J. Am. Chem. Soc. 1991, 113, 7692-7697

The Preparation and Fate of Cubylcarbinyl Radicals

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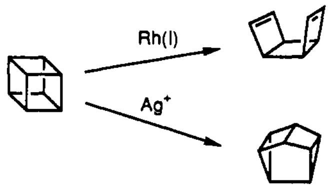
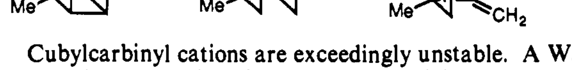
Abstract: The cubylcarbinyl radical has been generated from cubylcarbinyl bromide and from the *N*-hydroxy-2-pyridinethione ester of cubylacetic acid under various conditions favoring hydrogen-atom transfer to the radical. Only when selenophenol in high concentration is used as the hydrogen donor is any methylcubane formed. Otherwise the cubylcarbinyl radical rearranges. There is no evidence of a 1,2-shift into the homocubyl system. Instead, one, two, or three bonds of the cubane nucleus cleave, leading to a variety of olefinic products. For the most part, these have been characterized. A mechanistic scheme accounting for their formation is presented; sequential σ-bond breaking occurs regioselectively, favoring processes in which there is good overlap between the radical orbital and that of the breaking bond. The distribution of products is shown to depend qualitatively on the time the radical intermediates are let live, that is, on the concentration and effectiveness of the hydrogen atom transfer agent. From product distributions, the rate constant for ring cleavage of cubylcarbinyl radical is calculated to be at least $2 \times 10^{10}\ s^{-1}$, substantially greater than that of any radical derived to date from a saturated hydrocarbon system. Methodology is given for the synthesis of cubylcarbinol, cubylacetic acid, 1,4-bis(hydroxymethyl)cubane, methylcubane, and a variety of other new cubane compounds.

Introduction

Cubane and many substituted cubanes are very stable compounds, indeed remarkably so considering the extreme strain energy of the skeleton (>166 kcal/mol).[1] There is no symmetry-allowed pathway for ring opening. When reagents or substituents open other paths, the system rearranges. Thus, for example, oxidative addition to Rh(I) triggers opening of the frame to the *syn*-tricyclooctadiene system (eq 1).[2] Argentiation (or protonation) induces rearrangement to cuneane (eq 2).[3] 4-Methyl-1-hydroxycubane opens via homoketonization giving, ultimately, a 2-vinylcyclobut-3-enylketene (eq 3).[4]

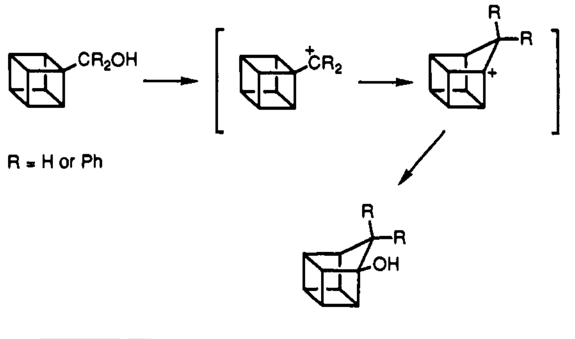


(1)
(2)



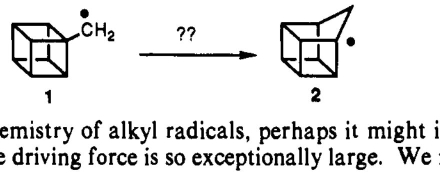
(3)

Cubylcarbinyl cations are exceedingly unstable. A Wagner-Meerwein 1,2-bond shift occurs very quickly, even when the cationic carbon is stabilized by two phenyl groups. Rearrangement into the homocubyl system is driven by the concomitant release of strain (eq 4).[5,6]



(4)

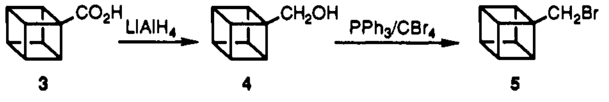
A similar release of strain should accompany the rearrangement of the cubylcarbinyl radical (**1**) to the 1-homocubyl radical (**2**, eq 5).[6] Although a 1,2-shift has never been observed to occur in the chemistry of alkyl radicals, perhaps it might in this case where the driving force is so exceptionally large. We report here the first examples of the chemistry of the cubylcarbinyl radical, but we find that even in this highly driven system 1,2-bond migration does not happen.



(5)

Synthesis of Cubylcarbinyl Radical Precursors

Organotin hydride reduction of an alkyl halide is a convenient and effective way to produce the corresponding radical.[7] In the cubane series there are experimental problems in obtaining the necessary halides; they are very fragile and rearrange easily. Nonetheless, with persistence one finds how to overcome the problems. Thus, we found that if a gentle, basic workup were used,[8] reduction of cubanecarboxylic acid (**3**)[5a,9] with lithium aluminum hydride gave cubylcarbinol (**4**) in quantitative yield (eq 6). Reaction of cubylcarbinol with triphenylphosphine and carbon tetrabromide[10] in methylene chloride at room temperature afforded cubylcarbinyl bromide (**5**) in 71% yield. A careful, very mild workup was necessary to avoid its rearrangement to 1-homocubyl bromide (**6**).



(6)

1,4-Bis(bromomethyl)cubane (**7**) was prepared from 1,4-bis(carbomethoxy)cubane via the corresponding 1,4-bis(hydroxymethyl)cubane (**8**) by methods like those shown for the preparation of **5** (eq 7). Unlike previous investigators,[8] we had no difficulty in the reduction of the diacid to the diol. (We used a mild, basic

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(1) (a) Kybett, B. D.; Carroll, S.; Natalis, P.; Bonnell, D. W.; Margrave, J. L.; Franklin, J. L. *J. Am. Chem. Soc.* **1966**, *88*, 626. (b) Kirklin, D. R.; Churney, K. L.; Domalski, E. S. *J. Chem. Thermodyn.* **1989**, *21*, 1105.

(2) Cassar, L.; Eaton, P. E.; Halpern, J. *J. Am. Chem. Soc.* **1970**, *92*, 3515.

(3) Cassar, L.; Eaton, P. E.; Halpern, J. *J. Am. Chem. Soc.* **1970**, *92*, 6366.

(4) Hormann, R. E. Ph.D. Dissertation, University of Chicago, Chicago, IL, 1987.

(5) (a) Cole, T. W., Jr. Ph.D. Dissertation, University of Chicago, Chicago, IL, 1966. (b) Luh, T.-Y. Ph.D. Dissertation, University of Chicago, Chicago, IL, 1974.

(6) MINDO/3 gives the difference in the heats of formation of cubylcarbinyl cation and homocubyl cation as about 18 kcal/mol, favoring the latter; for the corresponding radicals the difference is about 20 kcal/mol in the same direction.

