3.5 times the T_1's of the olefinic proton was taken before the next pulse. The T_1 values for (*Z*)-**4f-OBDMS**, (*E*)-**4f-OBDMS**, (*Z*)-**6f-OBDMS**, and (*E*)-**6f-OBDMS** were determined by the inversion recovery method: C(3) methylene protons, 2.6, 1.9, 1.8, and 1.9 s, respectively; olefinic protons, 8.5, 7.9, 6.5, and 6.5 s, respectively.

Calculations. Semiempirical molecular orbital calculations and molecular mechanics calculations were performed through the AMPAC[39] system and MM2,[35] respectively, on FACOM M-780/30, FACOM VP-400E, and FACOM VP-200 computers.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research No. 02453092 from the Ministry of Education, Science and Culture, Japan, and a grant from the Asahi Glass Foundation.

Registry No. **4a**, 137494-86-1; **4b**, 137494-88-3; **4c**, 116760-09-9; **4c**-OBDMS, 137494-96-3; **4c** *p*-nitrobenzoate, 137494-97-4; **4d**, 116760-07-7; **4d**-OBDMS, 135107-28-7; **4d** *p*-nitrobenzoate, 137494-95-2; (*E*)-**4e**, 137494-87-2; (*E*)-**4f**, 135107-35-6; (*E*)-**4f**-OBDMS, 135107-37-8; (*Z*)-**4f**, 135107-34-5; (*Z*)-**4f**-OBDMS, 135107-36-7; (*Z*)-**4f**-OBDMS epoxide, 137494-98-5; **5a**, 137494-89-4; **5b**, 137494-90-7; **5b** *p*-nitrobenzoate, 137495-03-5; **5c**, 137494-99-6; **5c** *p*-nitrobenzoate, 137495-02-4; **6a**, 116759-95-6; **6b**, 116759-97-8; **6c**, 137495-04-6; **6c** trimethylsilyl ether, 137495-06-8; **6d**, 116760-08-8; **6d**-OBDMS, 135107-29-8; **6d** trimethylsilyl ether, 137495-05-7; (*E*)-**6e**, 137494-91-8; (*E*)-**6f**, 135107-41-4; (*E*)-**6f**-OBDMS, 135144-13-7; (*E*)-**6f**-OEt, 137515-44-7; (*Z*)-**6f**, 135107-40-3; (*Z*)-**6f**-OBDMS, 135107-44-7; **7a**-OHFB, 137494-92-9; **7a**-OMs, 130829-59-3; **7b**-OHFB, 137494-93-0; **7b**-OMs, 130829-60-6; **7c**, 130829-56-0; **7c**-OBDMS, 137495-08-0; **7c**-OEt, 130829-67-3; **7d**, 121455-49-0; **7d**-OBDMS, 137495-07-9; **8a**, 137494-94-1; **8b**, 28054-89-9; **8c**, 137495-09-1; **8c**-OBDMS, 137495-11-5; **8c**-OEt, 137495-20-6; **8d**, 121455-53-6; **8d**-OBDMS, 137495-10-4; **9a**, 137515-53-8; **9b**, 137515-54-9; **9c**, 137495-13-7; **9c**-OEt, 137495-21-7; **9d**, 121455-48-9; **9d** trimethylsilyl ether, 137495-14-8; **10a**, 130829-58-2; **10b**, 97654-82-5; **10c**, 130829-57-1; **10c**-OBDMS, 137515-55-0; **10c**-OEt, 137495-22-8; **10d**, 97382-24-6; **10d**-OBDMS, 137495-15-9; C_3F_7COCl, 375-16-6; 1-methoxybicyclo[2.2.2]octan-2-one, 53921-93-0; ethylidenetriphenylphosphorane, 1754-88-7; bicyclo[2.2.2]octan-1-ol, 20534-58-1; 2-methylenebicyclo[2.2.2]-oct-1-yl acetate, 137495-00-2; 2-methylenebicyclo[3.2.1]oct-1-yl acetate, 137495-01-3; bicyclo[3.2.1]octan-1-ol, 134654-98-1; bicyclo[3.2.1]octane-1-carboxylic acid, 2534-83-0; bicyclo[3.2.2]nonane-1,2-diol, 110977-44-1; bicyclo[3.2.2]nonan-1-ol, 28054-86-6; bicyclo[3.3.1]nonan-1-ol, 15158-56-2; 1-bromobicyclo[3.3.1]nonane, 15292-76-9; bicyclo[4.2.2]decane, 284-26-4; 1-bromobicyclo-[4.2.2]decane, 137495-12-6; bicyclo[4.2.2]decan-1-ol, 79312-80-4; bicyclo[4.3.1]decan-1-ol, 22516-95-6; 3-homoadamantan-1-ol, 14504-80-4; 1-ethoxy-2-methylenebicyclo[2.2.2]octane, 137495-16-0; 1-ethoxy-(*E*)-2-ethylidenebicyclo[2.2.2]octane, 137495-17-1; 1-ethoxy-2-methylenebicyclo[3.2.1]octane, 137495-18-2; 1-ethoxy-2-methylenebicyclo[3.2.2]nonane, 137495-19-3.

Supplementary Material Available: ^{13}C NMR spectra for substrates and precursor alcohols (28 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Conformations of Oxocane

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Conformational analysis of oxocane (oxacyclooctane) has been examined by molecular mechanics (MM2), variable-temperature ^{13}C NMR, and lanthanide-induced shift (LIS) ^1H and ^{13}C NMR. MM2 calculations find the BC-3 conformer and its enantiomer BC-7 to be favored, with the four next best forms and their energies relative to BC-3 being BC-1 (1.1 kcal/mol), TBC-1 (1.1), BC-4 (1.5), and TCC-1 (1.6). Barriers to pseudorotational interconversion of BC-3 and BC-7 are calculated to be 5.0 kcal/mol through BC-5 and 6.7 kcal/mol through BC-1. The former would allow fast BC-3/BC-7 equilibration even at −170 °C, which would leave reported low-temperature ^1H NMR spectra compatible with a BC-3 structure as well as BC-1. Calculated barriers for BC ring inversion and interconversion of the BC family with the crown family (TCC-1) are 8.2 and 8.5 kcal/mol, respectively. A new two-step synthesis of oxocane and its 2,2,7,7-d_4 analogue is reported, the latter allowing unequivocal assignment of chemical shifts. ^{13}C NMR spectra of oxocane between 138 and 290 K show BC-family/crown-family interconversion in the vicinity of 215 K ($\Delta G^* = 10.0 \pm 0.3$ kcal/mol), with the crown family comprising 4% of the equilibrium at 174 K ($\Delta G° = 1.1 \pm 0.1$ kcal/mol). The ^1H and ^{13}C LIS induced by Yb(fod)$_3$ on oxocane agree well with BC-3 and BC-7 being the predominant conformers at room temperature but do not acceptably fit a BC-1 structure. Thus, all available data from calculation and experiment are in accord with BC-3 being the favored conformation of oxocane.

The conformational properties of cyclooctane are well understood.[2] Both experiment (NMR,[3] electron diffraction,[4] vibrational analysis[5]) and theory (MM2,[4,6,7] MM2′,[8] ab initio 4-21G,[6] etc.[9]) are in complete agreement that at room temperature the major conformer (94%) is the boat-chair (BC; see Figure 1[10]), which undergoes rapid pseudorotation through the TBC with a barrier too low to detect by NMR[3c] (calculated by MM to be 2.8–3.4

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(1) (a) Fayetteville. (b) Saarbrücken. (c) Jefferson. (d) Zürich.

(2) For reviews, see: (a) Anet, F. A. L. *Top. Curr. Chem.* **1974**, *45*, 169. (b) Anet, F. A. L.; Anet, R. In *Dynamic Nuclear Magnetic Resonance Spectroscopy*; Jackman, L. M., Cotton, F. A., Eds.; Academic: New York, 1975; pp 543–619. (c) Anet, F. A. L. In *Conformational Analysis of Medium-Sized Heterocycles*; Glass, R. S., Ed.; VCH: New York, 1988; pp 35–95.

