(neat) was used as an external standard. The reproducibility was within ±0.03 ppm.

Preparation of Crystalline Host-Guest Complexes. Preparation of the crystalline complexes was carried out by employing a modification of the method reported for cyclodextrins by Cramer.[41] Method A: for water-soluble guests, the crystalline complexes were obtained by slow cooling of a heated solution of an appropriate molar ratio of CP44 and guest in 1-2 N HCl. Method B: for water-insoluble liquid guests, the crystalline complexes were obtained by vigorous shaking of the guest (excess) with a solution of CP44 in a small amount of 1-2 N HCl, followed by deliberate recrystallization of the resulting precipitate from a small amount of 0.1 N HCl. Method C: for water-insoluble solid guests, the crystalline complexes were obtained by vigorous shaking of a solution of the guest (excess) in hexane and a solution of CP44 in a small amount of 1-2 N HCl, followed by deliberate recrystallization of the resulting precipitate from a small amount of 0.1 N HCl.

CP44·4HCl·Durene·4H$_2$O. The crystalline complex was obtained by method C as colorless transparent prisms which, after air-drying for 30 min, were characterized as CP44·4HCl·durene·4H$_2$O: HPLC (LiChrosorb RP-2 (5 μm), CH$_3$CN/MeOH/H$_2$O/28% aqueous NH$_3$ = 55:10:34:1, detected at 280 nm) CP44/durene = 1.0:1.0.[42] Anal. Calcd for $C_{34}H_{40}N_4$·4HCl·$C_{10}H_{14}$·4H$_2$O: C, 61.68; H, 7.76; N, 6.54; Cl, 16.55. Found: C, 61.47; H, 7.48; N, 6.70; Cl, 16.50. This crystal was applied to the X-ray analysis.[3,24] Drying in vacuo of these crystals at 60 °C for 40 h gave white opaque prisms (hygroscopic), which were not suitable any more for X-ray analysis: mp 245-245.5 °C dec (sealed under argon); HPLC host/guest = 1.0:1.0. Anal. Calcd for $C_{34}H_{40}N_4$·4HCl·$C_{10}H_{14}$·1.5H$_2$O: C, 65.10; H, 7.57; N, 6.90. Found: C, 65.32; H, 7.12; N, 7.28.

CP44·4HCl·(Naphthalene)$_n$·4H$_2$O. The crystalline complex was obtained by method C as colorless transparent prisms which, after air-drying for 30 min, were analyzed by HPLC (LiChrosorb RP-2 (5 μm), CH$_3$CN/MeOH)H$_2$O/28% aqueous NH$_3$ = 50:15:34:1, detected at 280 nm): CP44/naphthalene = 1.0:1.4.[24,42] Drying in vacuo of these crystals at 60 °C for 4 h gave white opaque prisms: mp 253.5-254 °C dec (sealed under argon);[43] HPLC host/guest = 1.0:1.0. Anal. Calcd for $C_{34}H_{40}N_4$·4HCl·$C_{10}H_8$: C, 67.86; H, 6.73; N, 7.19. Found: C, 67.99; H, 6.77; N, 7.13.

CP44·4HCl·(1,3-Dihydroxynaphthalene)$_2$. The crystalline complex was obtained by method A from 1.8 N HCl solution (host/guest = 1:2) as faint brown transparent needles which, after drying in vacuo at 80 °C for 20 h, were characterized as CP44·4HCl·(1,3-dihydroxynaphthalene)$_2$:[24] mp 238.5-239.5 °C dec; ^{1}H NMR (D$_2$O) host/guest = 1:2. Anal. Calcd for $C_{34}H_{40}N_4$·4HCl·$(C_{10}H_8O_2)_2$: C, 66.80; H, 6.23; N, 5.77; Cl, 14.61. Found: C, 66.70; H, 6.26; N, 6.00; Cl, 14.61. In IR spectrum (KBr) the characteristic bands of the guest at 3300 and 1275 cm^{-1} shifted to 3160 and 1260 cm^{-1}, respectively.