(7) Kuivila, H. G. *Synthesis* **1970**, 499.

(8) $LiAlH_4$ reduction of the cubane 1,4-diacid has been reported to lead only to rearranged material: Edward, J. T.; Farrell, P. G.; Langford, G. E. *J. Am. Chem. Soc.* **1976**, *98*, 3075.

(9) This acid is readily available via Barton decarboxylation of 4-carbomethoxycubanecarboxylic acid (Eaton, P. E.; Tsanaktsidis, J. Unpublished results).

(10) (a) Kocienski, P. J.; Cernigliaro, G.; Feldstein, G. *J. Org. Chem.* **1977**, *42*, 353. (b) Hayashi, H.; Nakanishi, K.; Brandon, C.; Marmur, J. *J. Am. Chem. Soc.* **1973**, *95*, 8749.

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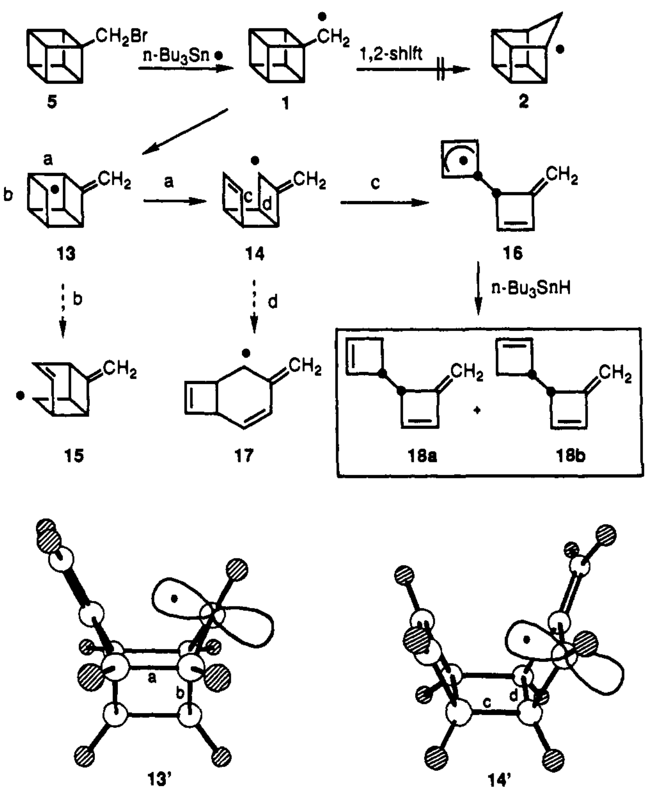
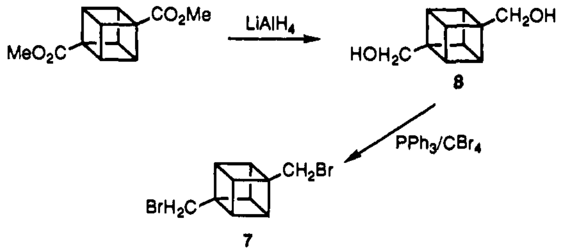
Scheme I

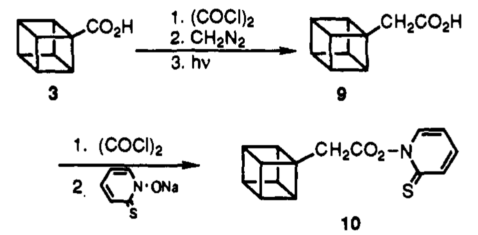


workup.) The dibromide 7 itself proved to be somewhat less sensitive than 5 to cationic rearrangement.



(7)

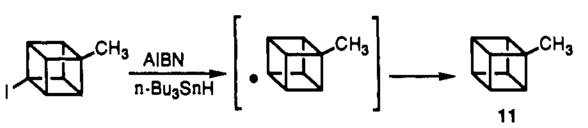
Following on a useful discussion with Professor Newcomb, we decided also to use the Barton[11] *N*-hydroxy-2-pyridinethione ester of cubylacetic acid as a precursor for cubylcarbinyl radical. Newcomb and his group at Texas A & M have demonstrated the utility of such esters in kinetic studies of fast-reacting radicals.[12] Cubylacetic acid (9) was synthesized by Arndt–Eistert homologation of cubanecarboxylic acid (eq 8).[13] Its *N*-hydroxy-2-pyridinethione ester (10), purified by chromatography on silica gel, is stable in the dark for considerable periods of time.



(8)

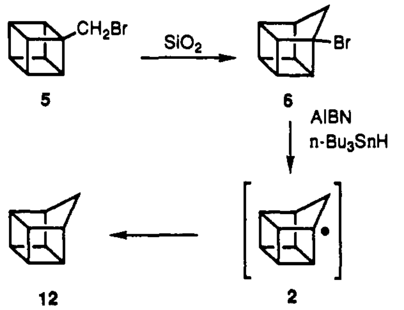
Does Cubylcarbinyl Radical Undergo a 1,2 Carbon Shift?

AIBN-initiated reaction of cubylcarbinyl bromide with tri-*n*-butyltin hydride in benzene at 78 °C afforded a 1/1 mixture of two isomeric olefins (vide infra) as the only volatile products; the remaining material was "polymeric". The absolute yield of the olefins was somewhat over 50% as determined by immediate integration of the proton spectrum of the crude from a run done in an NMR tube with benzene-d_6 as solvent; residual protiobenzene was used as the internal standard. The NMR spectrum of the crude mixture showed no trace of methylcubane (**11**), an authentic sample of which was prepared by tin hydride reduction of 4-iodo-1-methylcubane (eq 9).



(9)

As no methylcubane is formed on reduction of **5**, cubylcarbinyl radical must rearrange before it can be trapped by hydrogen donation from the tin hydride. As no homocubane (**12**) is formed, either cubylcarbinyl radical does not undergo the hypothesized 1,2-shift or the product of this putative shift, the 1-homocubyl radical (**2**), is unstable and ring-opens. The latter was shown *not* to pertain. 1-Homocubyl bromide (**6**) was prepared by purposeful rearrangement of cubylcarbinyl bromide on silica gel; reduction of **6** with tri-*n*-butyltin hydride under conditions like those used for reduction of **5** gave homocubane[14] cleanly via what must be the sufficiently long-lived 1-homocubyl radical (eq 10).



(10)

What Is the Fate of Cubylcarbinyl Radical?