0022-3263/92/1957-0291$03.00/0

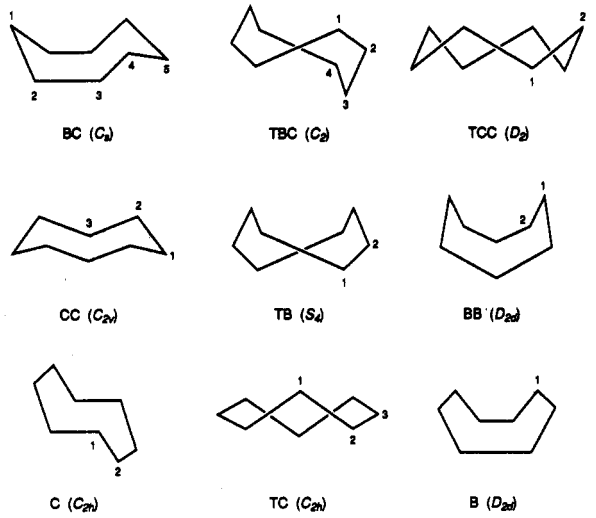


Figure 1. Conformations of cyclooctane and oxocane.[2] Numbers show the location of the oxygen in oxocane. The CC is a stretched crown with the 1–5 distance greater than 3–7. In TCC the distance between midpoints of 2–3 and 6–7 is greater than that between 1–8 and 4–5. In TB, $\omega_{1,2}$ is greater than $\omega_{1,8}$. Symmetries apply to cyclooctane.

kcal/mol[8,9,12]) and ring inversion through the C, TC, or BB over a barrier of 8.1 kcal/mol (NMR, $\Delta G^{\ddagger}$ at −112 °C;[3a] MM gives 7.5–9.2[8,9,12]). The remaining 6% is made up of pseudorotating crown-family forms (crown, CC, and/or TCC), of which TCC may be slightly preferred.[6,9] The BC and crown families are separated by a barrier of 11.2 kcal/mol ($\Delta G^{\ddagger}$ at −45 °C) and differ in enthalpy by 1.9 kcal/mol (NMR;[3c] barriers of 9.8–11.6 are calculated by MM[8,9,12]).

The conformational situation in the oxygen analogue oxocane (oxacyclooctane, **3a**) is less well defined.[2c] Oxocane is more complex than cyclooctane, because there are now five energetically distinct BC conformers which differ in the location of oxygen and corresponding numbers of other forms (Figure 1). Anet and Degen reported that 251-MHz ^{1}H NMR spectra show a conformational change at −122 °C (coalescence; $\Delta G^{\ddagger}$ = 7.4 kcal/mol).[14,15] This was assigned to ring inversion, since the 63-MHz ^{13}C spectrum was unchanged to −170 °C.[2a,15] Even without detailed strain energy calculations it could be convincingly argued that BC forms would be preferred over other conformations and that the most favorable sites for oxygen in a BC must be BC-1 or BC-3. The residual ^{13}C spectrum at low temperature (only four resonances) demands a symmetric structure, which allows only BC-1 or a rapidly pseudorotating BC-3/BC-7 enantiomeric mixture. Arguing that pseudorotation should be frozen at such temperatures as it is for cyclooctanone,[16] i.e., that a second process should have been observed at low temperature if oxocane were BC-3/BC-7, Anet and Degen assigned BC-1 as the predominant conformer of oxocane,[2a,14] although Anet recently commented that the position of oxygen is not well defined.[2c]

The only published MM calculations on oxocane are by Burkert,[17] who developed his own force field for ethers. He found BC-3 to be lowest in energy, favored by 0.4 kcal/mol over BC-1 and by more than 1.5 kcal/mol over any other conformer. Anet also mentions that unpublished MM calculations by his group found BC-3 to be better than BC-1 but without numerical detail or further comment on the NMR interpretation.[18]

Conflict between these MM predictions and the experimental assignment led us to seek evidence to clarify the picture. Here we report calculations using the MM2 force field[19] and low-temperature and lanthanide-shift NMR experiments. The results are in good accord with the BC-3 structure and, we think, argue strongly against BC-1 as the major conformer. They also demonstrate the presence of a minor conformer similar to that of cyclo-

Table I. Calculated Relative Energies of Oxocane Conformers

conformer[a]	rel energy, kcal/mol	
	Burkert[17]	MM2
BC-1	0.41	1.07
BC-2	2.82	3.23
BC-3	0.00	0.00
BC-4	1.58	1.54
BC-5	2.62	2.90
TBC-1		1.10
TBC-2		4.86
TBC-3		2.63
TBC-4		3.94
CC-3[b]	2.10	2.33[c]
TCC-1	*d*	1.60
TCC-2	*d*	2.60
BB-1	3.30	3.33
BB-2	5.53	*e*
TB-1		3.20
TB-2		7.19
TC-1		9.24[c]
TC-3		10.84[c]

[a] Numbering for location of oxygen is shown in Figure 1. No symmetry constraints were used by either Burkert or us except as indicated in note *c*. Our BC-1 and BC-3 minima are C_s; BB-1 is not. [b] We assume that Burkert's "crown" corresponds to our CC-3. [c] Forced C_s symmetry; no minimum was found without symmetry constraint. These may be saddle points rather than minima, see discussion. [d] Not a minimum. Goes to crown during minimization. [e] BB-2 input minimizes to TB-2. It is not clear whether the shape of Burkert's "BB-2" is BB or TB.

(3) (a) Anet, F. A. L.; Hartman, J. S. *J. Am. Chem. Soc.* **1963**, *85*, 1204. (b) Anet, F. A. L.; St. Jacques, M. *J. Am. Chem. Soc.* **1966**, *88*, 2585. (c) Anet, F. A. L.; Basus, V. J. *J. Am. Chem. Soc.* **1973**, *95*, 4424. (d) Meiboom, S.; Hewitt, R. C.; Luz, Z. *J. Chem. Phys.* **1977**, *66*, 4041.

(4) Dorofeeva, O. V.; Mastryukov, V. S.; Allinger, N. L.; Almenningen, A. *J. Phys. Chem.* **1985**, *89*, 252.

(5) Pakes, P. W.; Rounds, T. C.; Strauss, H. L. *J. Phys. Chem.* **1981**, *85*, 2476. Dorofeeva, O. V.; Gurvich, L. V.; Mastryukov, V. S. *J. Mol. Struct.* **1985**, *129*, 165.

(6) Siam, K.; Dorofeeva, O. V.; Mastryukov, V. S.; Ewbank, J. D.; Allinger, N. L.; Schäfer, L. *J. Mol. Struct. (Theochem)* **1988**, *164*, 93.

(7) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; ACS Monograph 177; American Chemical Society: Washington, DC, 1982; pp 100–104.

(8) Ivanov, P. M.; Osawa, E. *J. Comput. Chem.* **1984**, *5*, 307.

(9) Anet, F. A. L.; Krane, J. *Tetrahedron Lett.* **1973**, 5029.

(10) We use the conformational notation and nomenclature of Hendrickson[11] and Anet,[2a] in which, for example, BC-1 denotes the boat-chair conformation with oxygen at position 1 (numbering as shown in Figure 1).

(11) Hendrickson, J. B. *J. Am. Chem. Soc.* **1964**, *86*, 4854; **1967**, *89*, 7047.

(12) With MMX[13] we find for cyclooctane a BC/TBC pseudorotation barrier of 2.8 kcal/mol, a BC/TB ring inversion barrier of 9.2 kcal/mol, and a TBC/TCC BC–crown family barrier of 9.8 kcal/mol.

(13) Gilbert, K.; Gajewski, J. Serena Software, Bloomington, IN. MMX is identical with MM2 for these compounds. Parallel MM2 and MMX calculations of all conformations in Table I give structures and energies that are identical within 0.03 kcal/mol or less.

(14) Anet, F. A. L.; Degen, P. J. *J. Am. Chem. Soc.* **1972**, *94*, 1390.

(15) Degen, P. J. Ph.D. Dissertation, University of California at Los Angeles, 1972.

(16) Anet, F. A. L.; St. Jacques, M.; Henrichs, P. M.; Cheng, A. K.; Krane, J.; Wong, L. *Tetrahedron* **1974**, *30*, 1629. Anet, F. A. L.; St. Jacques, M.; Henrichs, M. *Intra-Sci. Chem. Rep.* **1970**, *4*, 251.

(17) Burkert, U. *Z. Naturforsch. B, Anorg. Chem. Org. Chem.* **1980**, *35B*, 1479.

(18) Anet, F. A. L.; Degen, P. J.; Krane, J. *J. Am. Chem. Soc.* **1976**, *98*, 2059.

(19) Allinger, N. L.; Yuh, Y. QCPE 395, Quantum Chemistry Program Exchange, Indiana University, Bloomington, IN 47405. Allinger, N. L.; Chang, S. H.-M.; Glaser, D. H.; Hönig, H. *Isr. J. Chem.* **1980**, *20*, 51.

