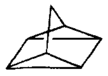
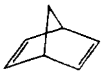
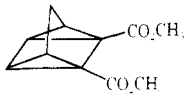
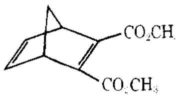
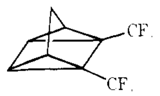
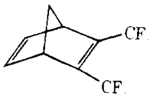
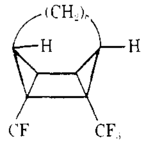
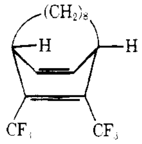
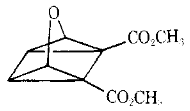
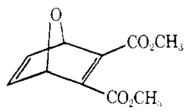
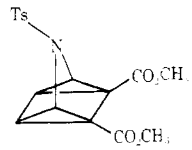
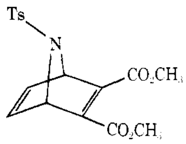
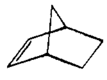
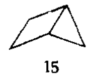
# *Communications*

## The Ease of Oxidation of Highly Strained Polycyclic Molecules

*Summary:* A quantitative measure of the ease of oxidation of highly strained polycyclic compounds has been provided and the effect of substituents has been evaluated.

*Sir:* Although recent years have witnessed a plethora of studies on the chemical and physical properties of highly strained polycyclic molecules, including studies on their ease of reduction,[1] relatively little is known about the stability of such systems under oxidative conditions. It might have been assumed that highly strained polycyclic ring systems would be stable to oxidation, since examples of the synthesis of bicyclo[1.1.0]butane derivatives under oxidative conditions existed.[2] However, one of us[3] recently demonstrated that quadricyclane (1) could be oxidized by silver ion in methanol. It has also been shown that 1 was subject to electrochemical oxidation in methanol.[4,5] We now wish to report that highly strained polycyclic molecules can be oxidized with surprising ease.

**Table I. Half-Wave Oxidation Potentials for a Series of Strained Polycyclic Compounds and Their Isomers vs. SCE**

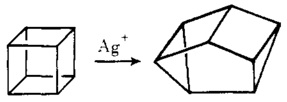
| column I | | column II | |
|---|---|---|---|
| compd | $E_{1/2}$, V | compd | $E_{1/2}$, V |
| <br>1 | 0.91 | <br>2 | 1.56[a] |
| <br>3 | 1.64 | <br>4 | 2.06 |
| <br>5 | 2.19 | <br>6 | ~2.51[b] |
| <br>7 | ~2.60[b] | <br>8 | 2.41 |
| <br>9 | 1.95 | <br>10 | 2.26 |
| <br>11 | 1.95,<br>2.36 | <br>12 | 2.20,<br>2.37[c] |
| <br>13 | 2.12 | <br>14 | 1.95[d] |
| <br>15 | 1.91 | <br>16 | 2.03[e] |

[a] Lit.[6] value 1.54 V. [b] Values above 2.5 V are less accurate than the other values listed because they appear as shoulders on the curve for solvent oxidation. [c] Curves for these two values overlap. Thus, these values are slightly less accurate than the rest of the values in this table. [d] Lit.[6] value 2.02 V. [e] Lit.[7] value 1.96 V.

Table I lists the half-wave oxidation potentials for a series of strained polycyclic molecules and their isomers. The values were obtained versus a saturated calomel electrode (SCE) using single sweep voltametry (sweep rate 100 mV/s) on a Princeton Applied Research Model 174 polarographic analyzer equipped with platinum electrodes. The solvent was high purity acetonitrile which contained 0.1 M lithium perchlorate (supporting electrolyte) and ~$10^{-3}$ M substrate.

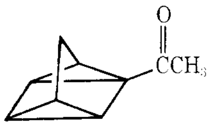
As can be seen from Table I, quadricyclane (1) has an amazingly low oxidation potential. Hence, it is not surprising that it was easily oxidized by silver ion in methanol. Even substitution of 1 by strong electron-withdrawing groups, such as in 3, failed to raise the oxidation potential to what one might expect for an olefin (to say nothing about what might be predicted for a saturated hydrocarbon).[8]

