been reported are cubanes covalently functionalized with sulfur or phosphorus. In this respect, we were drawn to the unknown dicubyl disulfide **1** and cubanethiol **2**. Attempts to prepare cubane thiols and disulfides have been recorded by Emrick and Eaton; however, the products were too labile to be characterized fully.[10] Cubyl alcohols and amines[11] are unstable, the former and its analogues apparently fragmenting to ketenes.[12] In general, although thiols are more acidic than their alcohol counterparts, thioketones are thermodynamically less stable than ketones. Accordingly, we reasoned that cubanethiol **2** might be less prone to decomposition by this pathway than cubanol, thus allowing studies of its structure and chemistry. At the very least, it was expected that the enhanced stability of the thiol might permit its capture by oxidation to form the unknown dicubyl disulfide. We now report isolation of **2** and the synthesis, X-ray structure, low-temperature NMR, and a bonding analysis of **1**.

The synthetic pathway is outlined in Scheme 1. Commercially available dimethyl-1,4-cubanedicarboxylate (**3**) provided iodocubane in three steps (70%) as previously described.[10,13] Base-initiated reaction of the monoiodide with tetramethylthiuram disulfide (TMTD) at −78 °C, to ensure carbanionic attack at sulfur rather than at carbon,[14] yielded *S*-cubyl-*N*,*N*-dimethyldithiocarbamate **4** (82%). Reduction of **4** ($LiAlH_4$, ether) followed by rapid oxidation of thiol **2** (stable in the cold; MS and NMR[15]) with I_2 delivered dicubyl disulfide **1** in 47% overall yield from the starting diester.[15,16]

X-ray crystal structure analysis of **1** results in C−C and S−S bond distances similar to those previously observed for cubanes and aliphatic disulfides.[15] The C−S−S−C dihedral angle of 86.5° in **1** is unexceptional when compared with disulfides bearing primary and secondary S−C carbons. However, it falls 20−30° lower than disulfides with tertiary carbons at sulfur.

Scheme 1. Synthesis of Dicubyl Disulfide (**1**)[a]



[a] Key: (a) (i) NaOH, MeOH, reflux 4 h. (ii) IBDA, I_2, C_6H_6, reflux 6 h. (iii) EtMgBr, *n*BuLi, THF, −78 °C; MeOH/NaOMe, reflux 1 h. (b) *n*-BuLi, TMTD, THF, −78 °C; MeOH/NaOMe, reflux 1 h. (c) $LiAlH_4$, Et_2O, reflux, 4 h, HCl. (d) I_2, pyridine, pentane, room temperature, 10 h.

Diadamantyl disulfide, for example, exhibits ϕ(CSSC) = 110.4°.[17] The cubyl geometry clearly pins back the β-carbons in **1** so as to avoid the steric effects engendered by the "bulkier" disulfides. Of additional note is the short C−S bond length of 1.771 Å. The value is 0.09 Å shorter than the average C−S bond length (1.863 Å) for aliphatic disulfides where the carbon is tertiary,[18] and can be compared with the shortest and longest aliphatic C−S bonds on record: 1.810 Å (MeSSMe)[19] and 1.952 Å ($Ph_3CSSCPh_3$).[20,21] The X-ray structure of dithiocarbamate **4** (not shown) with *r*(C−S) at 1.760 Å further confirms this phenomenon.[22] To substantiate these observations within a coherent series, we have optimized the geometries of MeSSR (R = *t*-Bu, Me, C_8H_7) with DFT at the Becke3LYP/6-31G(3df) level. The predicted (R)C−S bond lengths of 1.874, 1.826, and 1.785 Å compare well with the experimental values of 1.871 (av),[23] 1.810,[19] and 1.771 Å, respectively.