CP44·4HBr·(1,3-Dihydroxynaphthalene)$_2$. The crystalline complex was obtained similarly as above from 2.2 N HBr solution as faint brown transparent needles which, after drying in vacuo at 80 °C for 20 h, was characterized as CP44·4HBr·(1,3-dihydroxynaphthalene)$_2$:[24] ^{1}H NMR (D$_2$O) host/guest = 1:2. Anal. Calcd for $C_{34}H_{40}N_4$·4HBr·$(C_{10}H_8O_2)_2$: C, 56.46; H, 5.26; N, 4.88; Br, 27.83. Found: C, 56.33; H, 5.18; N, 5.01; Br, 28.34.

Crystalline Complex with *p*-Xylene. The crystalline complex was obtained by method B as colorless transparent plates, which was found to be a 1:1 complex by HPLC under the same conditions as for the complex with naphthalene. However, this complex could not be characterized by X-ray analysis due to its fast decomposition.

Acknowledgment. This work was supported by the Ministry of Education, Science and Culture, Japan (Grant-in-Aids 56209005).

Registry No. 1, 74043-83-7; 1·4HCl, 74043-85-9; 2, 1807-55-2; 3, 74043-79-1; 4, 98587-50-9; 5, 74043-80-4; 6, 74043-82-6; CP44·4HCl·durene, 98587-51-0; CP44·4HCl·naphthalene, 98587-52-1; CP44·4HCl·(1,3-dihydroxynaphthalene)$_2$, 98587-53-2; CP44·4HBr·(1,3-dihydroxynaphthalene)$_2$, 98587-55-4; CP44·4HCl·*p*-xylene, 98611-61-1; CP44·ANS, 74043-84-8; CP44·TNS, 77929-42-1; 1,4-dibromobutane, 110-52-1.

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[41] Cramer, F.; Henglein, F. M. *Chem. Ber.* **1957**, *90*, 2561-2571.

[42] For each lot of the crystals obtained from separate experiments, the host/guest ratio was determined for several *single* crystals. The ratio was always found to be constant for the crystals within the same lot. As to the complex with durene, the ratio was found to be 1.0:1.0 regardless of the lot. As to the complex with naphthalene, however, the ratio was found to be varied from 1.2 to 1.4 depending on the lot.

[43] This value (253.5-254 °C) is remarkably higher than the melting point (dec) of the free host CP44·4HCl (244.5-245 °C when sealed under argon). When sealed under vacuum, however, the melting point (dec) of the complex dropped to the value (240-241 °C), which is close to the melting point (dec) of the free host (242-243 °C when sealed under vacuum). This may indicate the sublimation of naphthalene from the complex when heated to higher temperatures under vacuum.

Oxygen-17 Nuclear Magnetic Resonance Chemical Shifts of Dialkyl Peroxides: Large Conformational Effects

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^{17}O NMR chemical shifts are reported for 17 dialkyl peroxides including 2,3-dioxabicyclo[2.2.1]heptane (**3a**), the bicyclic peroxide nucleus of prostaglandin endoperoxides such as PGH$_2$ (**1**). The ^{17}O resonance for **3a** occurs at extraordinarily low field compared to homologous but less rigid and strained bicyclic peroxides. The chemical shifts, δ_O, of the ^{17}O resonances of seven bicyclic secondary dialkyl peroxides including **3a** show a fair linear correlation with those, δ_C, of the corresponding carbons of the hydrocarbon analogues with O replaced by CH$_2$ according to the equation $\delta_O = 12.9\delta_C - 75.7$ with $r = 0.95$. An excellent correlation ($r = 0.99$) was found for a series of four homologous bicyclic peroxides **3a-d** and the corresponding bicyclic hydrocarbons **9a-d**. A remarkably different correlation, $\delta_O = 1.00\delta_C - 220$ ($r = 0.93$), is observed for four acyclic peroxides and the corresponding hydrocarbons. For the acyclic peroxides, ROOR, and the corresponding hydrocarbons, RCH$_2$CH$_2$R, both δ_O and δ_C occur at lower field as R varies from primary to secondary to tertiary in accord with the dominance of a paramagnetic over a diamagnetic contribution to the total screening constant.