As noted above, AIBN-initiated reaction of cubylcarbinyl bromide with tri-*n*-butyltin hydride in benzene at 78 °C afforded a 1/1 mixture of two isomeric olefins. Each has six olefinic hydrogen absorptions in its proton NMR spectrum. Many plausible structures can be drawn for these olefin isomers. A priori mechanistic reasoning was applied to limit the choices. Numerous paths (without any 1,2-shifts) can be written for rearrangement of cubylcarbinyl radical. Presumably, all start with collapse of the initially generated cubylcarbinyl radical with rupture of a strained cubane bond (Scheme I), giving the methylene secocubyl radical **13**. This is similar to the now-familiar cleavage of cyclobutylcarbinyl radical to pent-4-enyl radical.[15a–c] In the cubane case further bond ruptures are required to account for the high proportion of olefinic hydrogen in the products. These can be expected to be regioselective, under stereoelectronic control, just as Beckwith has shown for cyclobutylcarbinyl cases.[15b] Drawing **13′**, from an AM1 minimization, shows the geometric arrangement more nearly correctly than the stylized drawing **13**. The radical orbital in **13′** is near-parallel to one (marked a) of the two single bonds at each vicinal carbon and approximately perpendicular to the other (marked b). As the favored process should entail maximum orbital overlap, rupture of the parallel bond is predicted; this would give **14** selectively. (Rupture of the perpendicular bond would have given radical **15**.) Further rupture within **14**, selecting bond c over bond d for the same reason (cf. drawing **14′**), would give the allyl radical **16** (rather than **17**). Finally, hydrogen transfer to **16**, a delocalized radical, would produce a mixture of

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[11] Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.

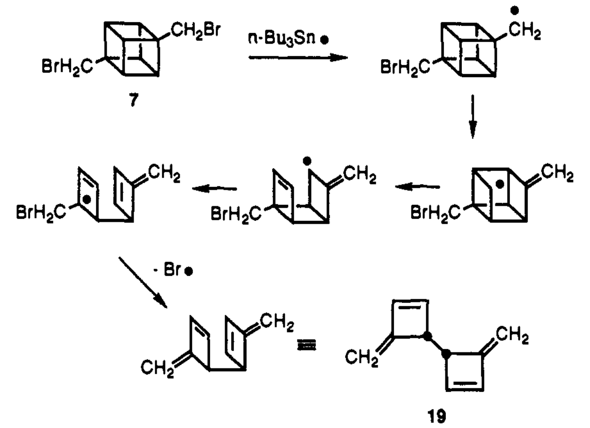
[12] Newcomb, M.; Glenn, A. G. *J. Am. Chem. Soc.* **1989**, *111*, 275.

[13] We thank Dr. Karl Ludwig-Hoffmann for his early work in this area.

[14] (a) Dunn, G. L.; DiPasquo, V. J.; Hoover, J. R. E. *Tetrahedron Lett.* **1966**, 3737. (b) Dauben, W. G.; Whalen, D. L. *Ibid.* **1966**, 3743. (c) Dunn, G. L.; DiPasquo, V. J.; Hoover, J. R. E. *J. Org. Chem.* **1968**, *33*, 1454.

[15] (a) Castaing, M.; Pereyre, M.; Ratier, M.; Blum, P. M.; Davies, A. G. *J. Chem. Soc.* **1979**, 287. (b) Beckwith, A. L. J.; Moad, G. *Ibid.* **1980**, 1083 and references cited therein. (c) Ingold, K. U.; Maillard, B.; Walton, J. C. *Ibid.* **1981**, 970 and references cited therein.

Scheme II

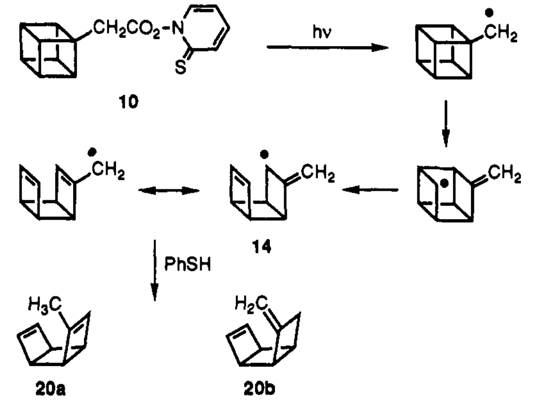


the diastereomeric trienes **18a** and **18b**.

The olefins actually formed on tin hydride reduction of **5** are prone to ready polymerization and oxidation. The spectroscopic data are fully consistent with structures **18a** and **18b** (but are not sufficient for de novo proofs of structure).[16] The mass spectrum of each diene (GC/MS) shows the molecular ion ($m/z = 118$) of C_9H_{10}. The infrared spectrum of the mixture has typical vinylic C—H and cyclobutene C═C stretches at 3048 and 1663 cm^{-1}, respectively. The exocyclic methylene out-of-plane deformation is clear at 862 cm^{-1}. The proton NMR spectrum of the mixture has two sets of absorptions with similar chemical shifts, multiplicities, and coupling constants; some parts overlap. The carbon NMR spectrum is similarly complicated. The absorptions can be divided and assigned to the separate compounds by reference to spectra from mixtures with different proportions of the isomers. These were obtained by effecting partial separation of the olefins on silver nitrate doped silica gel. For each compound there are six olefinic and four aliphatic proton NMR signals and six olefinic and three saturated carbon NMR signals. The spectra of one of the olefins are discussed here; those for the other are similar. Among the olefinic absorptions, two can be assigned as arising from the exocyclic methylene group (4.59, 4.50 ppm, small coupling). The triplet (157 Hz) at 97 ppm in the carbon NMR spectrum is confirmatory. The small vicinal coupling (2.5 Hz) between the olefinic protons at 6.64 and 6.32 ppm is appropriate for a cyclobutene. The remaining two vinyl protons appear at 6.06–6.01 ppm as multiplets. The geminal methylene group resonances are at 2.55 and 2.51 ppm, appropriately coupled (13 Hz).

As with cubylcarbinyl bromide (a.k.a. bromomethylcubane), AIBN-initiated reaction of 1,4-bis(bromomethyl)cubane with triphenyltin hydride gave no product in which the cubyl ring survived. A single volatile product, $C_{10}H_{10}$ by GC/MS, was formed in 45% yield (determined separately by proton NMR integration against *n*-octadecane as an internal standard). This material was prone to polymerization; a colorless sample isolated by preparative GLC went to a yellow, insoluble polymeric material within 2 min at room temperature. The compound is thought to be **19**, 4,4′-bis(3-methylenecyclobutene), on the basis of a mechanistic scheme in which, like before, an intermediate cubylcarbinyl radical triggers a cascade of bond ruptures (Scheme II). The proton and carbon NMR spectra of the product are in accord with this. Each spectrum shows only five kinds of absorptions, in agreement with the 2-fold symmetry of structure **19**. The carbon NMR spectrum reveals the exocyclic methylene at 97.5 ppm. The small coupling constant (2.5 Hz) between the olefinic absorptions at 6.63 and 6.31 ppm in the proton NMR spectrum conforms with the cyclobutene skeleton.

