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Table II. Reaction of Various D,L-Substrates

substrates	yield,[a] %	product	$[\alpha]^{25}_{\mathrm{D}}$,[b] deg	mp, °C
Cbz-L-Asp + D,L-Phe-OMe[c]	46	Cbz-L-Asp-L-Phe-OMe	−16.0	118–120
Cbz-D,L-Asp + L-Phe-OMe	54	Cbz-L-Asp-L-Phe-OMe	−15.0	119–121
Cbz-D,L-Asp + D,L-Phe-OMe	52	Cbz-L-Asp-L-Phe-OMe	−15.7	118–120
Moz-L-Asp + D,L-Phe-OMe	59	Moz-L-Asp-L-Phe-OMe	−11.9	105–108
Moz-D,L-Asp + L-Phe-OMe	50	Moz-L-Asp-L-Phe-OMe	−12.0	104–107
Moz-D,L-Asp + D,L-Phe-OMe	51	Moz-L-Asp-L-Phe-OMe	−11.9	105–107

[a] Cbz(or Moz)-L-Asp was used as basis to calculate the yield. [b] The optical rotations were measured in methanol ($c = 1$). [c] Two equivalents of the D,L derivative were used in every reaction.

matopac. Melting points were taken on a Büchi 510 melting point apparatus and are uncorrected. Optical rotation was measured on Polartronic Universal polarimeter (Schmidt & Haensch).

1. Synthesis of P-Asp-Phe-OMe. (Moz-Asp-Phe-OMe as Example). Into a 1-L flask were added Moz-Asp (5.94 g, 20 mmol), L-Phe-OMe·HCl (4.30 g, 20 mmol), McIlvaine buffer (pH 6.2, 50 mL), triethylamine (2.8 mL, 20 mmol), and papain (2 g), and the mixture was stirred to reach clear solution. Ethyl acetate (750 mL) was added, and the final mixture was incubated on a orbital shaker at 37 °C for 72 h. At the end of the reaction, the organic layer was separated and washed with 2% citric acid (3 × 50 mL) and water (2 × 50 mL) and dried over anhydrous sodium sulfate. Evaporation of solvent under reduced pressure gave the crude product, which was crystallized from water/acetone (2:1, 100 mL) to give 6.86 g (75%) of pure Moz-Asp-Phe-OMe: mp 107–108 °C; $[\alpha]^{25}_{\mathrm{D}}$ −13.0° (c 1, MeOH). It was identical with the authentic sample of Moz-Asp-Phe-OMe prepared by thermolysin-catalyzed reaction. In addition, deprotection gave Asp-Phe-OMe.

2. Continuous-Flow Reaction by Immobilized Papain Column. Immobilization was prepared according to the procedure of Oyama.[7] Into a 1000-mL Wheaton Bio-reaction flask were added papain (25 g), Amberlite XAD-7 (150 mL), and McIlvaine buffer (500 mL). The mixture was stirred at room temperature for 3 h and packed into a column (20 × 800 mm). After draining out the buffer solution, a solution of 0.2 M each of the substrates dissolved in ethyl acetate presaturated with McIlvaine buffer was passed through the wet column (flow rate of 0.5 mL/min). After 1.5 bed volumes were eluted, a small aliquot was taken from eluent and quantitated with HPLC by the method of Durrant.[6] It was found to have 0.09 M of the product in ethyl acetate solution. The yield is calculated to be 45% by taking into account the volume of ethyl acetate.

Registry No. BOC-Asp-OH, 13726-67-5; Cbz-Asp-OH, 1152-61-0; Moz-Asp-OH, 20890-95-3; Cbz-DL-Asp-OH, 4515-21-3; Moz-DL-Asp-OH, 115705-34-5; H-Phe-OMe·HCl, 7524-50-7; H-DL-Phe-OMe, 15028-44-1; BOC-Asp-Phe-OMe, 40944-73-8; Cbz-Asp-Phe-OMe, 33605-72-0; Moz-Asp-Phe-Me, 68802-03-9; papain, 9001-73-4.

