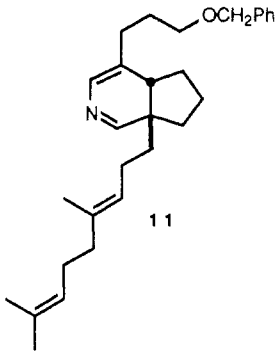
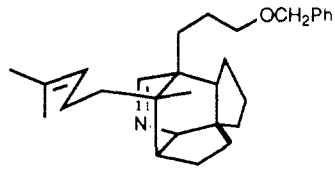




isolated and fully characterized. Chromatographic analysis of the reaction mixture indicates that **12** is produced immediately upon addition of acetic acid to **11**, whereas **8** is produced only upon warming the solution. The conversion of **11** to **12** may be formulated as an intramolecular Diels–Alder reaction of the protonated form of **11**. The Diels–Alder reaction has been demonstrated with **11** itself, but it is slow in toluene at 110 °C.[6] The transformation of **12** into **8** is presumably a π-cyclization of the prenyl double bond onto the immonium moiety of **12**. It is noteworthy that the process is highly stereoselective with respect to the isopropenyl group and delivers **8** with the double bond situated only in the terminal position. We believe that a process such as this may be involved in the biosynthesis of the *Daphniphyllum* alkaloids.

The total synthesis reported here is notable for its brevity and high yield; only nine laboratory operations are required from homogeranyl iodide, and the overall yield from this material is 44%. At the present time, we have prepared more than 3 g of **10** in this manner.

Acknowledgment. This work was supported by a research grant from the National Science Foundation, CHE-8418427, an American Chemical Society Organic Division Graduate Fellowship to R.B.R. from Smith Kline & French Laboratories, and a National Science Foundation Graduate Fellowship to M.M.H. We thank Professor S. Yamamura for supplying us with methyl homosecodaphniphyllate.

Supplementary Material Available: Physical data for compounds **4**, **5**, **6**, **8**, **9** (free base), **10**, **11**, and **12** (4 pages). Ordering information is given on any current masthead page.

(6) Diels–Alder reactions involving 2-azadienes are precedented. See, inter alia: (a) Eddaif, A.; Laurent, A.; Mison, P.; Pellissier, N.; Carrupt, P.-A.; Vogel, P. *J. Org. Chem.* **1987**, *52*, 5548. (b) Cheng, Y.-S.; Ho, E.; Mariano, P. S.; Ammon, H. L. *Ibid.* **1985**, *50*, 5678. (c) Boger, D. L.; Weinreb, S. N. In *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: San Diego, CA, 1987; pp 255–260. (d) Boger, D. L. *Tetrahedron* **1983**, *39*, 2876–2882.

A New and Practical Method of Decarboxylation: Photosensitized Decarboxylation of *N*-Acyloxyphthalimides via Electron-Transfer Mechanism

Keiji Okada,* Kazushige Okamoto, and Masaji Oda*

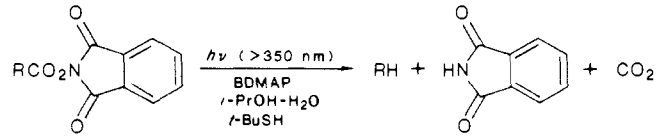
Department of Chemistry, Faculty of Science
Osaka University, Toyonaka, Osaka 560, Japan

Received June 14, 1988

Photosensitized electron-transfer reactions have recently attracted considerable attention in organic photochemistry. Many mechanistic investigations concerning the reactivities of cation and anion radicals have been currently published.[1] However, synthetically useful application based on this methodology has been limited to fewer examples.[2] We report a new and practical method of decarboxylation of carboxylic acids via *N*-acyloxyphthalimides with use of the photosensitized electron-transfer reaction. The decarboxylations of unactivated carboxylic acids were classically achieved by thermolysis of peresters[3] or by two-step conversion via haloalkanes through Hunsdiecker reaction.[4,5] Recently Barton and his co-workers developed an elegant method of decarboxylation which proceeds via radical addition to *O*-ester of thiohydroxamic acid derivatives.[6] More recently Hasebe and Tsuchiya reported a new photolytic method with oxime esters.[7] Although these recently developed methods much improved the yields and the procedures for the decarboxylation reactions, the use of anhydrous conditions and the relatively narrow range of excitation wavelength for its direct photolysis in the latter still place several restrictions. The present photosensitized decarboxylation through *N*-acyloxyphthalimides, which are readily derived from various carboxylic acids and *N*-hydroxyphthalimide by use of DCC and are easily isolated as stable compounds,[8] proceeds in high yields in aqueous solvents with irradiation of visible light (350–450 nm).