Scheme III



Can the Cubylcarbinyl Radical Be Captured?

We have looked to see if it is possible to trap cubylcarbinyl radical before rearrangement or in "mid-rearrangement" by using better hydrogen donors than a tin hydride. The photoinitiated decomposition of the *N*-hydroxy-2-pyridinethione ester (**10**) of cubylacetic acid in the presence of various radical traps was employed for this purpose. Thiophenol is one of the fastest hydrogen donors available for radical trapping. The reported rate constant for primary carbon radical abstraction of hydrogen from thiophenol is 1.3×10^8 M^{-1} s^{-1} in benzene at 25 °C.[17] The photolysis (tungsten lamp) of the Barton ester **10** at room temperature in benzene-d_6 containing thiophenol was followed using proton NMR as the analytical tool. No detectable amount of methylcubane was observed to form whether the thiophenol was present at low concentration (0.3 M, 5 equiv) or high concentration (2.4 M, 41 equiv). In both instances a mixture (1/1) of two isomeric compounds, C_9H_{10} (GC/MS), was obtained as the major product (Scheme III). The ^{13}C NMR spectrum of each showed four olefinic carbon absorptions. Again, mechanistic reasoning was applied to limit the choice of structures. The number of olefinic carbons indicates that product formation follows upon the rupture of two cubane C–C bonds, thus suggesting that the products arise from hydrogen donation to **14** and its Kekulé isomer, giving **20a** and **20b**, respectively.

In accord with the assignment of structure to **20a**, the proton NMR spectrum of this compound shows three olefinic and four aliphatic absorptions in addition to a methyl absorption. The carbon NMR spectrum shows that one of the four olefinic carbons is quaternary. Equally, the NMR spectral data for **20b** are consistent with the structure assigned. The exocyclic olefinic carbon is clear at 106 ppm in the carbon spectrum. The proton spectrum has four olefinic and six aliphatic absorptions. Two of the olefinic hydrogens are exocyclic; their absorptions are at 4.66 and 4.69 ppm. Two of the aliphatic absorptions are substantially coupled (17 Hz), appropriate to a geminal methylene on a cyclobutane. The ^1H-^1H COSY spectrum of **20b** shows that these methylene protons and the two exocyclic olefinic protons are coupled significantly; this observation reasonably excludes the alternative structures from radical **15** in Scheme I.

The major products from the photo-initiated decomposition of the *N*-hydroxy-2-pyridinethione ester of cubylacetic acid in the presence of thiophenol were always dienes **20a** and **20b**. However,

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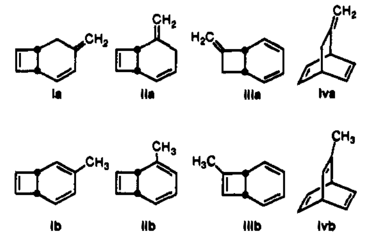
(16) Had bond b or d broken (see Scheme I), the olefins ia–iva and, *necessarily*, their isomers ib–ivb (cf. Scheme III) would have been among the products. However, the olefin mixture obtained showed no methyl-group absorptions in the proton NMR spectrum.



(17) Franz, J. A.; Bushaw, B. A.; Alnajjar, M. S. *J. Am. Chem. Soc.* **1989**, *111*, 268.

trienes **18a** and **18b** were observed (NMR) in the early stages of reactions run in 0.3 M thiophenol. These disappeared during the course of the reaction presumably via photopolymerization. When 2.4 M thiophenol was employed, trienes **18a** and **18b** were not observed at all. Clearly, hydrogen transfer from thiophenol at this high concentration is fast enough to trap the radicals resulting from rupture to two of the sigma bonds of the cubane skeleton before further cleavage can occur. But the transfer reaction was not sufficiently fast to intercept the cubylcarbinyl radical nor the methylene secocubyl radical **13** from cleavage of the first cubane bond.

The failure of thiophenol to capture cubylcarbinyl radical prompted us to use selenophenol, shown by the Newcomb group to be a better radical trap able to transfer the hydrogen atom 10–20 times faster than thiophenol.[18] Nonetheless, photolysis of Barton ester **10** in the presence of selenophenol (68 mM, 1.7 equiv) gave no detectable amount of methylcubane. Instead, a 1/1 mixture of the tricyclic dienes **20a** and **20b** was produced. However, when the concentration of selenophenol was increased to 0.31 M (5.0 equiv), methylcubane was formed in 2% yield along with 40% each of **20a** and **20b** based on starting ester. These yields were determined by averaged NMR integration against methylene chloride added as an internal standard. When an even higher concentration of selenophenol was employed (1.7 M, 50 equiv), more methylcubane was formed (ca. 9%) and lesser amounts (about 30% each) of dienes **20a** and **20b**. Thus, it is indeed possible to trap the cubylcarbinyl radical before rearrangement, but this does require an exceptionally efficient trap at high concentration.

Even under these circumstances, we have not been able to observe the product from hydrogen transfer to the methylene secocubyl radical (**13**, Scheme I). It might be that the rearrangement of cubylcarbinyl radical to the tricyclic radical **14** is concerted and proceeds without the intermediacy of **13**. On the other hand, **13** might be formed in a stepwise reaction but be extremely labile and short-lived. The fairly rigid geometry of this intermediate is such that the orbital of the radical is well-aligned with the vicinal σ bond for ready cleavage to **14**. When we took the reaction to its limits and ran the decomposition of **10** in *neat* selenophenol (ca. 8.5 M), we did find a new absorption in the proton NMR of the crude at 4.82 ppm. This might arise from the exocyclic methylene group in the putative secocubane **13**, but the compound could not be isolated and identified with certainty.

How Fast Does the Cubylcarbinyl Radical Rearrange?

Once formed, the cubylcarbinyl radical (**1**) can do many things. Here we are concerned with whether it is trapped by hydrogen transfer from selenophenol (giving methylcubane) before it rearranges (giving ultimately dienes **20a** and **20b**).[19] The rates for these competing reactions are given by $k_h[\mathbf{1}][\mathrm{PhSeH}]$ and $k_r[\mathbf{1}]$, respectively. If we make the steady-state assumption for [**1**] and if [PhSeH] is essentially constant throughout the reaction (it is used in large excess), then the ratio of the yield of methylcubane to the total yield of dienes **20a** and **20b** is $k_h[\mathrm{PhSeH}]/k_r$.[20] The rate constant for hydrogen abstraction from selenophenol by a primary carbon radical is 1.7×10^9 $\mathrm{M}^{-1}\,\mathrm{s}^{-1}$ in toluene at 20 °C.[18] If this is nearly unchanged in benzene-d_6, the solvent used in our experiments, this value can be taken for k_h. Then, from the observed yields of products, the rate constant k_r is calculated to be about 2×10^{10} s^{-1} by using the data from either trapping experiment (0.31 or 1.7 M selenophenol). As some of the olefin products are lost to polymerization, this figure is probably low.[21] Even so, *the rate of ring opening of cubylcarbinyl radical is more than 2 orders of magnitude faster than that of the cyclopropylcarbinyl radical* ($k_r = 1.0 \times 10^8$ s^{-1}).[12] Thus, cubylcarbinyl radical is the least long-lived radical derived to date from any saturated hydrocarbon system.