Localization of Aromaticity in Fused-Ring Cycloarene Systems: Prediction by an Effective Molecular Mechanics Model

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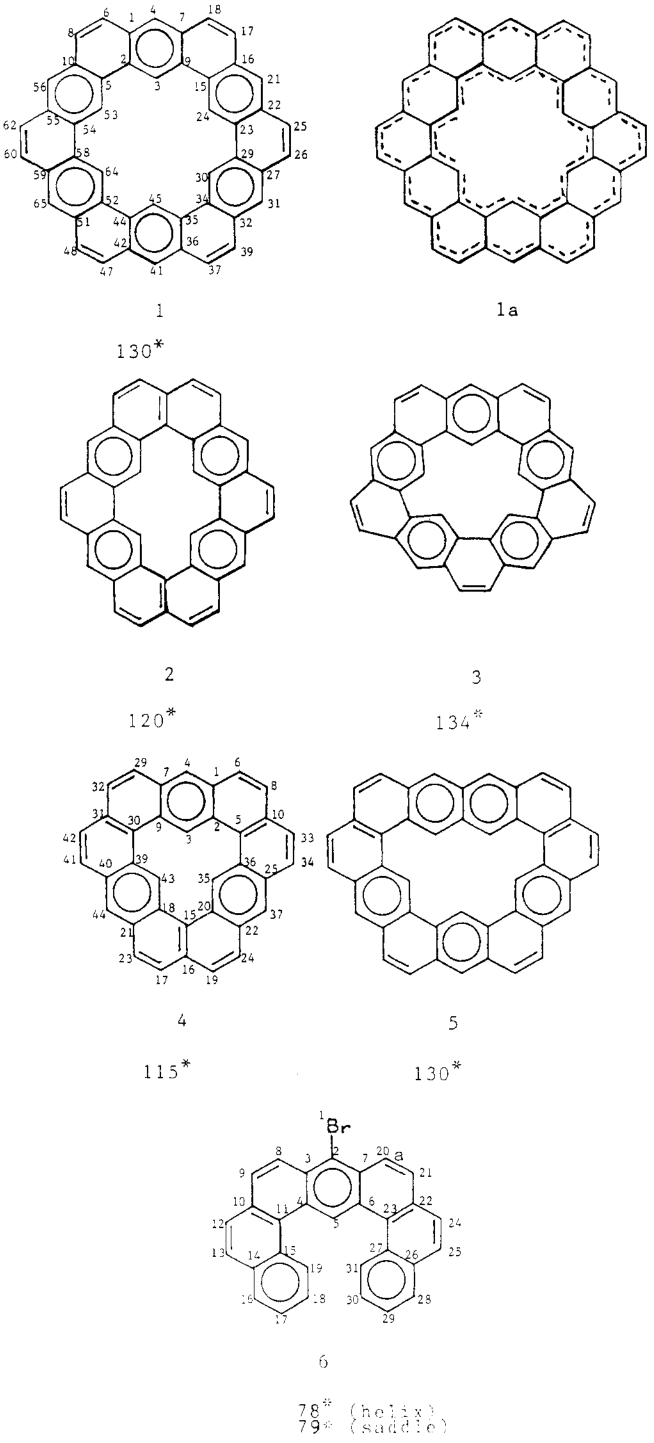

Figure 1. Cycloarenes and computed MMPMI strain energies. The asterisks (*) deonte MMPMI computed strain energies (kcal/mol). Final geometries are described in the supplementary material.

Condensed polycyclic aromatic molecules of the circulene and cycloarene families[1–3] have been the subject of synthetic and theoretical scrutiny for some time. Cycloarenes (exemplified by molecules **1**–**5**) have been of considerable theoretical interest concerning their possible superaromatic nature and their highly strained internal hydrogens, but to date kekulene[3] (**1**) and the related molecule **2**[4] appear to be the sole nontrivial representatives

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(1) (a) Jenny, W.; Peter, R. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 979. (b) Peter, R.; Jenny, W. *Helv. Chim. Acta* **1966**, *49*, 2123.