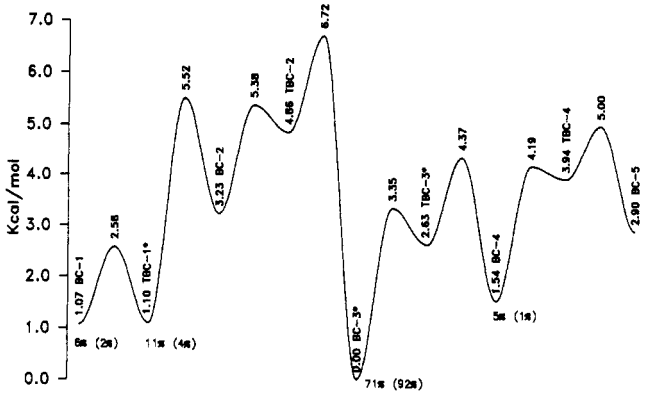


Figure 2. Maxima and minima for oxocane BC/TBC pseudorotation as calculated by MMX, joined by arbitrary lines. Conformers marked with an asterisk are enantiomers of the structures in Figure 1. Populations are shown for 298 K and in () for 173 K.

octane and the nitrogen analogue azocane.[20,21]

Molecular Mechanics. Table I shows relative strain energies of many conformations of oxocane as calculated by Burkert[17] and by MM2. Both force fields find BC-3 to be the most favorable and BC-1 next and agree that BC-3 should dominate the conformational equilibrium to the extent of 70–75% at room temperature and 85–90% at −100 °C. MM2 finds a much greater difference between BC-3 and BC-1 (1.1 vs 0.4 kcal/mol).

If these were the only significant conformers, the BC-3:BC-1 ratio would be 80:20 (Burkert) or 92:8 (MM2) at 25 °C. However, there are other striking differences between the results. Burkert did not examine TBC forms, and MM2 finds that one of them, TBC-1, is nearly as good as BC-1 and should amount to about 11% of the equilibrium. Furthermore, Burkert found a 2.1 kcal/mol "crown" to be the only minimum in the crown family, with TCC forms relaxing to it during minimization. We presume that this crown is analogous to our CC-3. MM2 finds true minima in this family only at TCC-1 (1.6 kcal/mol) and TCC-2 (2.6). CC-3 (2.3 kcal/mol) can be found by constraining C_s symmetry, but it is actually a saddle point, the barrier between enantiomeric TCC-1 forms on the crown-family pseudorotational path (which is approximated by driving the appropriate dihedral angles of TCC-1 and TCC-2). Neither CC-1 or CC-2 are minima to MM2; the former relaxes to CC-3 when C_s symmetry is constrained and the latter to TCC-1 under any circumstances. These results correspond to a 1% (Burkert) or 6% (MM2) crown-family contribution to the 25 °C equilibrium.

The BB-1 conformer found by MM2 is not quite C_s. It is a very shallow minimum, less than 0.01 kcal/mol below the true C_s form which is the barrier to a pseudorotation that interconverts enantiomeric TB-1s. We have been unable to find any TC minima without using symmetry constraints and have not found C or B minima at all.

No MM calculations of the dynamics of oxocane conformational interconversion have been reported. In order to evaluate the probable rate of BC-3/BC-7 pseudorotation, the central issue in whether the reported low-temperature NMR spectra are consistent with that process as well as a BC-1 structure, we have used MMX[13] to calculate the BC/TBC barriers. Results are in Table II.

Pseudorotation of the oxocane BC is considerably more complex than that in cyclooctane, owing to the absence of symmetry in all forms except BC-1 and BC-5. While cyclooctane has only one BC, one enantiomeric pair of TBCs, and one BC/TBC barrier, oxocane has five energetically different BCs, four TBCs, and eight distinct barriers. As Anet pointed out, smooth transformation of a BC to a TBC results from driving $\omega_{1,2}$, $\omega_{2,3}$, or $\omega_{3,4}$ of the BC until the conformation becomes TBC.[9] We have followed this procedure for all of those rotations (Figure 2). As in cyclooctane,[9] the barrier is reached slightly (5–20°) on the TBC side of eclipsing $\omega_{2,3}$, except for the BC-2/TBC-2 change where it is almost exactly eclipsed. Whereas Anet found that driving $\omega_{1,2}$ of cyclooctane gave the same conformational change as driving $\omega_{2,3}$ except with a much higher barrier, these drives by MMX for both cyclooctane and all five oxocane BCs find the same barrier as driving $\omega_{2,3}$ or $\omega_{3,4}$. While BC-3 is the *most* favorable BC form, its TBC-2 partner is the *least* favorable TBC, and the barrier between those two is the highest on the entire pseudorotational itinerary.

The lowest pseudorotational barrier to BC-3/BC-7 interconversion is 5.0 kcal/mol via the path through BC-5. That would not inhibit fast exchange on the dynamic NMR scale even at the lowest observed temperatures. Even if the 6.7 kcal/mol BC-3/TBC-2 barrier had been frozen in the −150 °C region to provide a composite spectrum of equilibrating BC-3/BC-7 plus equilibrating BC-1/TBC-1/TBC-8, the tiny amount of the latter could be difficult to detect (<2% at −150 °C using MM2 energies). Thus, according to MM2, rapid BC-3/BC-7 equilibration is a completely viable alternative to a BC-1 structure for interpretation of the reported NMR data from oxocane.

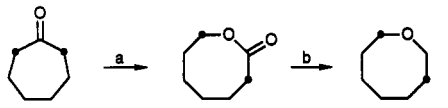
Table II. Calculated Energy Barriers for Oxocane Interconversions[a,b]

BC pseudorotation, BC/TBC		
BC/TBC pair	BC ω driven	barrier, kcal/mol
BC-1/TBC-1*	1–2; 2–3; 3–4	2.58
BC-2/TBC-1*	1–2; 2–3; 3–4	5.52
BC-2/TBC-2	1–8; 7–8; 6–7	5.38
BC-3/TBC-2*	1–2; 2–3; 3–4	6.72
BC-3/TBC-3	1–8; 7–8; 6–7	3.35
BC-4/TBC-3*	1–2; 2–3; 3–4	4.37
BC-4/TBC-4	1–8; 7–8; 6–7	4.19
BC-5/TBC-4*	1–2; 2–3; 3–4	5.00
BC family/crown family, TCC/TBC[c]		
TCC/TBC pair	TCC ω driven	barrier, kcal/mol
TCC-1/TBC-2	2–3	8.54
TCC-1/TBC-3*	3–4	8.52
TCC-1/TBC-3	6–7	9.96
TCC-1/TBC-3	7–8	10.07
TCC-2/TBC-4	6–7	11.95
TCC-2/TBC-1	2–3	14.31
ring inversion, BC/TB		
BC/TB pair	BC ω driven	barrier, kcal/mol
BC-1/TB-1	5–6[d]	9.84
BC-2/TB-2*	4–5[d]	11.42
BC-2/TB-2*	5–6	11.73
BC-3/TB-1	4–5	8.16
BC-3/TB-1*	5–6[d]	8.03
BC-4/TB-2	4–5[e]	14.33
BC-4/TB-1*	5–6[e]	10.18
BC-5/TB-1*	4–5[e]	15.30

[a] Energies are relative to BC-3 as 0.00. Barriers were calculated by driving in 1° increments after initial calculations at 5° or 10° increments. [b] Numbering as in Figure 1. Conformers marked with an asterisk indicate enantiomers of Figure 1 structures. [c] Driving any other TCC-1 or TCC-2 ω proceeds to a TBC through one of the listed processes or its mirror image. [d] Driving the TB ω in the reverse direction reaches the same BC, but over a different barrier. [e] Driving the TB ω in the reverse direction reaches a different barrier and a final conformer other than this BC.

(20) Lambert, J. B.; Khan, S. A. *J. Org. Chem.* **1975**, *40*, 369.
(21) Anet, F. A. L.; Degen, P. J.; Yavari, I. *J. Org. Chem.* **1978**, *43*, 3021.

Scheme I[a]



1a, • = CH_2 **2a**, • = CH_2 **3a**, • = CH_2
1b, • = CD_2 **2b**, • = CD_2 **3b**, • = CD_2

[a] (a) *m*-$ClPhCO_3H$ (87%); (b) $HSiCl_3/(t\text{-}BuO)_2/h\nu$ (44%).