Short exocyclic C_{cube}−C bonds have been observed previously and rationalized in terms of high s-character at the cubyl carbons.[1,24,25] For MeSSR (R = *t*-Bu, Me, C_8H_7), the carbon percent s-character as determined by NBO transformation[26] from the DFT calculations is 18, 22, and 27%, respectively, implying a linear correlation between this quantity and C−S bond length. Interestingly, the latter suggests the C−S bond length should be similar to that found for C(sp^2)−S bonds, as is observed for aryl disulfides (1.772 Å (av)).[27]

Beyond geometry, are there consequences that result from the relatively high s-character of the cubyl C−S bonds? Recently, it has been reported that the disulfide rotation barrier is doubled by replacing carbon in CSSC with electronegative oxygen to give the dialkyoxy disulfide moiety OSSO ($\Delta G^{\ddagger}_{rot}$ = 18−19 kcal/mol).[28] Given the hybridization-enhanced electronegativity of C in the compressed C−S bond of **1**, it is conceivable that the S−S torsional barrier might be magnified relative to the 8−10 kcal/mol observed for simple disulfides.[29] Optimization of the trans S−S rotational transition states for MeSSR (R = Me, *t*-Bu, C_8H_7) with the same DFT basis set predicts torsional barriers of 6.1, 6.9, and 5.9 kcal/mol, respectively. While these gas-phase values for the methyl and *tert*-butyl analogues are about 1 kcal/mol less than those measured in solution,[29b] the direction and magnitude of $\Delta\Delta G^{\ddagger}_{rot}$ for the

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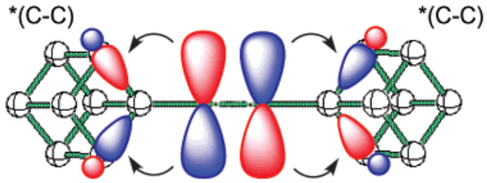

Figure 1. In the torsional trans transition state for **1**, the p$-\pi$ lone pairs on sulfur transfer charge to the low-lying σ^*(C$-$C) orbitals of the cage.

corresponding benzyl and *tert*-butyl congeners (+0.6$-$0.9 kcal/mol) are accurately reproduced (+0.8 kcal/mol). Surprisingly, in contrast to the OSSO system, the cubyl derivative is predicted to show a slightly *lower* S$-$S rotation barrier. Barrier calculations for the full symmetrical disulfides (R$-$S$-$S$-$R, R = Me, *t*-Bu, C_8H_7) at the lower Becke3LYP/6-31G*//Becke3LYP/6-31G* level provide a consistent result: $\Delta E^{\ddagger}_{\mathrm{rot}} = 5.7$, 6.0, and 5.2 kcal/mol, respectively.

To verify the counterintuitive barrier prediction for dicubyl disulfide **1**, we examined the compound's low-temperature proton-decoupled ^{13}C NMR spectra in CD_2Cl_2 in a mixture with *t*-BuSSBu-*t* (**5**) and chiral Pirkle alcohol (ca. 1:1:100, respectively).[28b,30] From -85 to -110 °C, the lowest achievable temperature with this mixture, the Cβ of both disulfides broadened about equally in agreement with similar S$-$S rotation barriers below 8.0 kcal/mol.[29] As predicted, disulfide **1** exhibits exchange between its S$-$S conformational enantiomers with an energy requirement apparently equal to or below that of all other alkyl analogues.[29] The result is at odds with previous observations that S$-$S barrier height increases with the introduction of both electronegativity and increasing size in the disulfide substituent.[28,29b]

How does one understand this phenomenon? NBO analysis[26] for the MeSSR trans transition states (R = *t*-Bu, C_8H_7) illustrates that the p$-\pi$ sulfur lone electron pair adjacent to the C_8H_7 moiety engages in a $LP_S \rightarrow \sigma^*$(C$-$C) interaction (Figure 1) that is twice as strong as that for the *t*-Bu structure. This factor elicits a small reduction in the rotational barrier for R = C_8H_7 relative to R = *t*-Bu (0.5 kcal/mol) in close agreement with the equally small *total* relative barrier reduction calculated (0.8 kcal/mol). Two factors contribute to these differences. First, the cubyl S$-$C bond is shorter by nearly 0.1 Å (Becke3LYP/6-31G(3df) geometries). Second, the highly condensed C_8H_7 cage enjoys lower energy σ^*(C$-$C) orbitals than the *t*-Bu system. We propose that both effects promote a slightly greater $LP_S \rightarrow \sigma^*$(C$-$C) bonding$-$antibonding interaction, reduce S$-$S lone pair repulsion, and thereby stabilize the torsional transition state structure of **1** by comparison with other noncubyl disulfides. Thus, ROSSOR exhibits high SS barriers by stabilizing the ground state, while **1** sustains a low barrier by stabilizing the transition state.