(2) Wilcox, C. F., Jr.; Lahti, P. M.; Rocca, J. R.; Halpern, M. B.; Meinwald, J. *Tetrahedron Lett.* **1978**, 1893.

(3) (a) Staab, H. A.; Diedrich, F. *Chem. Ber.* **1983**, *116*, 3487. (b) Diedrich, F.; Schneider, K.; Staab, H. A. *Chem. Ber.* **1983**, *116*, 3504.

(4) Funhoff, D. J. H.; Staab, H. A. *Angew. Chem., Int. Ed. Engl.* **1986**, *8*, 742.

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of this family synthesized, although efforts have been made to synthesize **3** and **4**[5] as well.

A major interest in the cycloarenes concerns whether they will posesses substantial bond delocalization *throughout* the molecule, which we will take as a measure of "super aromaticity", or whether delocalization will be confined to portions of the molecule. Naturally, the internal hydrogens of many of the cycloarenes would introduce molecular warping that could obfuscate the expectations of a purely planar connectivity model. Kekulene alone of the set **1**–**5** is expected[3a] to be essentially planar, despite accommodating four internal hydrogens, and hence in principle is the molecule expected to exhibit best the "true" effects of intrinsic superaromaticity, unperturbed by geometric strain-induced warping. However, the experimental crystal structure of kekulene[3b]—despite its planarity—is in best agreement with the localized Clar sextet formalism[6] (structure **1**) rather than being geometrically delocalized in a "superaromatic", annulenoid manner (**1a**).

Some theoretical formulations attempting to predict the properties of such large fused-ring aromatic systems (especially ring currents) by connectivity are implicitly or explicitly predicated on assumptions of molecular planarity and perfect bond delocalization, without direct inclusion or prediction of geometric bond alternation or nonplanarity. These methods are useful for qualitative descriptions of aromaticity in fused-ring systems. Still, where such treatments have been used for cycloarenes,[7] their applicability to real systems may be limited, especially where internal hydrogen strain requires geometric warping. Given the experimental results for kekulene, it would be more realistic to use a predictive model that accounts for geometric effects.

In our efforts to study cycloarenes of synthetic interest, we have found that molecular mechanics including π-electron effects (MMPMI[8]) provides good agreement with the limited experimental data available to date for such molecules. Given the ease of computations and good predictive quality of results, we feel that it is important to note the extension of the known usefulness of π-molecular mechanics[9] to very large, unusual conjugated π-systems like the cycloarenes.

Results

The MMPMI program we used in this work was obtained commercially[8] and modified to allow up to 75 π-atoms in a computation. Details of and references[10] for the force field and VESCF π-calculations in the program are described in the literature provided with the program. All results were obtained without use of symmetry constraints in the computations; hence, small differences in formally symmetry-equivalent bonding parameters may be observed. Where comparisons of experimental and computed parameters are given, averages of the computed parameters are used. Agreement between symmetry-equivalent parameters is typically better than 0.003 Å for bonds lengths and 0.3° for bond angles. It is worth noting that even the nominally symmetry-equivalent bond parameters in an acceptably refined experimental crystal structure analysis may differ by more than these amounts. For simplicity in evaluating bond parameters, Cartesian coordinates for MMPMI-optimized geometries in this study are available in supplementary material. Only bond parameters of particular interest are explicitly described below.

Table I. Kekulene Experimental and MMPMI-Calculated Bond Lengths

atom 1	atom 2	experiment[a,b]	MMPMI[a]	difference[a,c]
1	2	1.420	1.420	0.000
1	4	1.410	1.394	−0.006
1	6	1.454	1.440	−0.014
2	3	1.405	1.385	−0.020
2	5	1.463	1.457	−0.006
5	10	1.423	1.416	−0.007
5	53	1.403	1.387	−0.016
6	8	1.366	1.349	−0.017
8	10	1.457	1.446	−0.011
10	56	1.402	1.394	−0.008
21	22	1.418	1.396	−0.022
22	23	1.420	1.418	−0.002
22	25	1.448	1.441	−0.007
23	24	1.414	1.384	−0.030
23	29	1.463	1.455	−0.008
25	26	1.369	1.348	−0.021

[a] Bond lengths and differences in angstroms. See Figure 1 for atom numbers. All bonds lengths shown are symmetry-unique, and for MMPMI-computed results are arithmetic averages of computed symmetry related values. [b] Experimental bond lengths from ref 3b, except that symmetry-related bond lengths from the reference are averaged. [c] Difference between averaged experimental and MMPMI bond lengths.