It is of interest to compare the ease of oxidation of the compounds in column I with their isomers in column II. Compounds 1, 3, and 5 are all more easily oxidized than are their photochemical precursors 2, 4, and 6, respectively. Compounds 1, 3, and 5 are all converted back to the corresponding dienes in the presence of certain transition-metal catalysts.[9,10] Since a catalyst facilitates an isomerization in these examples, it can be safely assumed that the dienes are more thermodynamically stable than the corresponding quadricyclanes. Thus, superficially it would appear that the less stable compounds were the more easily oxidized. Consideration of the interconversion of 7 and 8 would seem to support this concept. In this case, the diene was more easily oxidized than the quadricyclane, 7. In line with relative stabilities, 8 was converted into 7, both photochemically and in the presence of a transition-metal complex.[10] Similar comparisons can be made for the interconversion of 13 and 14[11] and for the catalytic isomerization of 15 to 16.[12] While these two cases are more complicated in that a hydrogen transfer was involved, in each case the thermodynamically more stable isomer is the more difficult to oxidize. On the basis of this comparison, one might be tempted to equate ease of oxidation with thermodynamic stability or strain energy. We hasten to warn that such extrapolations, if valid at all, are only valid within certain very narrow limitations. Electron transfer undoubtably occurs from the highest occupied molecular orbital (HOMO) of the strained ring system in an anodic oxidation.[13] Such orbital energies do not correlate in general with either thermodynamic stability or strain energy. This is amply demonstrated by comparison of 17 with 18. Whereas, 18 is more easily oxidized than 17 ($E_{1/2}$ vs. $\text{SCE}_{18}$ = 1.73 V; $E_{1/2}$ vs $\text{SCE}_{18}$ = 1.54 V), 17 was readily isomerized to 18 in the presence of silver ion.[14] This represents a clear-cut case where the thermodynamically more stable isomer is also the more easily oxidized!



17 18

Comparison of 3, 9, and 11 illustrates the effect of heteroatom incorporation into the strained polycyclic molecule on its ease of oxidation. To a first approximation, the oxygen bridge of **9** and the nitrogen bridge of **11**[15] function primarily as slightly electronegative substituents. In connection with substituent effects, the oxidation curve of **19** was of interest. Two half-wave potentials were observed. The lower wave showed $E_{1/2}$ at 1.00 V while the second appeared at $E_{1/2}$ = 1.87 V. Two different oxidative processes are indicated. It is interesting to speculate as to whether these two waves reflect the oxidation of the two different cyclopropyl moieties.[16]



**19**

In summary, we have provided a quantitative measure of the ease of oxidation of highly strained polycyclic compounds. The effect of substituents has been evaluated. We are continuing to study both the mechanistic detail and products of these facile oxidations.

**Acknowledgment.** We are indebted to the National Science Foundation and the General Electric Foundation for a grant to P.G.G. which supported this investigation.

## References and Notes

(1) K. B. Wiberg and R. P. Cuila, *J. Am. Chem. Soc.*, **81**, 5261 (1959); W. R. Moore, H. R. Ward, and R. F. Merritt, *ibid.*, **83**, 2019 (1961); K. B. Wiberg, *Rec. Chem. Prog.*, **26**, 143 (1965); and G. W. Klumpp and J. J. Vrielink, *Tetrahedron Lett.*, 539 (1972) provide a few of the many examples of catalytic reduction. For an example of a chemical reduction see W. R. Moore, S. S. Hall, and C. Largman, *ibid.*, 4353 (1969).

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(4) A. J. Baggaley, R. Brettle, and J. R. Sulton, *J. Chem. Soc., Perkin Trans. 1*, 1055 (1975).

(5) Simple cyclopropane derivatives have been oxidized in a few instances. See T. Shono and Y. Matsumura, *J. Org. Chem.*, **35**, 4157 (1970); T. Shono, Y. Matsumura and Y. Nakagawa, *ibid.*, **36**, 1771 (1971); T. Shono and Y. Matsumura, *Bull. Chem. Soc. Jpn.*, **48**, 2861 (1975); M. Klehr and H. J. Schafer, *Angew. Chem., Int. Ed. Engl.*, **14**, 247 (1975). See also K. B. Wiberg and G. T. Burgmaier, *J. Am. Chem. Soc.*, **94**, 7396 (1972).

(6) T. Shono, A. Ikeda, J. Hayashi, and S. Hakozaki, *J. Am. Chem. Soc.*, **97**, 4261 (1975).

(7) T. Shono, Y. Matsumura, and Y. Nakagawa, *J. Am. Chem. Soc.*, **96**, 3532 (1974).

(8) Simple alkyl-substituted cyclopropanes show half-wave oxidation potentials vs. SCE of 2.0–2.5 V.[5] Unstrained saturated hydrocarbons exhibit half-wave oxidation potentials in excess of 2.5 V.

(9) S. J. Cristol and R. L. Snell, *J. Am. Chem. Soc.*, **80**, 1950 (1958); H. Hogeveen and H. C. Volger, *ibid.*, **89**, 2486 (1967).

(10) P. G. Gassman and T. H. Johnson, *J. Am. Chem. Soc.*, **98**, 861 (1976).

(11) P. v. R. Schleyer, *J. Am. Chem. Soc.*, **80**, 1700 (1958).

(12) P. G. Gassman, T. J. Atkins, and J. T. Lumb, *J. Am. Chem. Soc.*, **94**, 7757 (1972).