In summary, we have prepared dicubyl disulfide **1** in good yield from **3**. The compound exhibits a remarkably short C$-$S bond as does its precursor **4**. Both theory and low-temperature NMR evaluation suggest a somewhat diminished barrier relative to other disulfides. The effect is traceable to a relative stabilization of the torsional transition state for **1** as a consequence of bonding$-$antibonding interactions between the sulfur π-lone electron pairs and the polycyclic cage.

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Supporting Information Available: Physical data for **1**, **2**, and **4** and computational details (PDF); crystallographic data for **1** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Eaton, P. E.; Cole, T. W., Jr. *J. Am. Chem. Soc*. **1964**, *96*, 962$-$964 and 3157$-$3158.

(2) Eaton, P. E. *Angew. Chem., Int. Ed. Engl*. **1992**, *31*, 1421$-$1436.

(3) Fokin, A. A.; Lauenstein, O.; Gunchenko, P. A.; Schreiner, P. R. *J. Am. Chem. Soc.* **2001**, *123*, 1842$-$1847.

(4) (a) Service, R. F. *Science* **2000**, *287*, 564$-$565. (b) Zhang, M.-X.; Eaton, P. E.; Gilardi, R. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 401$-$404. (c) Kortus, J.; Pederson, M. R.; Richardson, S. L. *Chem. Phys. Lett.* **2000**, *322*, 224$-$230. (d) Hrovat, D. A.; Borden, W. T.; Eaton, P. E.; Kahr, B. *J. Am. Chem. Soc*. **2001**, *123*, 1289$-$1293.

(5) (a) Schmitt, R. J.; Bottaro, J. C.; Eaton, P. E. *Proc. SPIE-Int. Soc. Opt. Eng.* **1988**, *372*, 30$-$37. (b) Cuncle, G. T.; Willer, R. L. *Proc. SPIE-Int. Soc. Opt. Eng.* **1988**, *372*, 24$-$29. (c) Willer, R. L.; Klein, N.; Cunkle, G. T. European Patent Application 1989, EPXXDW EP 324609 A1 19890719.

(6) Mehrdad, M.; Sanjani, N. S. *Polym. Int.* **2000**, *49*, 260$-$264.

(7) (a) Nguyen, V. H.; Kassiou, M.; Johnston, G. A.; Christie, M. J. *Eur. J. Pharmacol.* **1996**, *311*, 233$-$240; (b) Curry, K.; Pajouhesh, H. PCT International Application 1999, PIXXD2 WO 9954280 A1 19991028.

(8) Mahkam, M.; Sanjani, N. S.; Entezami, A. A. *J. Bioact. Compat. Polym.* **2000**, *15*, 396$-$405.

(9) (a) Strel'nitskii, V. E.; Matyushenko, N. N.; Romanov, A. A.; Tolok, V. T. *Dopov. Akad. Nauk. Ukr. RSR, Ser. A* **1977**, *8*, 760. (b) Strel'nitskii, V. E.; Padalka, V. G.; Vakula, *Sov. Phys. Technol. Phys.* **1978**, *23*, 222$-$224. (c) Burdett, J. K.; Lee, S. *J. Am. Chem. Soc*. **1985**, *107*, 3063$-$3082. (d) Johnston, R. L.; Hoffmann, R. *J. Am. Chem. Soc*. **1989**, *111*, 810$-$819. (e) Vlahacos, C. P.; Jensen, J. O. *J. Mol. Struct.* **1996**, *362*, 225$-$234.

(10) Emrick, T. S. Ph.D. Dissertation, University of Chicago, 1997.

(11) Eaton, P. E.; Ravi Shankar, B. K.; Price, G. D.; Pluth, J. J.; Gilbert, E. E.; Alster, J.; Sandus, O. *J. Org. Chem.* **1984**, *49*, 185$-$186.

(12) (a) Hormann, R. E. Ph.D. Dissertation, University of Chicago, 1987. (b) Eaton, P. E.; Yip, Y. C. *J. Am. Chem. Soc.* **1991**, *113*, 7692$-$7697.