Tables I and II summarize comparison of the symmetry-unique experimental and MMPMI-computed bond lengths of kekulene[3b] and open-perimeter model compound **6**[2,11] (a model for **4**), with analogous bond lengths predicted by the MMPMI method. Computed strain energies are shown beneath appropriate structures in Figure 1. All values are in good agreement with experiment; MMPMI finds Clar-type localized structures for both **1** and **6**. Correlation between experimental and theoretical bond lengths is better in the less strained kekulene, as shown by the tabulated differences. In particular, for the strained model **6**, MMPMI tends to underestimate bond localization by giving bond lengths that are too long. For instance, the bond denoted a in Figure 1 is 1.30-Å long experimentally and computed to be 1.37 Å. The MMPMI trend toward underestimated localization implies that one might reasonably expect to observe experimentally at least the computed degree of bond localization, judging by the experimental–computational comparisons on available data.

For both **1** and **6**, we identify as aromatic those rings that show essentially the same bond lengths (circles inside ring). For **1**, alternate rings are clearly localized, with alternating single and double bond lengths in agreement with experiment. We emphasize that the crystal structure of **1** shows localized aromaticity despite being planar, showing that the essential π-character experimentally found for **1** is correctly reproduced by MMPMI. Likewise, only three of the rings in **6** are found to be delocalized, with other rings showing substantial bond alternation for both the helical and saddle-shaped minima computed for **6**. These results are essentially unchanged when the bromine

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(5) Staab, H. A.; Sauer, M. *Justus Liebigs Ann. Chem.* **1984**, *1984*, 742.

(6) Clar, E. *Polycyclic Hydrocarbons*; Academic: New York, 1964; Vol. I and II. (b) Clar, E. *The Aromatic Sextet*; Wiley: London, 1972.

(7) (a) Ege, G.; Vogler, H. Z. *Z. Naturforsch.* **1972**, *276*, 918. *Theor. Chim. Acta* **1973**, *26*, 55. (b) Cf. Randić, M.; Trinajstić, N. *J. Am. Chem. Soc.* **1984**, *106*, 4428 and references therein.

(8) The MMPMI program was obtained from Serena Software, Bloomington, IN, as program MMX87, and was adapted for use on the University of Massachusetts Chemistry Department UNIX Celerity C1260D computational facility by the author of this paper.

(9) Allinger, N. L.; Sprague, J. T. *J. Am. Chem. Soc.* **1973**, *95*, 3893. (b) Kao, J.; Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 975.

(10) The MMPMI program is based upon the work of Allinger and co-workers as extended by Serena Software.[8] For a useful summary and leading references concerning molecular mechanics, cf. Clark, T. *A Handbook of Computational Chemistry*; Wiley: New York, 1985.

(11) Clardy, J.; Arnold, E.; Wilcox, C. F., Jr.; Meinwald, J.; Rocca, J. R.; Lahti, P. M., unpublished data.

Table II. Comparison of Available Experimental Data to MMPMI-Computed Bond Lengths for Molecules 4 and 6