Irradiation of a *i*-PrOH–water (95:5) solution of 1,6-bis(dimethylamino)pyrene (BDMAP), *N*-acyloxyphthalimide (**1a**), and

Table I. Photosensitized Decarboxylation of the Esters **1a–c** in Aqueous *i*-PrOH Containing 2% *t*-BuSH[a]



1 2

R: **a**: *t*-Bu—(CH2)3—, **b**: (PhCH2)2CH—, **c**: 9-triptycyl

	hydrocarbon[b] yield (%)	phthalimide[c] yield (%)	sensitizer[c] recovery (%)	ΔG^d (kcal/mol)	k_q^e (M^{-1} s^{-1})
1a	88	92	82	−30.5	7.9×10^9
1b	98	84	84	−31.0	8.3×10^9
1c	84	87	75	−33.0	8.9×10^9

[a] [substrate] = $0.5–3.1 \times 10^{-3}$ M, [sensitizer] = $0.8–1.7 \times 10^{-3}$ M in *i*-PrOH–H_2O (95:5, 100 mL) containing *t*-BuSH (2 mL). Irradiation was performed under argon for 2 h. [b] GC determination. [c] Isolated yield. [d] Calculated from Rehm–Weller equation.[15] [e] From the fluorescence quenching experiment in THF–H_2O (95:5) at [BDMAP] = 6.56×10^{-6} M.[16]

(1) (a) Matters, S. L.; Farid, S. In *Organic Photochemistry*; Padawa, A., Ed.: Marcel Dekker: New York, 1983; Vol. 6, pp 233–326. (b) Fox, M. A. *Acc. Chem. Res.* **1983**, *16*, 314. (c) Julliard, M.; Chanon, M. *Chem. Rev.* **1983**, *83*, 425. (d) Lewis, F. D. *Acc. Chem. Res.* **1986**, *19*, 401. (e) Kavarnos, G. J.; Turro, N. J. *Chem. Rev.* **1986**, *86*, 401.

(2) (a) Mariano, P. S.; Stavinoha, J. L. In *Synthetic Organic Photochemistry*; Horspool, W. M., Ed.; Plenum Press: New York, 1984; pp 142–257. (b) Portella, C.; Deshayes, H.; Pete, J. P.; Scholler, D. *Tetrahedron* **1984**, *40*, 3635. (c) Mizuno, K.; Ichinose, N.; Otsuji, Y. *Chem. Lett.* **1985**, 455. (d) Lan, J. Y.; Schuster, G. B. *J. Am. Chem. Soc.* **1985**, *107*, 6710. (e) Goodson, B.; Schuster, G. B. *Tetrahedron Lett.* **1986**, *27*, 3123. (f) Saito, I.; Ikehara, H.; Kasatani, R.; Watanabe, M.; Matsuura, T. *J. Am. Chem. Soc.* **1986**, *108*, 3115. (g) Gassman, P. G.; Bottorff, K. J. *Ibid.* **1987**, *109*, 7547. (h) Yoon, U.-C.; Kim, J.-U.; Hasegawa, E.; Mariano, P. S. *Ibid.* **1987**, *109*, 4421.

(3) (a) Wiberg, K. B.; Lowry, B. R.; Colby, T. H. *J. Am. Chem. Soc.* **1961**, *83*, 3998. (b) Eaton, P. E.; Cole, T. W., Jr. *Ibid.* **1964**, *86*, 3157. (c) Meinwald, J.; Shelton, J. C.; Buchanan, G. L.; Courtin, A. *J. Org. Chem.* **1968**, *33*, 99.

(4) (a) Wilson, C. V. *Org. React.* **1957**, *9*, 332. (b) Sheldon, R. A.; Kochi, J. K. *Org. React.* **1972**, *19*, 279.

(5) (a) Ruivila, H. G. *Synthesis* **1970**, 499. (b) Della, E. W.; Patney, H. K. *Ibid.* **1976**, 251. (c) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron Lett.* **1983**, *24*, 4979 and references cited therein.