Two other barriers are of interest for comparison with experiment, ring inversion and the BC/crown-family change. In view of the added complexity of oxocane over cyclooctane we have not tried to carry out a complete treatment of these processes, because in addition to the added number of potentially participating conformers there are several possible pathways for each.[9] We have only examined some of the paths that Anet found relatively favorable for cyclooctane, to see if the calculated barriers are in reasonable accord with experimental results.

In cyclooctane the lowest calculated BC/crown-family barrier is for TBC/TCC, which Anet obtained by driving $\omega_{1,8}$ of TBC, with maintenance of approximate C_2 symmetry throughout the change.[9] Driving TBC forms of either cyclooctane or oxocane by MMX does not maintain the C_2 relations or result in TCC structures. However, driving TCCs in the reverse direction *does* reach TBCs, although it always reaches a BC first. The resulting cyclooctane barrier, 9.8 kcal/mol, is very close to that calculated by Anet (10.3) and to the experimental one (11.2). The lowest of the five corresponding oxocane barriers is 8.5 kcal/mol (Table II), which will be compared with experiment below.

The other experimentally detected barrier is for ring inversion, 7.4 kcal/mol.[14,15] Anet's cyclooctane calculations showed TBC/C to be the most favorable path and TBC/TC nearly as good, with BC/BB and BC/TB significantly higher but about equal to each other.[9] The lowest oxocane barrier we have found is 8.2 kcal/mol (BC-3/TB-1/BC-7), which agrees acceptably with the experimental finding. We have not located a path through a BB and have not sought TBC/TC barriers in view of the fact that the TCs are themselves much higher than 8.0 kcal/mol.

Synthesis. Few syntheses of oxocane have been reported, and most are impractical (many steps and/or very low overall yields).[14,22-24] The only useful one is by Olah, who converted 1,7-heptanediol to oxocane in one step (51%) with Nafion-H catalyst, a perfluorinated resin-sulfonic acid.[25] Although that process is direct and acceptably efficient, we wanted a procedure which would also allow preparation of a specifically deuterated oxocane for unequivocal assignment of ^{13}C and ^{1}H NMR chemical shifts and thus devised the two-step sequence shown in Scheme I. While **2a** cannot be reduced to the ether by $NaBH_4/BF_3$ or $LiAlH_4/AlCl_3$,[15] photochemical free-radical reduction by $HSiCl_3$[26] cleanly produces oxocane (**3a**). We made no effort to optimize the yield in this reaction; the reported 44% (which represents scrupulously purified material) can probably be improved. Use of cycloheptanone-2,2,7,7-d_4 gives the d_4 analogue **3b**. Comparison

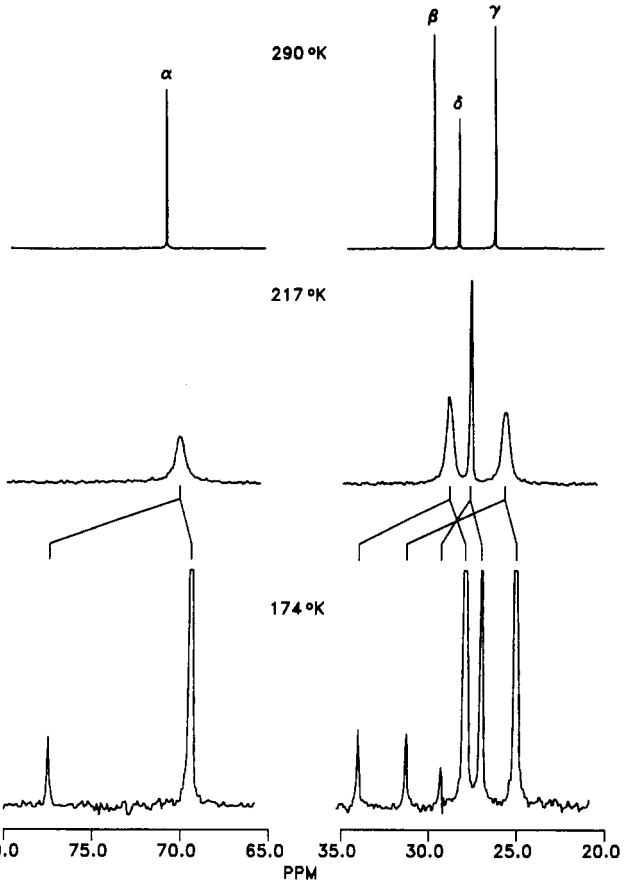


Figure 3. 126-MHz ^{13}C NMR spectra of oxocane in CBr_2F_2/CD_2Cl_2 (3:1 v/v) at 290, 217, and 174 K.

of ^{13}C NMR spectra of **3a** and **3b** allows unequivocal assignment of the chemical shifts in **3a** as δ 70.2 = C(α), 29.0 = C(β), 27.5 = C(δ), and 25.5 = C(γ).

Low-Temperature NMR. Anet and Degen's report that 63-MHz ^{13}C NMR spectra of oxocane are unchanged from 25 to −170 °C[2a,15] was several years before examination of azocane found BC/crown-family interconversion at −54 °C with a barrier of 10.5 kcal/mol ($\Delta G^{\ddagger}$) and $\Delta G°$ of 1.2 kcal/mol,[20,21] a process which is easily overlooked owing to the low population of the crown family. Analogous reinvestigation of oxocane has not been published.[27]

^{13}C NMR spectra of oxocane from 17 to −135 °C (126 MHz) mimic those of azocane almost exactly, revealing a strongly biased conformational equilibrium. Above 0 °C there are only four averaged resonances in a 2:2:2:1 ratio. At −56 °C the α, β, and γ signals have broadened substantially, and they resharpen at lower temperatures (Figure 3). Just as with azocane, the δ-carbon resonance shows little broadening through this range. At −100 °C the four strong resonances are slightly upfield from their fast exchange positions, and each is accompanied by a corresponding lower field signal from a minor form in a ratio of 96:4 based on relative intensities.[28]

Rates of the exchange were determined by total lineshape analysis of the broadened spectra at 200, 217, and 233 K. Chemical shifts of the major conformer, relative

(22) Müller, A.; Vanc, W. *Ber. Dtsch. Chem. Ges.* **1944**, *77*, 669.
(23) Paquette, L. A.; Begland, R. W. *J. Org. Chem.* **1967**, *32*, 2723.
(24) Nerdel, F.; Buddrus, J.; Browdowski, W.; Weyerstahl, P. *Tetrahedron Lett.* **1966**, 5385.
(25) Olah, G. A.; Fung, A. P.; Malhotra, R. *Synthesis* **1981**, 474.
(26) (a) Nakao, R.; Fukumoto, T.; Tsurugi, J. *J. Org. Chem.* **1972**, *37*, 76. (b) Baldwin, S. W.; Doll, R. J.; Haut, S. A. *J. Org. Chem.* **1974**, *39*, 2470. (c) Baldwin, S. W.; Haut, S. A. *J. Org. Chem.* **1975**, *40*, 3885.

(27) After completion of this work we became aware of an unpublished ^{13}C NMR reinvestigation by the Anet group, which found the minor crown-family component at −100 °C ($\Delta G°$ = 1 kcal/mol), see ref 2c, p 75. See also: Moore, J. A.; Anet, F. A. L. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 7, p 700.
(28) Broadening resumes below 160 K, but since the lines do not again sharpen at the lowest temperature we can reach (138 K), this may result from viscosity rather than another conformational process.