(13) A detailed study of the relationship of oxidizability to ionization potential of strained polycyclic hydrocarbons has confirmed this point: P. G. Gassman and R. Yamaguchi, submitted for publication.

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

(15) The second wave which was observed for both **11** and **12** was attributed to the aryl sulfonamide moiety. Little change occurred in the oxidation in changing from **11** to **12**.

(16) This would require that the two different cyclopropyl rings of **19** have different half-wave oxidation potentials. This should be the case, since two different cation radicals would be generated from the oxidation of the two different rings. Obviously, the two waves which were observed reflect the existence of two close lying high-energy occupied molecular orbitals. The question which requires answering is whether these two high-energy orbitals are associated with the two different cyclopropyl moieties, respectively. We are currently carrying out studies designed to determine the answer to this question.

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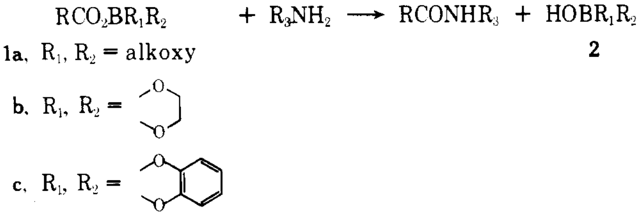
## A New Synthesis of Amides and Macrocyclic Lactams

*Summary:* New and general routes to amides and lactams of up to 32 atoms in circumference are described based on boron-containing active esters.

*Sir:* We wish to report that carboxylic acids react rapidly and smoothly with catecholborane to afford 2-acyloxy-1,3,2-benzodioxaborolanes (**1c**). As one aspect of a general program to prepare clinically interesting maytansinoids and ansamycins,[1] we herein document the use of this mild reaction as the essential carboxyl-activation step for the synthesis of amides and macrocyclic lactams.[2]

Simple acyloxyboranes such as **1a** and **1b** react with amines to furnish amides in moderate yield, but uniformly low conversion.[3] Mechanistic studies by Pelter in 1970 revealed that the leaving groups **2a,b** ejected in this process fragment to liberate 1 equiv of ROH which competitively destroys the active intermediate by attack at the boron atom of **1**.[4]


$$RCO_2BR_1R_2 + R_3NH_2 \longrightarrow RCONHR_3 + HOBR_1R_2$$

**1a**, $R_1, R_2$ = alkoxy **2**

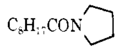
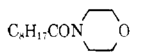
**b**, $R_1, R_2$ =

**c**, $R_1, R_2$ =

We reasoned that acyloxyborane **1c** might circumvent these difficulties, since its leaving group, 2-hydroxy-1,3,2-benzodioxaborolane, ought to resist disproportionation. Moreover, any breakdown of **2c** would form a relatively nonnucleophilic phenol still attached to boron. We further expected the aromatic ring's electron-withdrawing character to enhance the reactivity of the active ester. Modulation of this effect through substitution of polar groups on the arene would enable a high degree of control in designing preparatively useful reagents.

Catecholborane (**3**)[5] is available from Aldrich Chemical Company[6] and converts carboxylic acids (THF, room temperature, 30–60 min) to the corresponding acyloxybenzodioxaborolanes (IR $\lambda_{max}$ 1740 cm$^{-1}$) free of anhydride byproduct. At ambient temperatures catecholborane is ideally suited for the C-activation of complex substrates, since it is inert toward alkyl and aryl halides, alkenes, alkynes, amides, anhydrides, disulfides, esters, nitriles, nitro compounds, sulfides, and sulfones.[7] Subsequent addition of an amine to **1c** rapidly forms the amide in greatly improved yield (Table I). Even optically active acids such as $N$-benzoyl-L-leucine can be coupled with no measurable loss (<2%) of enantiomeric

**Table I. Formation of Amides from Nonanoic Acid Using Catecholborane**

| amine | product[a] | % yield[b] |
|---|---|---|
| benzylamine | $C_8H_{17}CONHCH_2Ph$ | 92 |
| pyrrolidine |  $C_8H_{17}CON$ | 85 |
| butylamine | $C_8H_{17}CONHCH_2CH_2$-$CH_2CH_3$ | 84 |
| morpholine |  $C_8H_{17}CON$ O | 74 |
| benzylmethylamine | $C_8H_{17}CON(CH_3)CH_2Ph$ | 74 |
| glycine ethyl ester | $C_8H_{17}CONHCH_2CO_2$-$CH_2CH_3$ | 63 |

[a] Obtained by inverse addition of the acyloxyborane to the amine (2 equiv) in THF at −78 °C. [b] Product identity was established by comparison with authentic samples. In some cases filtration through a short column of silica gel was necessary to obtain pure product.