model compound 6						compound 4		
atom 1	atom 2	expt[a,b]	helix[a]	saddle[a]	differences[a,c]	atom 1	atom 2	r[a,d]
1	2	1.918	1.907	1.904	−0.014			
2	3	1.391	1.414	1.414	0.023	1	4	1.410
3	4	1.416	1.428	1.426	0.012	1	2	1.428
3	8	1.436	1.450	1.450	0.014	1	6	1.444
4	5	1.404	1.405	1.408	0.001	2	3	1.407
4	11	1.460	1.458	1.458	−0.002	2	5	1.452
8	9	1.322	1.367	1.367	0.045	6	8	1.368
9	10	1.395	1.442	1.442	0.047	31	32	1.444
10	11	1.422	1.400	1.400	−0.022	30	31	1.399
10	12	1.421	1.436	1.437	0.015	31	42	1.443
11	15	1.441	1.449	1.448	0.007	30	39	1.455
12	13	1.298	1.372	1.372	0.074	31	32	1.369
13	14	1.428	1.437	1.438	0.010	40	41	1.444
14	15	1.424	1.416	1.415	−0.009	39	40	1.425
14	16	1.379	1.424	1.424	0.045	40	44	1.411
15	19	1.421	1.425	1.423	0.002	39	43	1.407
16	17	1.343	1.383	1.384	0.041	21	44	1.409
17	18	1.396	1.417	1.417	0.022	18	21	1.422
18	19	1.332	1.385	1.385	0.053	18	43	1.406

[a] Bond lengths and differences in angstroms. See Figure 1 for atom numbers. All MMPMI bond lengths are for symmetry-unique bonds, derived by taking the arithmetic average of values computed as described in the text. [b] Experimental bond lengths are from ref 10 and represent arithmetic averages of symmetry-equivalent bond lengths from the actual refined structure. [c] Differences between averaged experimental and MMPMI values for bond lengths in saddle configuration of model 6. [d] MMPMI bond lengths, with analogous bonds in model 6 in same row.

atom is replaced by a hydrogen. Of some interest is the MMPMI prediction that helical 6 is about 1 kcal/mol more stable than the saddle form, since the experimental crystal structure unequivocally is of the saddle form.[11]. A likely explanation for this is that more efficient crystal packing may be obtained[12] in the saddle form, which by MMPMI has a maximum "thickness" of 2 Å versus 4 Å for the helix. Overall, the finding of localized aromaticity in 6 turns out quite interesting by comparison to the result for the fully cyclic cycloarene 4, as we shall see.

Encouraged by our good correlation with experimental data, we carried out similar computations on related, still-unknown cycloarenes 2–5. *In all cases we find structures with Clar-type localized structures, rather than extensive superaromatic delocalization along the perimeters or elsewhere throughout the molecule.*

Molecule 2 is propeller-shaped, with four delocalized rings as predicted by the Clar model, and moderate extra delocalization in the upper and lower naphthalene fragments. The molecule is essentially divided into halves by the localized central phenanthrene-like double bonds (1.366 Å). In qualitative agreement with the prediction, Staab and co-workers have suggested[4] on the basis of zero-field splitting values for the triplet excited state that 2 is somewhat more delocalized than 1, although a complete crystal structure for 2 is not yet available.

A connectivity isomer of 2 is molecule 3, with five instead of four internal hydrogens for a 10-ring perimeter. Staab and co-workers have made efforts to synthesize 3 that to date have not yet been successful.[5] By MMPMI, a cup-shaped minimum is found for 3, with all hydrogens pointing in one direction. Other minima are possible here, but the amount of ring warping involved in such structures makes it probable that they are higher in energy than the cup-shaped structure. In agreement with the Clar model, the structure of 3 consists of alternating delocalized benzene rings connected by double bonds. Unlike 2, which requires some naphthalene units in any resonance structure maximizing the number of Clar sextets, 3 is well represented by a single resonance structure when the maximum number of benzenoid sextets is drawn. Thus, if 2 is indeed somewhat more delocalized than 1 as suggested by Staab (vide supra) and supported by MMPMI, we then expect strong localization analogous to that for 1 for the structure of 3.

The MMPMI structure of 4 is basically saddle-shaped, and notably similar to that of saddle-shaped model 6. The analogous three rings predicted to be delocalized sextets by the Clar model are indeed found to be the sole major delocalized portions of both molecules, showing that at the MMPMI level 4 gains essentially no extra superaromatic delocalization by closure of the perimeter of 6. Given the approximate 3-fold symmetry of 4, this is perhaps not surprising; if superaromatic effects do not occur in 4, the molecule should be either delocalized across its perimeter, or (as calculated) localized in a manner to maintain its symmetry. Therefore, the computed structural similarity of 4 and 6 is logically consistent by symmetry arguments. At present, 4 remains experimentally elusive,[5] but when the synthesis and crystal structure of 4 are achieved, the findings relative to this study and relative to the crystal structure of 6 should clearly demonstrate the presence or absence of any major superaromatic delocalization of geometry. Given the lack of experimental or computational superaromatic delocalization in ideal, planar kekulene, it would be rather surprising if it were present in nonplanar 4.