Conclusion

We have demonstrated that the cubylcarbinyl radical is very labile. Its rate of rearrangement is faster than that of any other saturated alkyl radical yet measured. It can be intercepted (in part) before rearrangement only when a very effective radical trap (PhSeH) is employed at high concentration. Otherwise, sequential σ-bond breaking occurs regioselectively, favoring processes in which there is favorable overlap between the radical orbital and that of the breaking sigma bond. If the intermediates are allowed to live long enough (poor radical trap), three cubane bonds rupture and the trienes **18a** and **18b** are ultimately formed. If the allowed lifetime is shortened (better radical trap), only two bonds have time to break, and the bicyclic dienes **20a** and **20b** are formed.

Experimental Section

NMR spectra were run in chloroform-d at ambient probe temperature unless otherwise noted: ^{1}H NMR at 400 MHz referenced to internal tetramethylsilane or chloroform; ^{13}C NMR spectra at 100.6 MHz referenced to the central line of the solvent. Proton chemical shifts are reported to a precision of ±0.01 ppm; coupling constants (added parenthetically) are reported to a precision of ±0.2 Hz. Carbon chemical shifts are given to a precision of ±0.1 ppm. Carbon multiplicities were assigned by INEPT spectroscopic technique where appropriate. FT-IR spectra were obtained at a digital resolution of 1 cm^{-1}. Low-resolution mass spectra (70 eV, EI mode) were obtained on material eluting from an OV-17 coated (0.25 μm film) capillary GC column (15 m × 0.248 mm) and are reported to unit mass. Solvents were removed in vacuo on a rotary evaporator; the bath was kept at room temperature. Selenophenol was purchased from Aldrich as 90% technical grade and was freshly distilled before use. It was obtained thereby as a colorless liquid, bp 36–38 °C at 0.1 Torr.[22]

Most cubane compounds are quite stable. Nonetheless, as they are all high energy content materials it is prudent and appropriate to run all reactions thereof behind safety shields. Great care should be taken to assure that crude reaction products are not concentrated at elevated temperature, particularly in the presence of acidic contaminants.

Cubylcarbinol (4). Cubanecarboxylic acid[5a,9] (3.2 g, 22 mmol) was dissolved in stirred THF (30 mL) in a 100-mL round-bottom flask chilled in an ice-water bath. Lithium aluminum hydride (1.5 g, 40 mmol) was added in small portions. The mixture was refluxed for 15 h. Excess hydride was quenched with ethyl acetate (ca. 20 mL). Saturated, aqueous potassium sodium tartrate solution was dripped into the slurry until a thick white paste formed. The mixture was filtered through a pad of anhydrous sodium sulfate on a sintered glass funnel. The pad was then washed well with ethyl acetate. The filtrate was concentrated to about 5 mL and then passed through a silica gel column (ca. 10 g) eluting with ethyl acetate/hexane (1:4 by volume). The filtrate was evaporated to dryness. The residue was crystallized from hexane. Two crops of the title compound were taken (2.7 g, 93%): mp 62–62.5 °C; IR (KBr) ν 3340, 2970; ^{1}H NMR δ 4.05 (m, 1 H), 3.85 (m, 6 H), 3.65 ppm (s, 2 H); ^{13}C NMR δ 63.8 ($\mathrm{CH_2}$), 58.5 (quaternary), 48.7 (CH), 46.8 (CH), 44.4 ppm (CH).

Cubylcarbinyl Bromide (5). A stirred solution of cubylcarbinol (0.91 g, 6.8 mmol) and triphenylphosphine (3.6 g, 14 mmol) in stirred methylene chloride (10 mL, passed through basic alumina and stored over sodium carbonate) in a 50-mL, round-bottom flask was cooled to 0 °C with an ice–water bath. A solution of carbon tetrabromide (2.6 g, 7.8 mmol) in dry methylene chloride (8 mL) was added dropwise. The mixture was stirred for 5 h at room temperature. A white precipitate was observed toward the end of this time. The whole reaction was poured into pentane (ca. 100 mL) at −10 °C, and the cold mixture was filtered. The filtrate was concentrated, and the residue was triturated with pentane (2 × 20 mL). The pentane solution was clarified and evaporated to afford a viscous liquid. This was pumped at 10 Torr for 5 h, and then vacuum-transferred (0.1 Torr, bath temperature 30–70 °C) to give colorless cubylcarbinyl bromide (0.95 g, 71%): ^{1}H NMR δ 4.01 (m, 1 H), 3.86 (m, 6 H), 3.66 ppm (s, 2 H); ^{13}C NMR δ 57.5 (quaternary), 48.7 (CH), 48.4 (CH), 43.4 (CH), 37.1 ppm ($\mathrm{CH_2}$). This material was employed without further purification.

1-Homocubyl Bromide (6). Silica gel (70–230 mesh, ca. 8 g) was added to a pentane solution of crude cubylcarbinyl bromide prepared as described above from 0.20 g of cubylcarbinol. The mixture was stirred at room temperature for 15 h. The solvent was removed; the residue was placed on top of a silica gel column that was then eluted with pentane.

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[18] Newcomb, M.; Manek, M. B. *J. Am. Chem. Soc.* **1990**, *112*, 9662. We thank Prof. Newcomb for supplying us a preprint of this paper.

[19] Whether or not **1** is trapped before rearrangement in some other way is irrelevant to the argument being made here.

[20] Cf. Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317.

[21] If the products unaccounted for arise from **14**, k_r would be 40–50% greater.

[22] (a) Miyoshi, N.; Ishii, H.; Kondo, K.; Murai, S.; Sonoda, N. *Synthesis* **1979**, 300. (b) Foster, D. G. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, 771.

The eluate was evaporated to dryness leaving 1-homocubyl bromide as a colorless liquid (0.17 g, 58%): ^{1}H NMR δ 3.43 (m, 5 H), 3.19 (m, 1 H), 3.17 (m, 1 H), 2.14 (d, J = 1.7 Hz, 2 H); ^{13}C NMR δ 64.0 (quaternary), 53.5 (CH$_2$), 52.5 (CH), 45.9 (CH), 42.3 (CH), 42.1 (CH), 39.6 ppm (CH).