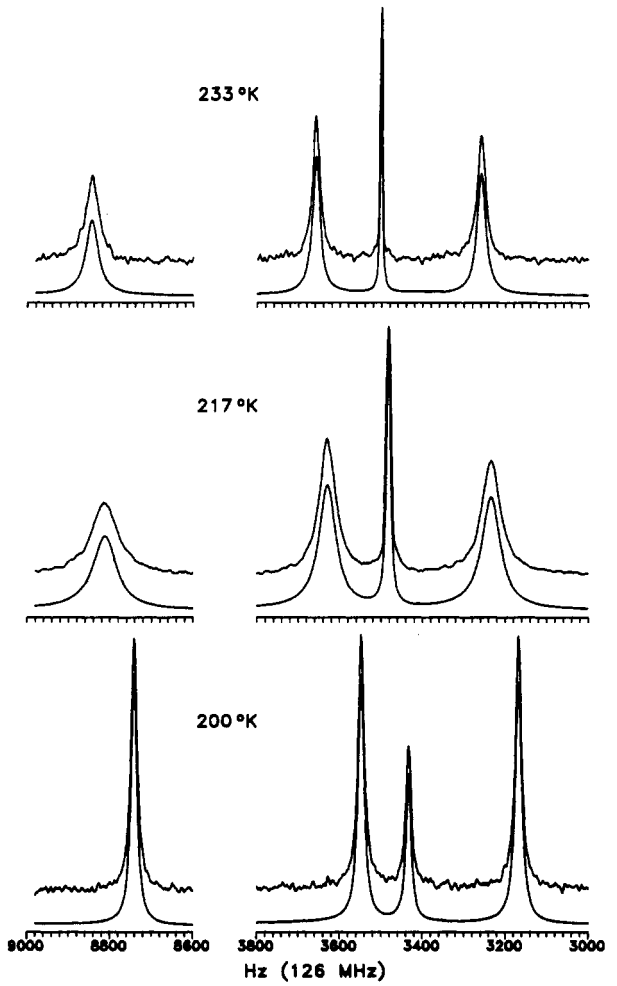


Figure 4. Experimental and calculated ^{13}C NMR spectra of oxocane at 233, 217, and 200 K.

populations, and rate constants were iteratively varied.[29,30] The resulting simulated spectra provide an excellent match (Figure 4) and lead to $\Delta G^{\ddagger}$ from absolute rate theory of 10.0 ± 0.3 kcal/mol at 217 K. The reason that the δ-carbon resonance shows little broadening compared to the others is because its chemical shift difference between the major and minor forms is comparatively small. The line-shape analysis also gives BC-family populations of 94.6, 93.3, and 92% at 200, 217, and 233 K, respectively,[31] which are in good agreement with 96% at 174 K. This corresponds to $\Delta G°$ of 1.1 ± 0.1 kcal/mol between the two forms.

The conformational change responsible for these effects cannot be BC ring inversion, which would be unobservable in ^{13}C spectra. It also cannot be complete inhibition of BC pseudorotation; while that could produce a four-line spectrum for the BC-1 form, any other reasonable BC or TBC component would give rise to seven lines. In principle it could be division of the BC pseudorotational itinerary into two segments, each of which maintains time-average C_s symmetry, but we reject that interpretation because no barrier on the BC cycle is calculated to even approach the 10 kcal/mol of the observed process. The only reasonable explanation is interconversion of the BC family with the TCC (crown) family, with each family continuing its own rapid pseudorotation to average C(2)/C(8), C(3)/C(7), and C(4)/C(6). This is, of course, the same process assigned to the 10.5 kcal/mol barriers of azocane[21] and cyclooctane.[3c] The MM2 estimate of 1.6 kcal/mol for the energy difference between BC-3 and TCC-1 is in acceptable accord with the observed $\Delta G°$, which indicates that the TCC family accounts for about 13% of the conformational mixture at 25 °C, somewhat more than that in cyclooctane (6%) and about the same as that in azocane (12%). The observed barrier is 1.5 kcal/mol higher than the MMX calculation, a somewhat poorer agreement than for the other processes but about the same discrepancy between MMX and experiment as for cyclooctane.

Table III. Calculated Relative Lanthanide Shifts for Oxocane

	expt		RS calcd[a] for			
	LIS[b]	RS[c]	BC-3	BC-1	TBC-1	TCC-1
C(α)	7.54	1.00	1.00	1.00	1.00	1.00
C(β)	3.15	0.42	0.42	0.40	0.41	0.42
C(γ)	2.10	0.28	0.27	0.30	0.30	0.28
C(δ)	1.93	0.26	0.28	0.23	0.25	0.27
H(α)	4.51	0.60	0.60	0.61	0.61	0.60
H(β)	2.10	0.28	0.26	0.26	0.25	0.26
H(γ)	1.53[d]	0.20[d]	0.17	0.23	0.21	0.19
H(δ)	1.53[d]	0.20[d]	0.21	0.15	0.18	0.21
distance[e]			2.64	2.64	2.72	2.72
angle 1[f]			40	26	34	32
angle 2[g]			6	0	18	14
R^h			0.050	0.084	0.051	0.034

[a] LIS relative to LIS of C(α), calculated for "best fit" location of Yb, see text. [b] LIS for 0.10 equiv $Yb(fod)_3$. [c] LIS relative to LIS of C(α); average over five aliquots of $Yb(fod)_3$. [d] Not resolved; slight shoulder on low-field side of band suggests that RS(H(δ)) > RS(H(γ)). [e] Yb–O distance, Å. [f] Angle from less hindered MM2 lone pair to O to Yb, toward the more hindered lone pair and in the lp–O–lp plane. An angle of 65° bisects the lp–O–lp angle. [g] Angle from Yb to O to the lp–O–lp plane, in the direction of C(2) from that plane. [h] Agreement factor, see ref 35.

LIS NMR. BC-1 and BC-3 differ considerably in distances between oxygen and the various carbons and protons and in distances as they would be averaged by rapid ring inversion and pseudorotation. This suggested that lanthanide shift experiments might allow distinction between the two forms if one is greatly predominant. For example, calculation of the pseudocontact shift (LIS; eq 1)[32] for each time-averaged proton and carbon set produced

$$\text{LIS} = k(3\cos^2\theta - 1)/r^3 \quad (1)$$

by a lanthanide atom 2.7 Å from oxygen on the axis between oxygen and the less hindered MM2 lone pair (lp) shows striking differences. For BC-1 the shift of C(γ) is predicted to be about 25% greater than that of C(δ), while for BC-3 the two are nearly the same. In addition, the shifts of H(β) and H(γ) are predicted to be similar and 50% larger than that of H(δ) if the conformation is BC-1,

(29) Stephenson, D. S.; Binsch, G. DNMR5, QCPE 365; modified for the PC by LeMaster, C. B.; LeMaster, C. L.; True, N. S. QCMP 059, Quantum Chemistry Program Exchange, Bloomington, IN 47405.

(30) Chemical shifts of both observable species are temperature dependent, at least in part because they represent equilibrating conformer mixtures in which contributing populations change with temperature. For line-shape fitting we obtained chemical shifts for the TCC family by extrapolation vs $1/T$ from lower temperatures where separate BC-family and TCC-family signals are observable. These shifts were not varied during fitting, because broadened line positions and shapes are not significantly sensitive to them. On the other hand, calculated line positions and shapes are highly dependent on the chemical shifts of the major form, so they were included as variable parameters in the iterative line-shape analysis rather than being determined by a corresponding extrapolation.

(31) In a system with very different populations, exchange-broadened line widths depend on populations as well as exchange rate. For example, with reasonable assignments of 217 K chemical shifts to the BC family and TCC family, no mixture containing less than 6.5% of TCC can simulate a C(α) line as broad as the observed 72 Hz, irrespective of the rate.

(32) McConnell, H. M.; Robertson, R. E. *J. Chem. Phys.* **1958**, *29*, 1361.

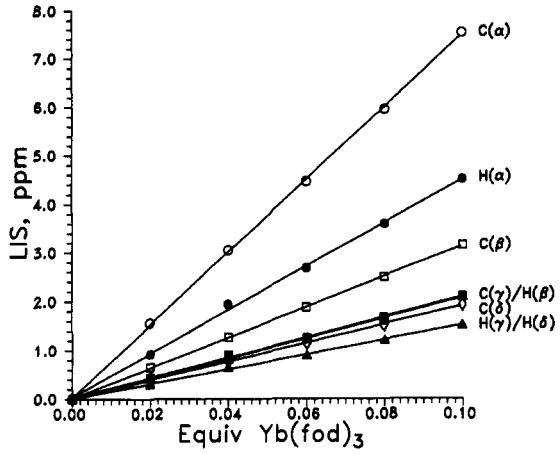


Figure 5. Dependence of oxocane LIS on $Yb(fod)_3$ concentration.

but for BC-3 H(β) and H(δ) would be about equal and substantially larger than H(γ). Accordingly, LIS experiments were conducted. $Yb(fod)_3$ was used as the shift reagent (LSR) because Yb acts almost completely by the pseudocontact mechanism in ^{13}C as well as ^1H spectra.[33,34] Results are in Table III. As in analogous studies, shifts were measured at low $Yb(fod)_3$:**3a** ratios to minimize changes in the stoichiometry of the complexes. All resonances showed good linearity of LIS vs $Yb(fod)_3$ concentration over five incremental additions of the LSR (Figure 5).