The 11-ring molecule 5 to date has not been synthesized, although ring-current calculations have been carried out using a connectivity model.[7a] As in the other cases with MMPMI, sextet localization is found at the positions denoted in the structure. Of particular interest is the two-ring delocalized unit in the optimized structure, showing that nonsextet delocalization is possible for these systems; symmetry requires that there be either no delocalization or two-ring delocalization at the rings where this is predicted. Like 2, compound 5 appears likely to be somewhat more delocalized than kekulene, but still not even close to showing superaromatic delocalization on a large-scale.

Overall, although we find some evidence of slightly extended delocalization in some portions of molecules 2–5, no larger trend toward full-perimeter delocalization is

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(12) Calculations using similar molecular mechanics models show a small barrier to helix–saddle interconversion in 6. I thank Professor C. F. Wilcox, Jr., of Cornell University for communicating this result to me.

observed. Localization is strongest where a single resonance structure can represent the maximum number of Clar sextets in a structure, as is the case for kekulene 1 and for 3. The MMPMI level of approximation thus finds that expectations of superaromaticity based on simple connectivity arguments for cycloarenes are unlikely, at least if full-perimeter bond delocalization is the criterion of superaromaticity.

Summary

Molecular mechanics with π-electron effects included (MMPMI) is an excellent tool by which to investigate the large, strained cycloarenes and related fully conjugated fused-ring aromatic systems. Semiempirical and ab initio computations on such systems are prohibitively expensive, whereas lower level connectivity-based and Hückel-type theories give no realistic geometric information. By use of MMPMI for synthetically likely cycloarenes, Clar-type structures are predicted in agreement with the limited experimental data to date. Given the recent interest in cycloarenes,[2–5] our findings indicate MMPMI to be a realistic, yet economical model for structural predictions for the potentially large number of such large, multiring π-systems. Finally, our results indicate that cycloarenes will *not* exhibit superaromatic geometric delocalization in general. Hopefully, crystal structure data for molecules such as 2 and 4 will become available in the near future to test these predictions and (we presume) strengthen trust in use of MMPMI and related algorithms for prediction of geometric and π-delocalization properties in very large aromatic systems. Finally, we hope that MMPMI will also prove useful in predicting the geometries of the open-ring precursors to cycloarenes and their abilities to be cyclized to the desired products, a problem that Staab and co-workers[3–5] have shown to be of much concern in planning syntheses of these fascinating molecules.

Acknowledgment. I am grateful to the University of Massachusetts for a Faculty Research Grant in partial support of this research, and to the National Science Foundation for a grant (CHE-8712319) in support of the University of Massachusetts Chemistry Department Computational Facility.

Registry No. 1, 15123-47-4; 2, 15123-45-2; 3, 115914-24-4; 4, 39486-88-9; 5, 39195-00-1; 6, 67996-29-6.

Supplementary Material Available: MMPMI optimized cartesian coordinates and numbering schemes for all molecules, as well as ORTEP-type structural pictures (structural diagrams were produced by using a set of programs for IBM compatible personal computers, kindly provided by Professor John L. Ragle of the University of Massachusetts) (13 pages). Ordering information is given on any current masthead page.