(13) (a) Abeywickrema, E. W.; Della, E. W. *J. Org. Chem.* **1980**, *45*, 4226$-$4229. (b) Tsanaktsid, J.; Eaton, P. E. *Tetrahedron Lett.* **1989**, *30*, 6967$-$6968. (c) Eaton, P. E.; Galoppini, E.; Gilardi, R. *J. Am. Chem. Soc.* **1994**, *116*, 7588$-$7596.

(14) (a) Grunwell, J. R. *J. Org. Chem.* **1970**, *35*, 1500$-$1501. (b) Jen, K.-Y.; Cava, M. P. *Tetrahedron Lett.* **1982**, *23*, 2001$-$2004. (c) Gronowitz, S.; Hornfeldt, A. B.; Temciuc, M. *Synthesis* **1993**, 483$-$484.

(15) NMR and crystallographic details are found in the Supporting Information.

(16) Unsuccessful reagents for sulfurization include S_8, SO_2Cl_2, RSCl, thiourea, Ph_3CSSCl, *S*-alkyl-*O*-ethylxanthate, and *N*-hydroxy-2-thiopyridone.

(17) Rindorf, G.; Jorgensen, F. S.; Snyder, J. P. *J. Org. Chem.* **1980**, *45*, 5343$-$5349.

(18) The Cambridge structural database; http://www.ccdc.cam.ac.uk/.

(19) Microwave structure: Sutter, D.; Dreizler, H.; Rudolph, H. D. *Z. Naturforsch.* **1965**, *20a*, 1676$-$1681.

(20) Ostrowski, M.; Jeske, J.; Jones, P. G.; du Mont, W.-W. *Chem. Ber*. **1993**, *126*, 1355$-$1359.

(21) Our unpublished X-ray structure of $Ph_3CSSCPh_3$ yields r(C$-$S) = 1.939, 1.904 Å and r(S$-$S) = 2.006 Å: Harpp, D. N.; Williams, C. R.

(22) Priefer, R.; Farrell, P. G.; Harpp, D. N. Unpublished results.

(23) The average of eight tertiary C$-$S bond lengths for $RC(Me_2)$$-SS-$R' as obtained from the CSD; ref 18.

(24) (a) Gilardi, R.; Maggini, M.; Eaton, P. E. *J. Am. Chem. Soc.* **1988**, *110*, 7232$-$7234. (b) Della, E. W.; Head, N. J. *J. Org. Chem.* **1992**, *57*, 2850$-$2855.

(25) An s-character of 31% has been estimated for cubane itself on the basis of the $^1J(^{13}$C$-$H) correlation: Della, E. W.; Hine, P. T.; Patney, H. K. *J. Org. Chem.* **1977**, *42*, 2940$-$2941.

(26) Foster, J. P.; Weinhold, F. *J. Am. Chem. Soc.* **1980**, *102*, 7211. Reed, A. E.; Curtis, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.

(27) A CSD substructure search (ref 18) identified over 200 aryl disulfide X-ray structures with an average C$-$S bond length of 1.772 Å.

(28) (a) Snyder, J. P.; Nevins, N.; Tardif, S. L.; Harpp, D. N. *J. Am. Chem. Soc.* **1997**, *119*, 12685$-$12686. (b) Borghi, R.; Lunazzi, L.; Placucci, G.; Cerioni, G.; Foresti, E.; Plumitallo, A. *J. Org. Chem.* **1997**, *62*, 4924$-$4927. (c) Cerioni, G.; Cremonini, M. A.; Lunazzi, L.; Placucci, G.; Plumitallo, A. *J. Org. Chem.* **1998**, *63*, 3933$-$3936.

(29) (a) Thompson, Q. E.; Crutchfield, M. M.; Dietrich, M. W.; Pierron, E. *J. Org. Chem.* **1965**, *30*, 2692$-$2696. (b) Fraser, R. R.; Boussard, G.; Saunders, J. K.; Lambert, J. B. *J. Am. Chem. Soc.* **1971**, *93*, 3822$-$3823.

(30) (a) *(R)-l*-1-(9-Anthryl)-2,2,2-trifluoroethanol, as in: Pirkle, W. H. *J. Am. Chem. Soc.* **1966**, *88*, 1837. (b) Cf.: Grilli, S.; Lunazzi, L.; Mazzanti, A.; Mazzanti, G. *J. Org. Chem.* **2001**, *66*, 748$-$754.

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