The ^1H LIS experiments are complicated by the fact that without LSR the β, γ, and δ proton resonances are unresolved even at 500 MHz. However, the LIS of one of these sets is sufficiently different from the other two that in the presence of $Yb(fod)_3$ they separate into two bands. The more downfield resonance is from four protons in **3a** but two protons in **3b** and thus must correspond to H(β). Although H(γ) and H(δ) remain unresolved, a slight shoulder on the downfield side of their resonance suggests that the LIS of H(δ) is slightly (<10%) greater than that of H(γ).

The observed shifts are qualitatively in better accord with BC-3 expectations than with BC-1, particularly in that the shifts of C(δ) and H(δ) are *not* substantially smaller than all others as predicted for BC-1. However, the location of Yb for the trial McConnell–Robertson calculation mentioned above is quite arbitrary. While many investigations have found that a Ln–O distance of 2.5–3.0 Å is usually about right,[33,34] the angular orientation of Yb vis-à-vis the molecule is less easy to assign on a priori grounds. The real question is whether there is a reasonable location for Yb which will result in calculated shifts that suitably agree with the experimental results. Accordingly, we carried out a series of predicted RS calculations in which the oxocane geometry was kept at the BC-3 and BC-1 MM2 minima but the position of Yb was varied throughout the space 2.0–3.5 Å from oxygen and at angles from one MM2 lone pair to the other within 45° from the lp–O–lp plane. Initial search used 5° increments in angles and 0.1-Å increments in distance, with final refinement in steps of 2° and 0.02 Å. The Willcott "agreement factor" (R)[35] was used as the test for fit between experiment and calculation.

These calculations allow one to find the Yb location for which differences between calculated and experimental shifts are statistically minimized, so-called "best fit" locations (Table III). If the oxocane structure is accommodated by the LIS data, the differences between experimental and calculated shifts must all be small and the Yb location must be reasonable. This is true for BC-3, where the R factor is very good (5%) and only one difference between calculated and experimental RS is greater than 0.02 (10% or less of the observed RS). On the other hand, the best location of Yb on BC-1 leaves significant differences between experiment and prediction for C(δ), H(γ), and H(δ). Application of the statistical R-factor ratio test[35] to the BC-1/BC-3 pair shows the latter structure to be more probable to the 95% confidence level. An even stronger argument against BC-1 is the fact that for any reasonable Yb location (2.5–3.0 Å from O and 0–65° from the less hindered lone pair), the BC-1 structure predicts that the RS of H(δ) should be 0.06–0.08 less than that of H(γ), a situation that would have let them be easily resolved in the experiment.

Thus, provided that the conformation is not changed upon complexation with the LSR, these data seem to argue strongly against BC-1 as the predominant solution conformation of oxocane and are in good accord with BC-3. On the other hand, they do not uniquely distinguish the latter. Similar calculations for TBC-1 and TCC-1, two other forms with relatively favorable MM2 energies, show even better agreement of TCC-1 with the LIS data, and TBC-1 is just as good as BC-3. However, predominance of TCC-1 is experimentally excluded by the undetectability of the 10 kcal/mol barrier in ^1H spectra, where the protons would have been divided into two sets. Exclusion of TBC-1 as the predominant solution conformer remains based only on calculation, not experiment.

Finally, we would note that the presence of 5–10% of BC-1 in a predominantly BC-3/BC-7 conformer mixture would bring the observed LISs into even better agreement with calculation. BC-1 predicts much smaller RSs for C(δ) and H(δ) than for BC-3. Both of those observed RSs are a little lower than the BC-3 prediction, perhaps reduced by a BC-1 contribution.

Conclusions. The MM2 calculations indicate that oxocane undergoes rapid BC-3/BC-7 pseudorotational interconversion even at the temperatures which were examined in the earlier NMR investigation,[14,15] so the C_s symmetry observed in those experiments does not exclude BC-3 and BC-7 as the favored conformers. MM2 also finds that BC-3 should be preferred over BC-1, in accord with all other molecular mechanics calculations.[17,18] In addition, the LIS results agree well with BC-3 and BC-7 being the predominant conformers but do not acceptably fit a BC-1 structure. Thus, all available data from both experiment and calculation are in accord with BC-3/BC-7 being the major conformers of oxocane, and BC-1 is now rendered unlikely on experimental as well as theoretical grounds. Finally, detection of a small but significant contribution of the crown family to the oxocane conformational equilibrium completes demonstration of the total analogy of oxocane with cyclooctane and azocane.

Experimental Section

General. Instruments used were as follows: 60-MHz ^1H NMR,

(33) Hofer, O. *Top. Stereochem.* **1976**, *9*, 111 and references cited therein. Chiasson, J. B.; Jankowski, K. In *Lanthanide Shift Reagents in Stereochemical Analysis*; Morrill, T. C., Ed.; VCH: New York, 1986; pp 19–53 and references cited therein.

(34) Schneider, H.-J.; Weigand, E. F. *Tetrahedron* **1975**, *31*, 2125. Schneider, H.-J.; Agrawal, P. K. *Tetrahedron* **1984**, *40*, 1025 and references cited therein. Schneider, H.-J.; Buchheit, U.; Agrawal, P. K. *Tetrahedron* **1984**, *40*, 1017 and references cited therein.

(35) Willcott, M. R., III; Lenkinski, R. E.; Davis, R. E. *J. Am. Chem. Soc.* **1972**, *94*, 1742. Davis, R. E.; Willcott, M. R., III. *J. Am. Chem. Soc.* **1972**, *94*, 1744.

Varian EM360; 90-MHz ^1H and 22.5-MHz ^{13}C NMR, JEOL FX-90Q; variable-temperature 126-MHz ^{13}C NMR, Bruker WM-500; 500-MHz ^1H NMR, Varian VXR-500S with Sun 4/110 computer; IR, Perkin-Elmer 283; MS, Hewlett- Packard 5982A; GC-MS used a 30-m DB-1 capillary column; preparative GC, Aerograph A90-P3, 6 mm × 3 m 20% Carbowax 20M on Chromosorb W. All ^{13}C NMR spectra were obtained with complete ^1H decoupling. PCMODEL[13] was used for MM2 and MMX input preparation and some MMX calculations. Unless otherwise specified, commercial reagents were used without purification, Na_2SO_4 or $MgSO_4$ was the drying agent for organic solutions, and $CDCl_3$ was the NMR solvent with TMS as internal reference.

2-Oxocanone (2a). The procedure is adapted from oxidation of an acetylbicycloheptane.[36] Baeyer–Villiger oxidation of cycloheptanone has been reported using $PhCO_3H$,[37] CF_3CO_3H,[38] and peroxymaleic acid,[15] but not 3-$ClPhCO_3H$. A solution of 19.88 g of 80–85% 3-$ClPhCO_3H$ (92.2 mmol if 80%) and 6.92 g (61.7 mmol) of cycloheptanone in 160 mL of CH_2Cl_2 was stored under N_2 in the dark at 23–24 °C for 90 h,[39] precipitated 3-$ClPhCO_2H$ was filtered and washed with CH_2Cl_2, and the filtrate was washed with Na_2SO_3, $NaHCO_3$, and brine. Distillation afforded 6.87 g (87%) of **2a** as a colorless liquid which ^{13}C NMR and MS indicated to be ca. 95% pure, contaminated only by **1a** and a little PhCl from decomposition of 3-$ClPhCO_3H$: bp 85–90 °C (8 Torr) (lit. bp 83–85 °C (10.5 Torr);[40] 80–82 °C (10.5 Torr)[38]); IR (film) 1730, 1235 cm^{-1}; ^1H NMR (90 MHz) δ 4.36 (t, J = 5.4 Hz, 2 H), 2.57 (t, J = 6.2 Hz, 2 H), 1.90–1.45 (br m, 8 H) (lit.[15] 251 MHz, $CHCl_2F$, δ 4.40 (t), 2.60 (t), 1.90 (m), 1.67 (m)); ^{13}C NMR (22.5 MHz) δ 176.8, 67.9, 31.3, 30.9, 28.4, 25.9, 24.0 (lit.[15] 63 MHz, $CHCl_2F$, δ 177, 68.8, 5 peaks 32.0–24.3); MS m/z (rel intensity) 128 (M^+, 1), 110 (8), 100 (28), 98 (30), 70 (34), 69 (64), 56 (36), 55 (100).

We have stored **2a** under N_2 for weeks at −10 °C with less than 15% dimerization.[37,38] At 8 °C it undergoes 15% dimerization in 4 days, and after 10 days it has dimerized to the extent of ca. 85% (^{13}C NMR assay).