1,4-Bis(hydroxymethyl)cubane (8).[8] 1,4-Bis(carbomethoxy)cubane (Enichem Synthesis, 1.2 g, 5.5 mmol) was dissolved in THF (70 mL). Lithium aluminum hydride (0.60 g, 16 mmol) was added in small portions. The mixture was refluxed for 20 min, and then stirred at room temperature for 10 h. Ethyl acetate (ca. 20 mL) was added to quench the excess hydride. Saturated, aqueous sodium sulfate solution was added slowly until a thick paste resulted. This was filtered through a sintered glass funnel; the filtercake was washed with ethyl acetate. The filtrate was dried over anhydrous sodium sulfate and evaporated. The residue was crystallized from ethyl acetate to give 1,4-bis(hydroxymethyl)cubane as colorless crystals (two crops, 0.81 g, 91%): mp 175–176 °C; ^{1}H NMR δ 3.80 (s, 6 H), 3.78 (d, J = 5.6 Hz, 4 H), 1.23 ppm (t, J = 5.6 Hz, 2 H); ^{13}C NMR δ 63.8 (CH$_2$), 59.3 (quaternary), 43.7 ppm (CH).

1,4-Bis(bromomethyl)cubane (7). A solution of 1,4-bis(hydroxymethyl)cubane (0.40 g, 2.4 mmol) and triphenylphosphine (2.1 g, 8.0 mmol) in stirred methylene chloride (15 mL) was chilled to about −5 °C in an ethanol–ice bath. A solution of carbon tetrabromide (1.9 g, 5.7 mmol) in methylene chloride (10 mL) was added slowly over 20 min. The mixture was stirred at 0 °C for 3 h, and then poured into stirred pentane (100 mL) at 0 °C. The pentane solution was cooled in an ice-water bath for about 20 min, and then filtered. The filtrate was evaporated to dryness. The white, solid residue was triturated with cold pentane (3 × 20 mL). The pentane solution was evaporated slowly. The title compound crystallized as a white solid (0.56 g, 79%): mp 65–66 °C; ^{1}H NMR δ 3.72 (s, 6 H), 3.66 ppm (s, 4 H); ^{13}C NMR δ 58.5 (quaternary), 44.4 (CH), 36.3 ppm (CH$_2$).

Cubylacetic Acid (9). *All parts of this sequence should be run behind safety shields.*[23] Oxalyl chloride (6 mL) was added slowly to a solution of cubanecarboxylic acid (2.0 g, 14 mmol) in methylene chloride (10 mL). Caution: The reaction is exothermic. After gas evolution had ceased, the mixture was refluxed for 20 min. The excess oxalyl chloride was removed at 0.1 Torr at room temperature (*do not heat!*). The residue was dissolved in ether (50 mL). Ethereal diazomethane (ca. 0.5 M, ca. 100 mL) was added slowly. After 10 min the excess diazomethane was blown off with nitrogen. The solvent was removed at room temperature under vacuum to leave a yellow solid, which was, *without manipulation*, immediately taken up in THF (100 mL). Water (40 mL) was added to the solution and the whole reaction irradiated for 3 h with the output from a 400-W medium-pressure Hanovia mercury arc filtered through Pyrex and running water. The THF was removed, and the residue was extracted with ethyl acetate (2 × 100 mL). The extract was dried over sodium sulfate and evaporated. The residue was crystallized from hexane to give cubylacetic acid as a rancid-smelling, colorless solid (1.7 g, 77%): mp 141–142 °C; ^{1}H NMR δ 4.03 (m, 1 H), 3.92 (m, 3 H), 3.87 (m, 3 H), 2.68 ppm (s, 2 H); ^{13}C NMR δ 177.5 (carbonyl), 54.1 (quaternary), 49.0 (CH), 48.3 (CH), 44.3 (CH), 38.1 ppm (CH$_2$).

***N*-Hydroxy-2-pyridinethione Ester of Cubylacetic Acid (10).** Cubylacetic acid (0.16 g, 1.0 mmol) was added to oxalyl chloride (1 mL) dissolved in stirred methylene chloride (5 mL, excess) in a 25-mL Schlenk flask. When gas evolution stopped, the mixture was refluxed for 5 h. The excess oxalyl chloride and solvent were removed under reduced pressure. The residue was dissolved in THF (5 mL). A catalytic amount (ca. 2 mg) of 4-(*N*,*N*-dimethylamino)pyridine was added; the clear solution became turbid. The stirred mixture was cooled in a water bath at room temperature. *N*-Hydroxy-2-pyridinethione sodium salt (0.18 g, 1.2 mmol, carefully dried at 0.01 Torr at 60 °C overnight) was added in small portions under a rapid stream of argon. The mixture was stirred for 12 h *in the dark*. The workup was carried out entirely in subdued light. The solution was filtered through a plug of dry glass wool. The apparatus and filter were rinsed with THF (3 mL). Silica gel (2.8 g, 70–230 mesh) was added to the THF solution, the solvent was evaporated, and the residue was transferred to the top of a silica gel chromatography column (10 g, 230–400 mesh). Elution with ethyl acetate/hexane (1:3 by volume) afforded a pale yellow solid identified as the title ester (0.20 g, 74%): mp 75 °C dec; ^{1}H NMR δ 7.69 (dd, J = 8.8, 1.6 Hz, 1 H), 7.54 (dd, J = 7.0, 1.6 Hz, 1 H), 7.20 (ddd, J = 8.8, 6.8, 1.6 Hz, 1 H), 6.62 (td, J = 6.8, 1.6 Hz, 1 H), 4.05 (m, 1 H), 3.98 (m, 6 H), 3.07 ppm (s, 2 H); ^{13}C NMR δ 175.9 (carbonyl), 166.7 (thiocarbonyl), 137.6, 137.5, 133.4, 112.4 (olefinic carbons), 53.5 (quaternary), 49.1 (CH), 48.3 (CH), 44.5 (CH), 35.6 ppm (CH$_2$). The ester proved to be stable in the dark for months when kept under argon in the refrigerator.