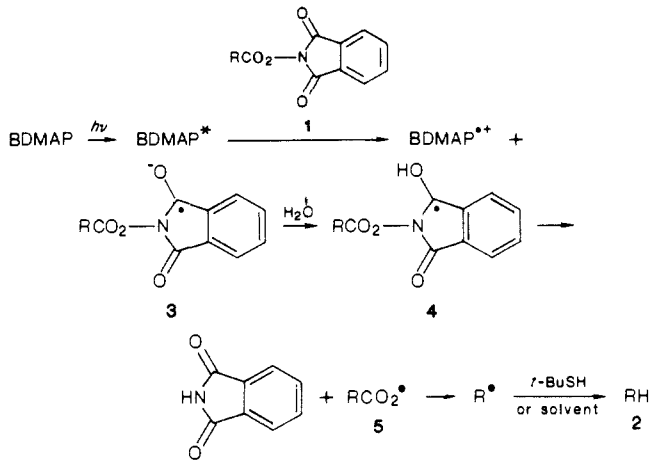
(6) (a) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1983**, 939. (b) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901. (c) Barton, D. H. R.; Zard, S. Z. *Pure Appl. Chem.* **1986**, *58*, 675.

(7) Hasebe, M.; Tsuchiya, T. *Tetrahedron Lett.* **1987**, *28*, 6207.

(8) Green, T. W. In *Protective Groups in Organic Synthesis*; John Wiley: New York, 1981; p 183.

0002-7863/88/1510-8736$01.50/0

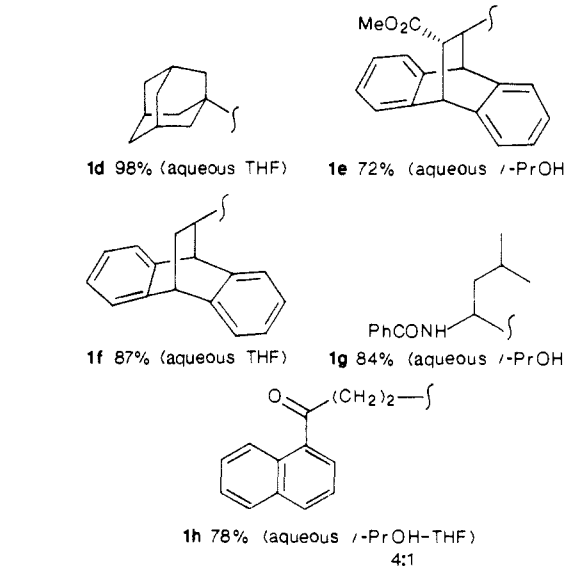
Scheme I

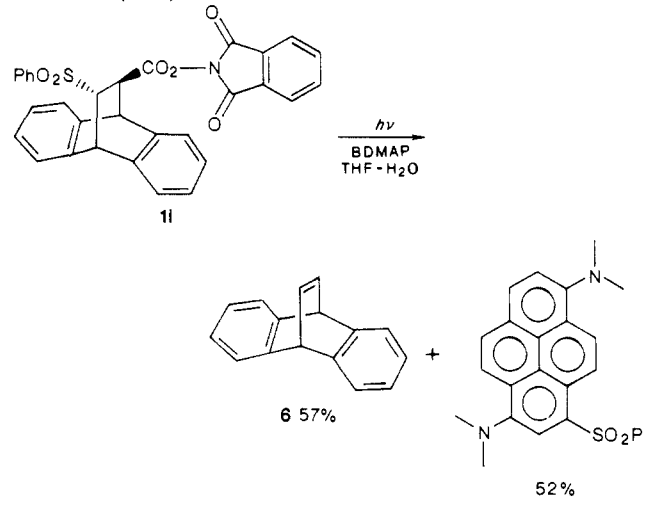


t-BuSH (2%) through a solution filter[9] (>350 nm) with a 100-W high-pressure Hg lamp under argon for 2 h gave **2a** in 88% yield along with phthalimide (92%) and di-*tert*-butyldisulfide (11%) with recovery of BDMAP (82%). The reaction also proceeds satisfactorily for secondary and tertiary carboxylic acid derivatives **1b** and **1c** (Table I). Similar irradiations (2 h) with longer wavelength light (>400 nm) through a 10% sodium nitrite filter give equally good results. In control experiments, the reaction in the dark or in the absence of BDMAP gave no decarboxylated products.[10] The sensitized decarboxylation in THF–water or acetonitrile–water also gives satisfactory results.[11] Quantum yields in aqueous THF at relatively high concentration of the substrates ($7–9 \times 10^{-3}$ M) are moderate (0.09–0.12).[12] While other sensitizers such as *N*-methylcarbazole (MCZ) and *N*-phenylcarbazole (PCZ) are also effective,[13] BDMAP is the most excellent in view of the large molecular extinction coefficient in the visible region and its low oxidation potential.[14]