2-Oxocanone-*3,3,8,8-d*$_4$ (2b). **1b** was prepared by repeated treatment of 8.1 g (72 mmol) of **1a** under N_2 with 4.0-mL samples of 0.20 M NaOMe in 99.8% D_2O until no α-proton resonance was detectable by 60-MHz NMR. Distillation afforded 2.65 g (32%) of **1b** with a d incorporation of 98–99%: bp 95 °C (65 Torr); MS m/z 116 (92–95% d_4), 115 (5–8% d_3), 114 (0% d_2), 113 (0% d_1), 112 (0% d_0). A 4.4-g (38-mmol) sample of **1b** was converted to **2b** as described above except that 50–55% 3-$ClPhCO_3H$ was used by dissolving it in the CH_2Cl_2 for the reaction and drying the solution ($MgSO_4$) before adding **1b**. **2b** (3.55 g, 71%) containing ca. 8% **1b** and 4% PhCl by ^{13}C NMR and GC-MS was obtained by micro Hickman distillation: bp 92–105 °C (bath temperature) (8 Torr); ^1H NMR like **2a** but without δ 4.36 and 2.57 resonance; ^{13}C NMR like **2a** but with δ 67.2 and 30.3 pentets (J = 22 and 20 Hz) instead of δ 67.9 and 30.9 singlets and the other resonances 0.0–0.2 ppm upfield of **2a**; GC-MS m/z (rel intensity) 132 (M^+, 1), 114 (14), 104 (19), 102 (41), 101 (30), 100 (73), 73 (30), 72 (49), 71 (100), 70 (85), 69 (26), 58 (51), 57 (46), 56 (92), 55 (67).

Oxocane (3a). The procedure was adapted from ref 26c.[41] A mixture of 2.22 g (17.3 mmol) of **2a** and 1.32 g (8.8 mmol) of 98% $(t\text{-BuO})_2$ in a 25-mL Pyrex septum-capped flask was deoxygenated by three evacuations and admissions of N_2, and 15.82 g (117 mmol) of $HSiCl_3$ was added through a double-tipped needle. The flask was mounted ca. 2 cm from a Hanovia Model 654A-36 200-W high-pressure Hg lamp and irradiated at 25 °C for 4.0 h. Excess $HSiCl_3$ was removed by distillation under N_2 followed by addition of CH_2Cl_2 and continued distillation until the bp reached 39 °C. The residue was diluted with CH_2Cl_2, chilled in ice, cautiously treated with 30 mL of water followed by 140 mL of 10% NaOH,[42] and stirred at 23–25 °C for 48 h. The CH_2Cl_2 layer was washed with brine, water, and brine. Most CH_2Cl_2 was removed by distillation through a short Vigreaux column. The ^1H NMR spectrum of the 3.62 g of residual material showed it to be 33% **3a**, 61% CH_2Cl_2, and 6% $(t\text{-BuO})_2$ and/or t-BuOH by weight. Final traces of CH_2Cl_2 were removed by repeated additions of 1 mL of pentane and distillation at 1 atm until the bp fell to 36 °C. The $(t\text{-BuO})_2$ and/or t-BuOH were destroyed by addition of 250 mg (11 mmol) of Na and heating under N_2 at 110 °C for 4 h.[43]

Products from three additional runs were combined for processing after removal of $HSiCl_3$, and the products from all four runs (8.45 g, 65.9 mmol total **2a**) were combined and distilled directly from residual Na and NaO-t-Bu to afford 3.27 g (44%) of pure **3a**: bp 140–141 °C (732 Torr) (lit. 140–142 °C (760 Torr);[25] 131–142 °C (760 Torr)[22]); IR (film) 2930, 2860, 1102 cm^{-1}; ^1H NMR (90 MHz) δ 3.66 (br, 4 H), 1.63 (br s, 10 H); ^1H NMR (500 MHz) δ 3.65 (t, J = 5.2 Hz, 4 H), 1.63 (br s, 10 H) (lit.[15] 251 MHz, $CHCl_2F$, δ 3.63 (t, J = 6 Hz), 1.62 (s)); ^{13}C NMR (22.5 MHz) δ 70.25 (C-2/C-8), 29.00 (C-3/C-7), 27.46 (C-5), 25.51 (C-4/C-6) (lit.[15] 63 MHz, $CHCl_2F$, δ 71.4, 29.7, 28.1, 26.2); MS m/z (rel intensity) 114 (M^+, 38), 68 (83), 67 (51), 56 (100), 55 (49), 41 (64) (lit.[15] m/z 114 (M^+), 41 (100)).

Oxocane-*2,2,7,7-d*$_4$ (3b). The same procedure starting with 3.38 g (25.6 mmol) of **2b**, 825 mg (5.57 mmol) of $(t\text{-BuO})_2$, and 26.09 g (193 mmol) of $HSiCl_3$, with crude **3b** after Na treatment being distilled from a micro Hickman apparatus, afforded 1.78 g (15.1 mmol, 59%) of **3b** which still contained a little $(t\text{-BuO})_2$. A pure sample (274 mg, 2.32 mmol, 9%) was obtained by preparative GLC (145 °C): ^1H NMR (90 MHz) δ 3.63 (s, 2 H), 1.62 (sharp s, 8 H); ^1H NMR (500 MHz) δ 3.64 (s, 2 H), 1.65 (br s, 2 H), 1.62 (br s, 6 H); ^{13}C NMR (22.5 MHz) δ 70.16 (s), 69.54 (pentet, J = 21.4 Hz), 28.89 (s), 28.28 (pentet, J = 19.0 Hz), 27.52 (s), 25.52 (s), 25.43 (s); MS m/z (rel intensity) 118 (M^+, 33), 71 (26), 70 (92), 69 (63), 59 (26), 58 (100), 57 (44), 56 (26), 55 (19). The d_4:d_3 ratio (m/z 118:117) was 92:8, identical with that of **1b** recovered from the preparation of the **2b** which was used.

Low-Temperature NMR Spectra. ^{13}C spectra were recorded at 126 MHz with gated proton decoupling. Accuracy of the spectrometer temperature meter is estimated as ±5 K. A solution of **3a** in 3:1 (v/v) CBr_2F_2/CD_2Cl_2 (30 mg/mL) was used for measurements between 151 and 290 K. Chemical shifts were measured relative to CBr_2F_2 and converted to the TMS scale by assigning CBr_2F_2 as 91.20 ppm. ^{13}C chemical shifts at selected high and low temperatues were as follows: at 290 K δ 70.9 (C(α)), 29.9 (C(β)), 28.4 (C(δ)), 26.4 (C(γ)) ppm; major subspectrum (96%) at 174 K δ 69.4 (C(α)), 28.0 (C(β)), 27.0 (C(δ)), 25.1 (C(γ)) ppm; minor subspectrum (4%) at 174 K δ 77.5 (C(α)), 34.0 (C(β)), 31.3 (C(γ)), 29.3 (C(δ)) ppm. The spectra exhibited resonance broadening at the lowest temperatures due at least in part to increased viscosity. A separate sample of **3a** was prepared in 11:1 (v/v) CBr_2F_2/CD_2Cl_2 (15 mg/mL) to enable several additional measurements down to 138 K. This sample had lower viscosity as evidenced by narrower resonances, but no additional subspectra or further evidence for exchange was obtained. The line-shape analysis was carried out on a PC using the program DNMR5.[29] For this analysis the NMR spectra were transferred from the spectrometer to a VAX computer where they were converted to ASCII files using a BASIC program and then downloaded to a PC disk for input to DNMR5.

LIS NMR Spectra. Samples of 54.7 mg (0.38 mmol) of **3a** and 63.5 mg (0.54 mmol) of **3b**, each in 1.00 mL of $CDCl_3$, were treated with 5 × 30 μL aliquots of a solution of 159 mg (0.150 mmol) of Yb(fod)$_3$ (Resolve-Al YbFOD; Aldrich) in 450 μL of $CDCl_3$ (0.33 M Yb(fod)$_3$). The 500-MHz ^1H NMR spectra, and in the cases of **3a** 22.5-MHz ^{13}C NMR spectra, were obtained before addition of the first aliquot and after addition of each

(36) Meinwald, J.; Tufariello, J. J.; Hurst, J. J. *J. Org. Chem.* **1964**, *29*, 2914.

(37) Friess, S. L. *J. Am. Chem. Soc.* **1949**, *71*, 2571.

(38) Huisgen, R.; Ott, H. *Angew. Chem.* **1958**, *70*, 312; *Tetrahedron* **1959**, *6*, 253. Sanger, W. F.; Duckworth, A. *J. Am. Chem. Soc.* **1955**, *77*, 188.