Methylcubane (11). 4-Iodo-1-methylcubane (0.59 g, 2.4 mmol) and AIBN (5 mg) were dissolved in neat tri-*n*-butyltin hydride (2.2 g, 7.6 mmol). The mixture was heated at 66–67 °C for 15 min, and then cooled to room temperature. The flask was attached to a liquid-nitrogen trap and pumped briefly at 0.1 Torr. Methylcubane, sufficiently pure for characterization, accumulated in the trap (0.21 g, 74%): ^{1}H NMR δ 4.04 (m, 1 H), 3.84 (m, 3 H), 3.63 (m, 3 H), 1.25 ppm (s, 3 H); ^{13}C NMR δ 55.6, 49.9, 48.7, 43.8 (cubyl), 19.8 ppm (methyl).[24]

Reaction of 1-Homocubyl Bromide (6) with Tributyltin Hydride. Formation of Homocubane (12). 1-Homocubyl bromide (25 mg, 0.13 mmol), tri-*n*-butyltin hydride (55 mg, 0.19 mmol), and AIBN (3.2 mg, 15 mol %) were dissolved in benzene-d_6 (0.35 mL) under argon in a 5-mm NMR tube. The PMR spectrum was taken and quantitated by reference to residual protiobenzene. The tube was heated in an oil bath at 84 °C for 20 min, after which the PMR spectrum showed no trace of starting material; the yield of homocubane was >95% by integration against residual protiobenzene. A pure sample was obtained by vacuum transfer (10 mtorr, room temperature) of the volatiles to a liquid-nitrogen trap and then preparative GLC separation ($^1/_4$ in. × 5 ft column of 25% OV-225 on Chromosorb G, 120 °C); MS (m/z) 118 (12), 117 (100), 115 (33), 103 (8), 91 (29), 77 (8), 65 (12), 52 (14), 39 (23); ^{1}H NMR δ 3.28 (m, 2 H), 3.22 (m, 4 H), 3.10 (m, 2 H), 1.65 ppm (s, 2 H); ^{13}C NMR δ 45.5, 44.5, 44.1, 41.8 ppm. These spectroscopic data are fully consistent with the reported values.[14]

Reaction of Cubylcarbinyl Bromide with Tri-*n*-butyltin Hydride. Formation of 18a and 18b. Distilled cubylcarbinyl bromide (0.71 g, 3.6 mmol), tri-*n*-butyltin hydride (1.6 g, 5.6 mmol), and AIBN (60 mg, 10 mol %) were dissolved in benzene (15 mL) under argon in a 25-mL, round-bottom flask equipped with a condenser. The reaction flask was lowered into a preheated oil bath at 78 °C, and the mixture was heated for 15 min. Another portion of AIBN (30 mg) was added through the top of the condenser. The mixture was heated for an additional 45 min at 78 °C, and then cooled to room temperature and transferred to a vacuum line. The volatile material was collected by vacuum transfer (0.03 Torr, room temperature) to a liquid-nitrogen trap. Preparative GLC separation ($^1/_4$ in. × 20 ft column of 20% SE-30 on Chromosorb G) afforded a major fraction consisting of a mixture of **18a** and **18b**: MS (m/z) 118 (11), 117 (100), 116 (16), 115 (53), 103 (14), 91 (47); IR (neat) ν 3048, 2916, 2897, 1663, 862 cm^{-1}. **18a** (or **18b**): ^{1}H NMR δ 6.64 (d, J = 2.5 Hz, 1 H), 6.32 (d, J = 2.5 Hz, 1 H), 6.06 (m, 1 H), 6.03 (m, 1 H), 4.59 (s, 1 H), 4.50 (s, 1 H), 3.31 (d, J = 7 Hz, 1 H), 2.97 (m, 1 H), 2.55 (dd, J = 4, 13 Hz, 1 H), 2.18 ppm (d, J = 13 Hz, 1 H); ^{13}C NMR δ 151.3 (149 Hz), 144.8 (145 Hz), 139.5 (145 Hz), 137.4 (145 Hz), 136.1 (147 Hz), 97.1 (157 Hz), 53.7 (136 Hz), 45.17 (136 Hz), 34.6 ppm (136 Hz). **18b** (or **18a**): ^{1}H NMR δ 6.66 (d, J = 2.5 Hz, 1 H), 6.31 (d, J = 2.5 Hz, 1 H), 6.06 (m, 1 H), 6.03 (m, 1 H), 4.60 (s, 1 H), 4.50 (s, 1 H), 3.31 (d, J = 7 Hz, 1 H), 2.97 (m, 1 H), 2.62 (dd, J = 4, 13 Hz, 1 H), 2.25 ppm (d, J = 13 Hz, 1 H); ^{13}C NMR δ 151.5 (149 Hz), 144.3 (145 Hz), 139.2 (145 Hz), 137.8 (145 Hz), 136.1 (147 Hz), 97.1 (157 Hz), 53.6 (135 Hz), 45.3 (136 Hz), 33.9 ppm (136 Hz). The reaction was repeated on much smaller scale in an NMR-tube experiment with deuteriobenzene as solvent. Integration against residual protiobenzene gave the total yield of **18a**/**18b** as approximately 52%.

Reaction of 1,4-Bis(bromomethyl)cubane with Triphenyltin Hydride. Formation of (19). 1,4-Bis(bromomethyl)cubane (0.40 g, 1.4 mmol), AIBN (24 mg, 10 mol %), and triphenyltin hydride (1.2 g, 3.4 mmol) were dissolved in benzene (32 mL) under argon. The stirred mixture was heated in an 82–85 °C oil bath for 45 min, and then cooled to room temperature and concentrated on a rotary evaporator (room temperature, 15 Torr) to about 5 mL. The flask was attached to a high-vacuum line, and the remaining volatiles were transferred at 0.03 Torr (room temperature) to a trap cooled in liquid nitrogen. Preparative GLC separation ($^1/_4$ in. × 5 ft column of 25% XE-60 on Chromosorb G) afforded 4,4′-bis(methylenecyclobutene) (**19**, 38 mg, 21%): ^{1}H NMR δ 6.63 (d, J = 2.5, 2 H), 6.31 (dd, J = 2.5, 0.5 Hz, 2 H), 4.65 (s, 2 H), 4.54 (d, J = 0.5 Hz, 2 H), 3.40 ppm (s, 2 H); ^{1}H NMR (C$_6$D$_6$) δ 6.58 (d, J = 2.5 Hz, 2 H), 6.26 (dd, J = 2.5, 0.5 Hz, 2 H), 4.73 (s, 2 H), 4.66 (d, J = 0.5 Hz, 2 H), 3.47 ppm (s, 2 H); ^{13}C NMR δ 150.8 (quaternary), 144.5 (CH), 137.8 (CH), 97.5 (CH$_2$), 51.8 ppm (CH). The reaction was repeated on a much smaller scale in an NMR-tube experiment with deuteriobenzene as solvent. Integration against added *n*-octadecane gave the yield of **19** as 45%.

Photolysis of 10 in the Presence of Hydrogen-Transfer Reagents. Ester **10** (9 to 15 mg) was dissolved in degassed benzene-d_6 in a 5-mm NMR tube wrapped with aluminum foil. A trapping agent (see text) was added. The total volume was adjusted to 1 mL by adding benzene-d_6. The solution was degassed by using several freeze–pump–thaw cycles.

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(23) We have had no problems with this procedure, but we stress that the crystalline bis(diazoketone) derived from the cubane 1,4-diacid chloride is a dangerous and shock-sensitive high explosive.

(24) The synthesis of [^{13}CH$_3$]methylcubane has been reported: Della, E. W.; Pigou, P. E. *J. Am. Chem. Soc.* **1984**, *106*, 1085.