A mechanism of electron transfer from the excited singlet state of BDMAP to the substrates is surmised from the large negative values of free energy change calculated by using the Rehm–Weller equation[15] and from the near diffusion-controlled rate constants of the quenching of fluorescence of BDMAP by **1a**,**b**, and **1c** (Table I).[16] An electron transfer from the excited singlet state of BDMAP to **1** gives the anion radical **3**,[17] which is protonated[2b,f,10,18] in the aqueous or protic solvents to give the radical **4**. Ready cleavage of the weak N–O bond at the β-position of the radical **4** produces the carboxy radical **5**, which in turn undergoes decarboxylation and hydrogen abstraction from *t*-BuSH or the solvents to afford the hydrocarbon **2** (Scheme I).

This decarboxylation is general and widely applicable to various *N*-acyloxyphthalimides (1d–h)[19] including an N-protected amino acid derivative. In addition, gram-scale decarboxylation is easily achieved as exemplified in the case of **1f**: Irradiation (>350 nm) of a THF–water (95:5, 200 mL) solution of **1f** (2.31 g), BDMAP (53 mg), and *t*-BuSH (4 mL) under argon with a 400-W Hg lamp for 7 h gave **2f** (1.04 g, 87%) and phthalimide (0.81 g, 94%) after chromatographic purification. Since the compound **1f** is readily available from cycloaddition of anthracene with acrylate esters followed by hydrolysis and condensation with *N*-hydroxyphthalimide, this method allows the use of acrylate esters as ethylene equivalents. Similarly, β-sulfonyl acrylate esters serve as acetylene equivalents:[20] Thus, irradiation of **1i** in THF–water under inert atmosphere in the absence of *t*-BuSH gave the expected olefin **6** in moderate yield (57%) along with 3-(phenylsulfonyl)-BDMAP (52%).





(9) An aqueous solution of 2,7-dimethyl-3,6-diazacyclohepta-2,6-diene perchlorate (0.2 g/L) was used: Murov, S. L. In *Handbook of Photochemistry*; Marcel Dekker: New York, 1973; p 99. Use of a Pyrex filter gave equally good results.

(10) While the sensitized reaction proceeded efficiently in anhydrous *i*-PrOH–*t*-BuSH, a more sluggish reaction was observed in dry THF–*t*-BuSH or in dry acetonitrile–*t*-BuSH. Direct irradiation gave poorer results. The detailed results will be reported elsewhere.

(11) Yields of hydrocarbon in THF–water (95:5) in the presence of *t*-BuSH (2%) under the conditions described in Table I: 86% for **2a**, 86% for **2b**, and 82% for **2c**. In acetonitrile–water (95:5) containing *t*-BuSH (2%): 84% for **2a**, 95% for **2b**, and 18% with the carboxylic acid (42%) for **2c**. In these solvents partial conversion of BDMAP to 3-(*tert*-butylthio)-BDMAP (20–40%) and 3,8-bis(*tert*-butylthio)-BDMAP (10–30%) was observed. Both of them would also sensitize the decarboxylation.

(12) Quantum yields were determined at 366-nm excitation by using potassium ferrioxalate actinometer in THF–water (95:5) in the presence of *t*-BuSH (2%) at [**1a**, **1b**, or **1c**] = $7–9 \times 10^{-3}$ M, [sensitizer] = 2.0×10^{-4} M under argon: Φ = 0.12 for **1a**, 0.10 for **1b**, and 0.09 for **1c**.

(13) Yields of hydrocarbon using MCZ (PCZ) (Pyrex filter under argon) in *i*-PrOH–water (95:5) in the presence of *t*-BuSH (2%): 93% (80%) for **2a** 99% (97%) for **2b**, and 81% (86%) for **2c**.