(39) ^{13}C NMR showed that the approximate **2a**:**1a** ratio is 35:65 after 10 h, 77:23 after 30 h, and 85:15 after 78 h. No resonance from other aliphatic compounds was detectable after 78 h, but by 102 h small resonances from the dimer[37,38] began to appear.

(40) Clossen, W. D.; Orenski, P. J.; Goldschmidt, B. M. *J. Org. Chem.* **1967**, *32*, 3160.

(41) Preliminary experiments with 0.05:1:4 peroxide/lactone/$HSiCl_3$ mol ratios and a 2-h irradiation time with the flask 10 cm from the source, as described in refs 26a and 26b, gave very low conversions, perhaps due to inhibition by the PhCl impurity in **2a**.

(42) Profuse rapid foaming occurs if addition of water and NaOH is too rapid. We have also had eruptions of the mixture about halfway through addition of the NaOH if addition is too uncautious.

(43) Milas, N. A.; Surgenor, D. M. *J. Am. Chem. Soc.* **1946**, *68*, 205.

aliquot. ^{13}C spectra consisted of 600 accumulations over 2250 Hz, and ^{1}H spectra were from nine accumulations over 4000 Hz.

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Registry No. **1a**, 502-42-1; **1b**, 17616-76-1; **2a**, 539-87-7; **2b**, 137435-12-2; **3a**, 6572-98-1; **3b**, 137435-13-3.

Use of 2,3-Bis(phenylsulfonyl)-1-propene as a Multicoupling Reagent

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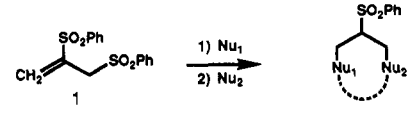
2,3-Bis(phenylsulfonyl)-1-propene (1) reacts with various amines to afford products derived from addition across the double bond as well as S_N2' displacement. When treated with 2-piperidinemethanol, bissulfone 1 gave the expected S_N2' product which was converted to the corresponding bromide and cyclized with tributyltin hydride to a bicyclic amine. Reaction of bissulfone 1 with furfurylamine followed by treatment with acetyl chloride afforded the product derived from a tandem S_N2' displacement–intramolecular Diels–Alder reaction. Several novel heterocyclic compounds were prepared by connecting two nucleophilic sites with a carbon–carbon bond and allowing this reagent to react with bissulfone 1. The reaction of 1 with the pyrrolidine enamine derived from cyclohexanone gave bicyclo[3.3.1]nonan-9-one in 78% yield. The soft nucleophile approach is not the only way to add carbon centers to bissulfone 1. Radical attack on the double bond of 1 leads to an intermediate sulfonyl-stabilized radical. This species readily fragments to produce a new vinyl sulfone which undergoes further radical cyclization to give six-membered ring sulfones.

Functionalized allylic reagents which contain both a leaving group and a π-activating substituent have been extensively utilized in organic synthesis.[1-11] These substituted 1-propenes have been referred to as multicoupling reagents.[5,12] In this context we have recently demonstrated that 2-alkoxy- or 2-thio-substituted 3-(phenylsulfonyl)-1-propenes[13] are versatile synthetic reagents. Owing to the phenylsulfonyl group's molecular weight and stability, the carbon backbone of such compounds can become very small without the drawback of volatility or thermal lability seen in other synthetic intermediates with the same carbon skeleton. They react with various electrophiles, leading to functionalized unsaturated sulfones, which can undergo further useful transformations. In connection with our program dealing with the chemistry of unsaturated sulfones,[14] we have been exploring the chemical reactivity of 2,3-bis(phenylsulfonyl)-1-propene (1).[15] This three-carbon backbone includes both a vinyl and allylic sulfone, which act in concert to provide unusual reactivity. Conveniently, bissulfone 1 is a crystalline compound, easily prepared and with indefinite shelf-life, adding to its attractiveness for use as a multicoupling reagent. The synthetic potential of bissulfone 1 was demonstrated by taking advantage of two properties of the phenylsulfonyl group: (1) its ability to activate double bonds toward Michael addition, and (2) its viability as a leaving group.[16] Indeed, treatment of 1 with a variety of nucleophiles results in S_N2' displacement followed by conjugate addition to give products of the general type 2. The present paper documents the results of these studies.



1 2

Results and Discussion

A. Heteroatom Additions. We began our studies by examining the reaction of 1 with various amines. Aniline was found to add efficiently across the double bond of 1

(1) Nelson, R. P.; Lawton, R. G. *J. Am. Chem. Soc.* **1966**, 488, 3884. Nelson, R. P.; McEuen, J. M.; Lawton, R. G. *J. Org. Chem.* **1969**, *34*, 1225. McEuen, J. M.; Nelson, R. P.; Lawton, R. G. *Ibid.* **1970**, *35*, 690.
(2) Ferris, A. F. *J. Org. Chem.* **1955**, *20*, 780.
(3) Villieras, J.; Rambourd, M. *Synthesis* **1982**, 924.
(4) Klager, K. *Montasch Chem.* **1965**, *96*, 1.
(5) Knochel, P.; Seebach, D. *Nouv. J. Chim.* **1981**, *5*, 75. Knochel, P.; Seebach, D. *Tetrahedron Lett.* **1981**, 3223. Knochel, P.; Seebach, D. *Ibid.* **1982**, 3897. Seebach, D.; Knochel, P. *Helv. Chim. Acta* **1984**, *67*, 261.
(6) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1984**, 1475; **1985**, 425; **1984**, 4383.
(7) Collard, J. N.; Benezra, C. *Tetrahedron Lett.* **1982**, 3725.
(8) Trost, B. M.; Lavoie, A. C. *J. Am. Chem. Soc.* **1983**, *105*, 5075.
(9) Donaldson, R. E.; Saddler, J. C.; Byrn, S.; McKenzie, A. T.; Fuchs, P. *J. Org. Chem.* **1983**, *48*, 2167.
(10) Anzeveno, P. B.; Matthews, D. P.; Barney, C. L.; Barbuch, R. J. *J. Org. Chem.* **1984**, *49*, 3134.
(11) Speckamp, W. N.; Dijkink, J.; Huisman, H. O. *J. Chem. Soc.* **1970**, 196. Speckamp, W. N.; Dijkink, J.; Dekkers, A. W.; Huisman, H. O. *Tetrahedron* **1971**, *27*, 3143.
(12) A multicoupling reagent has been defined as a species whose reactivity allows the sequential formation of two or more new carbon–carbon bonds.[5]
(13) Padwa, A.; Bullock, W. H.; Dyszlewski, A. D. *Tetrahedron Lett.* **1987**, 3193; *J. Org. Chem.* **1990**, *55*, 955. Padwa, A.; Bullock, W. H.; Dyszlewski, McCombie, S. W.; Shankar, B. B.; Ganguly, A. K. *J. Org. Chem.* **1991**, *56*, 3556.
(14) Padwa, A.; Carter, S. P.; Chiacchio, U.; Kline, D. N. *Tetrahedron Lett.* **1986**, 2683. Padwa, A.; Wannamaker, M. W. *Tetrahedron Lett.* **1986**, 5817. Padwa, A.; Bullock, B.; Dyszlewski, A. D. *J. Org. Chem.* **1987**, *52*, 4760. Padwa, A.; Kline, D. N.; Norman, B. H. *Tetrahedron Lett.* **1988**, 265. Padwa, A.; Norman, B. H. *Tetrahedron Lett.* **1988**, *2417*; **1988**, 3041. Padwa, A.; Harrison, B.; Norman, B. H. *Tetrahedron Lett.* **1989**, 3259. Padwa, A.; Harrison, B.; Murphree, S. S.; Yeske, P. E. *J. Org. Chem.* **1989**, *54*, 4232. Padwa, A.; Murphree, S. S.; Yeske, P. E. *J. Org. Chem.* **1990**, *55*, 4241. Padwa, A.; Norman, B. H. *J. Org. Chem.* **1990**, *55*, 4801.
(15) Padwa, A.; Yeske, P. E. *J. Am. Chem. Soc.* **1988**, 4110, 1617. Padwa, A.; Murphree, S. S.; Yeske, P. E. *Tetrahedron Lett.* **1990**, 2983.
(16) Magnus, P. D. *Tetrahedron* **1977**, *33*, 2019. Durst, T. *Compr. Org. Chem.* **1979**, *3*, 171.

0022-3263/92/1957-0298$03.00/0