A Practical Photochemical Synthesis of Bicyclo[1.1.1]pentane-1,3-dicarboxylic Acid

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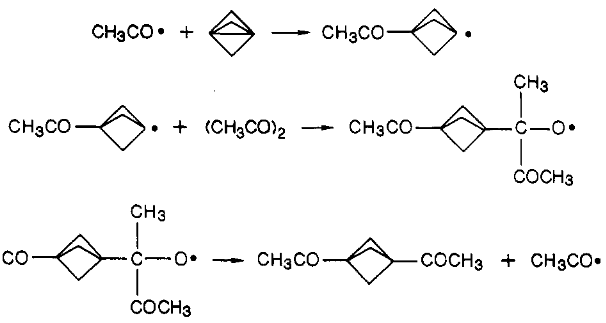
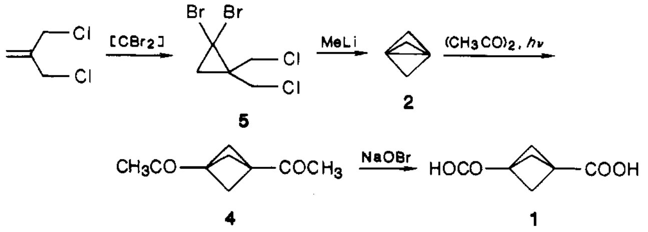
Bicyclo[1.1.1]pentane-1,3-dicarboxylic acid (1) represents a useful starting material for a variety of low molecular weight as well as polymeric structures containing the rigid and highly strained bicyclo[1.1.1]pentane moiety. The original route to 1 involved 12 steps and proceeded in a 2.3% overall yield from diethyl phenylmalonate.[1] Since [1.1.1]propellane[2] (2) has now become accessible in two easy steps from the commercially available methallyl dichloride,[3] and since radical addition across its central bond is facile,[3,4] efficient synthesis of 1 is merely a matter of an optimal choice of a reaction partner for radical addition. The choice of biacetyl is suggested by the report[3] that radical addition of acetaldehyde to 2 yields 1-acetyl-3-(1-hydroxyethyl)bicyclo[1.1.1]pentane (3), apparently via an addition of a bridgehead radical to the carbonyl group of acetaldehyde in preference to abstraction of the aldehydic hydrogen.

The hoped-for mechanism of the photoaddition of biacetyl is represented by the following chain process, where the key step is a β-fragmentation of an alkoxy radical:



Indeed, we find that irradiation of a solution of biacetyl and 2[5] in diethyl ether followed by hypobromite oxidation of the resulting diketone 4 yields the desired diacid 1 in an overall yield of 52% based on the starting tetrahalide[3] 5.



The diacid can also be prepared by hypohalite oxidation of 3, but the yield is less satisfactory. We now provide detailed descriptions of the recommended synthetic procedures for 1 and a few of its simple derivatives.

Experimental Section

Bioling points are uncorrected. Melting points were determined with a Boetius PHMK05 apparatus with a microscope attachment at a heating rate of 4 °C/min. Melting points taken in a sealed capillary are uncorrected. NMR spectra were run on a Nicolet NT-360 instrument in $CDCl_3$ solvent unless specified otherwise. IR spectra were recorded on a Nicolet 60SXR FTIR instrument. Mass spectra were taken on a 5995 Hewlett-Packard instrument. Elemental analyses were performed by Atlantic Microlab.

1,3-Diacetylbicyclo[1.1.1]pentane (4). A mixture of 89.1 g (0.30 mol) of 5[3] and 90 mL of pentane was placed in a 1-L three-neck round-bottom flask equipped with a mechanical stirrer,

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[1] Applequist, D. E.; Renken, T. L.; Wheeler, J. W. *J. Org. Chem.* **1982**, *47*, 4985.

[2] Wiberg, K. B.; Walker, F. H. *J. Am. Chem. Soc.* **1982**, *104*, 5239.

[3] Semmler, K.; Szeimies, G.; Belzner, J. *J. Am. Chem. Soc.* **1985**, *107*, 6410.

[4] Wiberg, K. B.; Waddell, S. T.; Laidig, K. *Tetrahedron Lett.* **1986**, *27*, 1553.

[5] We have prepared and used amounts up to 0.3 mol in a single run in the form of a dilute solution in diethyl ether. Yield, estimated from isolated yields of various addition products, is over 90%. Further scale up appears quite straightforward.

0022-3263/88/1953-4593$01.50/0