The tube was sealed with a tight-fitting plastic cap, and then placed in water at 20 °C in a Dewar flask having an unsilvered slit. After 5 min (for temperature equilibration), the aluminum foil was removed and the mixture photolyzed with a 300-W tungsten lamp placed 10 cm away. The progress of the reaction was monitored by proton NMR; the tube was rewrapped with aluminum foil during transfers between the NMR probe and the photolysis apparatus. The reaction was usually complete within 10 min as judged by the disappearance of the ^{1}H NMR signal of the methylene protons of the starting material. The tube was then opened, attached to a high-vacuum line, and the volatiles vacuum-transferred to a trap cooled in liquid nitrogen. The trapped material was analyzed by GC/MS and ^{1}H NMR spectroscopy.

Sufficient amounts of dienes **20a** and **20b** for spectroscopic identification were prepared from **10** (0.49 g, 1.8 mmol) and excess selenophenol (2.7 g, 17 mmol) in THF under similar photolysis conditions. The dienes were separated by preparative GLC (5 ft × $^1/_4$ in. column of 25% XE-60 on Chromosorb G; injector temperature 130 °C; detector, 150 °C).[25] Diene **20a** is a colorless liquid: ^{1}H NMR δ 6.05 (t, *J* = 2.4 Hz, 1 H), 5.89 (t, *J* = 2.4 Hz, 1 H), 5.76 (sym m, 1 H), 3.09 (m, 1 H), 2.96 (m, 1 H), 2.93 (m, 1 H), 2.78 (m, 1 H), 1.60 ppm (sym m, 3 H); ^{13}C NMR δ 146.2 (quaternary), 136.4, 135.8, 127.3 (CH, olefinic), 40.8, 40.2, 39.6, 34.0 (CH, aliphatic), 15.8 ppm (CH_3). Diene **20b** is also a colorless liquid: ^{1}H NMR δ 6.43 (t, *J* = 2.5 Hz, 1 H), 6.35 (t, *J* = 2.5 Hz, 1 H), 4.69 (m, 1 H), 4.66 (m, 1 H), 3.47 (m, 1 H), 3.41 (m, 1 H), 3.33 (m, 1 H), 2.78–2.72 (m, 2 H), 2.46 ppm (dm, *J* = 17 Hz, 1 H); ^{13}C NMR δ 150.8 (quaternary), 140.4, 137.1, 106.1 (CH_2, exocyclic olefinic), 45.3, 45.0, 44.1 (CH, aliphatic), 33.9 (CH_2, methylene), 27.2 ppm (CH).

The selenophenol experiments were quantitated by using methylene chloride (ca. 0.5 equiv) as an internal standard, itself calibrated by careful integration against the methylene proton signals of the accurately weighed starting ester. Selenophenol was added, the mixture was photolyzed for 10 min, and then the ^{1}H NMR spectrum was taken. The yields of methylcubane and of dienes **20a** and **20b** were determined by integration of the appropriate proton NMR signals against that of methylene chloride.

Acknowledgment. This work was supported by the National Science Foundation, the Office of Naval Research, and the National Institutes of Health. We thank Professor Martin Newcomb for stimulating conversations and helpful advice.

Registry No. 1, 135191-71-8; **2**, 53578-15-7; **4**, 134078-23-2; **5**, 135191-72-9; **6**, 135191-73-0; **7**, 135191-74-1; **8**, 60462-27-3; **9**, 135191-75-2; **10**, 135191-76-3; **11**, 23096-16-4; **12**, 452-61-9; **18a**, 135356-15-9; **18b**, 135191-77-4; **19**, 135191-79-6; **20a**, 135191-80-9; **20b**, 135191-78-5; 1,4-bis(carbomethoxy)cubane, 29412-62-2; 4-iodo-1-methylcubane, 125762-85-8.

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[25] (a) Decomposition of **20a** to methylcyclooctatetraene[26] and **20b** to an unidentified olefin was observed when the injection temperature was set to 190 °C and the detector temperature to 210 °C. (b) Methylcubane and diene **20a** collect in the same fraction. As only a small amount of methylcubane is formed and its spectroscopic properties are known, this does not interfere with the assignments to diene **20a**.

[26] Gasteiger, J.; Gream, G. E.; Huisgen, R.; Konz, W. E.; Schnegg, U. *Chem. Ber.* **1971**, *104*, 2412.

Lactones. 2. Enthalpies of Hydrolysis, Reduction, and Formation of the C_4–C_{13} Monocyclic Lactones. Strain Energies and Conformations

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Received March 28, 1991

Abstract: The enthalpies of hydrolysis of the monocyclic lactones from γ-butyrolactone to tridecanolactone were determined calorimetrically, and the acyclic ethyl esters having the same number of atoms were studied in the same fashion. The enthalpies of reduction of the lactones to the corresponding α,ω-alkanediols with lithium triethylborohydride also were determined. The enthalpies of formation of the lactones and the ethyl esters were derived from these data. They were converted to values for the gas phase by measuring the enthalpies of vaporization of ethyl esters and of lactones. In the cases of γ-butyrolactone and δ-valerolactone, the enthalpies of formation were in good accord with the previously reported values determined via combustion calorimetry. The strain energies of the lactones were obtained via isodesmic reactions. Valerolactone had a strain energy of 11 kcal/mol, and the largest strain energy was found with octanolactone (13 kcal/mol). The conformations of γ-butyrolactone and δ-valerolactone were studied via MP2/6-31G* geometry optimizations, and the conformations of the other lactones were studied with use of the molecular mechanics program MM3. The energies of the lactones estimated via molecular mechanics were compared with the experimental results.

1. Introduction

We have initiated a study of the conformations and energies of monocyclic lactones in order to gain more information on the role of the *E* and *Z* conformations on their properties and to have data that would allow more satisfactory modeling of this important functional group via molecular mechanics. The results of a study of the conformations of nonanolactone and of tridecanolactone have been presented.[1] We have now studied the enthalpies of formation and the strain energies of all the monocyclic lactones with 5–14-membered rings. Lactones with relatively small rings are forced to adopt an *E* ester conformation,[2] and in the case of methyl acetate, this conformation is 8.5 kcal/mol higher in energy than the *Z* form.[3] This is due to the lack of the dipole–dipole stabilization that is present in the *Z* form and both methyl–methyl and lone pair–lone pair steric repulsion in the *E* form.[4] How will these interactions affect the strain energies of the five- and six-membered ring lactones? In order to try to answer this question, we have carried out experimental studies aimed at giving additional thermochemical data, as well as theoretical calculations that will give information on the conformations and electronic interactions.

The enthalpy of formation of γ-butyrolactone has been determined from the enthalpy of combustion, and it is −100.56 ± 0.20 kcal/mol.[5,6] δ-Valerolactone also has been studied, and it

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