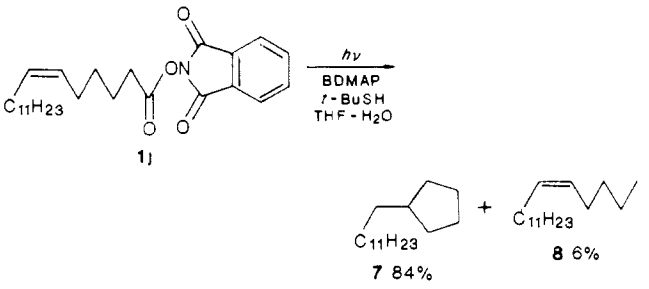
(14) BDMAP has a strong absorption in the visible region; λ_{max} (*i*-PrOH–water) = 367 nm (log ϵ = 4.36) with the tail up to 450 nm (log ϵ at 400 nm = 4.05). The oxidation potential of BDMAP ($E_{1/2}$ = +0.24 V vs SCE) and the reduction peak potentials of **1a**, **1b**, and **1c** (E_p = −1.39 V for **1a**, −1.37 V for **1b**, and −1.28 V vs SCE for **1c**) were determined by cyclic voltammetry in acetonitrile solution containing tetraethylammonium perchlorate (0.1 M). A considerably different value of oxidation potential of BDMAP has been reported: Zweig, A.; Maurer, A. H.; Roberts, B. G. *J. Org. Chem.* **1967**, *32*, 1322.

(15) (a) Rehm, D.; Weller, A. *Isr. J. Chem.* **1970**, *8*, 259. (b) Weller, A. *Z. Phys. Chem. Neue Folge* **1982**, *133*, 93.

(16) Life time of the S_1 state of BDMAP was estimated to be 5.3 ns from oxygen quenching of the fluorescence.

(17) Electron transfer from the T_1 state of BDMAP to **1a**, **1b**, and **1c** is also exothermic: ΔG = −7.8 kcal/mol for **1a**, −8.3 kcal/mol for **1b**, −10.3 kcal/mol for **1c**. For this reason, the reaction may proceed from both S_1 and T_1 states.

(18) One of the referees pointed out an alternative path: N–O bond cleavage before protonation. Since the photosensitized decarboxylation (2 h irradiation under argon) of the primary carboxylic acid derivative **1a** proceeds even in dry acetonitrile or dry THF in the absence of *t*-BuSH to give **2a** in 39% or 25% with the considerable amount of the recovery of **1a**, such a mechanism may be operative in part.



Furthermore, the present method of decarboxylation can be applied to the radical cyclization process:[21] Similar irradiation of **1j** in THF–water (95:5) in the presence of *t*-BuSH (2.2×10^{-3} M) under argon readily affords the cyclized hydrocarbon **7** (84%) accompanied by a small amount of the noncyclized hydrocarbon **8** (6%).

In summary, we have developed a new and efficient method of decarboxylation via photosensitized electron-transfer reaction initiated by visible light excitation. Further synthetic applications are in progress.

(19) *N*-(1-Naphthoyloxy)phthalimide, a typical aromatic carboxylic acid derivative, was not decarboxylated under these conditions, and 1-naphthoic acid was obtained in 71% yield.

(20) Lucchi, O. De.; Modena, G. *Tetrahedron* **1984**, *40*, 2585 and references cited therein.

(21) Curran, D. P. *Synthesis* **1988**, 417 and references cited therein.

Computer Software Reviews

MicroChem V2.5. Organic Modeling Unit. Intersoft Incorporated: One Concourse Plaza, 4711 Golf Road, Suite 412, Skokie, IL 60076. (312) 699-4143.

While DEC machines still reign supreme for molecular modeling tasks, useful microcomputer packages have been available in the IBM world for several years. Though the graphics interface of the Macintosh seems ideal for interactions between the structural chemist and computer, and Mac-based molecular drawing programs are the generally acknowledged leaders in the field, real molecular modeling for the Mac has been slow in appearing as a result of the lack of a floating-point coprocessor on the Mac Plus and SE.

Even without coprocessor support, the low end Macs are powerful graphics machines, and the first entry in the race to provide Mac-equipped chemists with desktop chemical modeling tools has appeared. While limited in scope, MicroChem Version 2.5 runs on the Mac Plus, SE and II—all in black and white. The entire set of MicroChem applications includes Organic, Inorganic (zeolites), Macromolecular (nonbiological polymers), and Drug Design (Group Additivity Properties) Modules. All of these modules use the same program to display 3-D structures. This review deals only with the Organic Modeling Unit.

MicroChem Organic comes on a single floppy that is not copy protected. Installation on a hard disk is, of course, trivial. Presumably in order to allow operation on 1Mb machines, MicroChem Organic is broken into six (yes 6!) separate applications. Without a RAM upgrade and MultiFinder, be prepared to launch and quit a lot.

The applications are the following: InputMol; BuildMol; AssembleMol; DisplayMol; TwistMol; and FormatMol. Together these applications require only 485 Kb of disk space. Also required are several data files, totaling only 22 Kb. Finally, a library of 32 predrawn structures, weighing in at 73 Kb, is included. MicroChem V2.5 runs fine on a stock Mac Plus with two 800K floppy drives.

FormatMol is a small utility designed to allow translation of data between several different formats. According to the documentation, MicroChem uses the Chemlab-II format, and can translate and write files in molfile (MDL), Sybyl (Tripos), and a version of the CSSR (Cambridge Crystallographic Database) formats. The latter is compatible with Chem-X (Chemical Design Ltd.). I did not test these utilities, but MicroChem molecule files are simply text files that can be opened and edited with MS Word. Undoubtedly, a knowledgable computational chemist would have minimal trouble inputing and exporting data between MicroChem and, e.g., a VAX-based program.

The five remaining applications perform three basic functions. InputMol, BuildMol, and AssembleMol allow the creation of 3-D molecular structures; DisplayMol allows examination of the structures and modification of the structures by rotation about acyclic bonds; and TwistMol allows calculation of conformational strain energies. Together, the package provides powerful tools for creation of presentation graphics and for examination of structures—with many frustrating limitations and quirks.

A brief description of the operation of each application is given here, followed by a summary of the performance of the package as a whole. Most of the testing was done using an 8 Mb Mac II, though all functions also operated as advertised on a 1 Mb floppy-based Mac Plus.

Assuming a MicroChem-readable 3-D molecule file is unavailable, InputMol affords basic tools for drawing structures into MicroChem. Using the drawing tools is quite simple, though somewhat awkward relative to molecular drawing approaches available in other Mac applications such as ChemDraw and Chemintosh. Even so, it is very simple to construct 2-D structural formulas containing most of the atoms (including silicon and aluminum) and "types" (e.g. sp^3, aromatic, cation) normally encountered by organic chemists. These formulas may then be converted to 3-D structures in one of two ways. First, each atom of a 2-D formula drawn on the active screen (called the "benchtop") may be tagged with fractional coordinates. Then, entry of unit cell dimensions and angles from a crystal structure affords a 3-D molecule. Cartesian coordinates may also be used. The resulting structures may then be viewed with DisplayMol as described below, or modified to produce new structures.

In general, of course, coordinates are not available. In this case, the 2-D formula is saved, and BuildMol is used to create an idealized 3-D structure. For acyclic fragments, BuildMol simply generates a geometrically correct structure based upon simple bond length and bond angle rules. The conformation that results is fairly random, but it depends to a large extent upon the 2-D input. No minimization occurs during this process. Cyclic fragments, on the other hand, are handled with a "conjugate gradients" method to minimize deviations from the preferred equilibrium bond angles and lengths. When a formula is opened from BuildMol, hydrogen atoms are automatically added in idealized positions. This allows the easy creation of crystal structures with H-atoms if coordinates for the hydrogens are not available by simply opening a crystal structure created with InputMol. When a 2-D formula is opened with BuildMol, a nonsense structure appears—waiting to be transformed into a 3-D molecular model. Choosing "Make 3-D Structure" from a menu then starts the process of model building.

It is possible to define the level of convergence required before BuildMol stops the process, and also to set a time limit on the calculation. Visual feedback is provided to indicate how close to convergence the program is while it is working. Acyclic fragments converge on an idealized structure quite rapidly. However, for ring compounds, be prepared to wait. While, e.g., cyclohexane converges very quickly, I found that fused ring systems are surprisingly slow to converge. For example, building a "3-D" model of phenanthroline on a Mac II took over an hour with use of the default "convergence parameter". Given that the default time limit set for building 3-D models is *24 hours*, one must be patient. The manual states that this default time limit "is sufficient for most molecules". It is true, however, that often the structure comes close to convergence, and the program spends considerable time tweaking. A graph showing the degree of convergence is, as mentioned above, displayed during the calculations. If one gets tired of waiting, it is possible to stop the program at any time, affording the 3-D structure present in memory at that time. In my experience, this often gives a perfectly adequate model for many applications.

Starting with a flat hexagon, I obtained a chair cyclohexane conformation after running BuildMol. The conformation obtained for acyclic fragments seems arbitrary. Boat cyclohexanes and specific ring fusion stereochemistry in saturated fused-ring systems may be obtained relatively easily with use of a feature present in InputMol. Specifically, InputMol allows each *ring* atom to be tagged with a "stereochemical" descriptor: front; plane; or back. Once an atom is tagged in InputMol, a visual cue (bold for "front", gray for "back") appears showing where