Many systematic investigations document the influence of molecular structure on the ^{17}O NMR spectra of organic oxygen-containing functional groups.[1] However, with the sole exception of di-*tert*-butyl peroxide,[1j,2] the ^{17}O NMR

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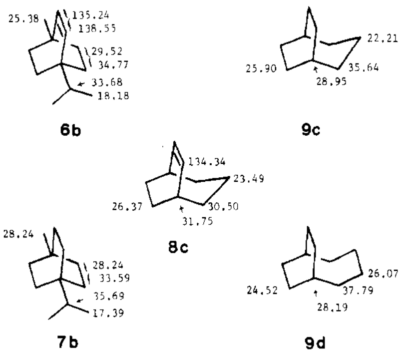
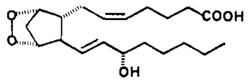
Chart I

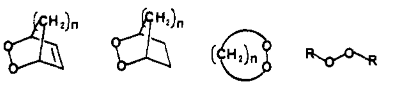


spectra of dialkyl peroxides are unknown. A recent surge in interest in dialkyl peroxides can be ascribed to the presence of this functional array in prostaglandin endoperoxides, such as PGH_2 (1), pivotal intermediates in the biosynthesis of prostaglandins, prostacyclins, and thromboxanes from essential fatty acids.[3] As a result, the



1

availability of dialkyl peroxides improved dramatically with the development of new synthetic methods. These include the use of diimide to achieve selective reduction of C=C bonds in the presence of the readily reducible O–O bond[4] and the peroxide transfer reaction.[5] The former method is especially valuable for preparation of bicyclic peroxides including the 2,3-dioxabicyclo[2.2.1]heptane (**3a**) nucleus of PGH_2 (1), as well as the homologues **3b–d** from the corresponding unsaturated peroxides **2a–d**. The reaction of alkyl trifluoromethanesulfonates with bis[tri-*n*-butyltin] peroxide provides another synthesis of **3a** and also efficient access to monocyclic peroxides such as **4a** and **4b** as well as acyclic peroxides such as **5a–c**.[5]



2a, n = 1
2b, n = 2
2c, n = 3
2d, n = 4

3a, n = 1
3b, n = 2
3c, n = 3
3d, n = 4

4a, n = 3
4b, n = 4

5a, R = Et
5b, R = *n*-Pr
5c, R = *i*-Pr

The availability of a variety of structurally different dialkyl peroxides including several homologous series now allows a systematic investigation of the influence of molecular structure on the ^{17}O NMR spectra of dialkyl peroxides and a comparison with other oxygen-containing functional groups as well as with the ^{13}C NMR spectra of analogous hydrocarbons with O replaced by CH_2.

Results and Discussion

Carbon-13 NMR Spectra. A substantial amount of empirical data and theoretical studies are available to explain the influence of substituents and structural features on the chemical shifts of carbon atoms.[6,7] Since it may be informative to compare the ^{17}O chemical shifts of dialkyl peroxides with the ^{13}C chemical shift of the corresponding carbon atom of a molecule in which O is replaced with CH_2, the ^{13}C NMR spectra of several hydrocarbons were recorded and interpreted. These data are summarized in Chart I. The ^{13}C chemical shifts of the alkene **6b** were assigned with the aid of two pulse sequences. Distortionless enhancement of polarization transfer (DEPT)[8] allowed differentiation between methine, methylene, and methyl carbons. Since the DEPT sequence generates transfer of polarization from hydrogen spins to the carbon spins by a scalar coupling interaction, subspectra containing only carbons attached to the same number of hydrogens are generated, but subspectra containing quaternary carbons are not obtainable. Differentiation between the isopropyl and bridgehead methyl carbons was based on the 2:1 relative intensities of these resonances, respectively. The chemical shifts of the quaternary carbons (δ 34.77 and 40.58) were confirmed by a gated spin echo sequence (GASPE) which takes advantage of resonance intensity modulations and thus can provide subspectra containing quaternary carbons.[9] It is particularly noteworthy that for **6b** these pulse sequences allow unmasking of absorptions which are accidently coincident, i.e., a quaternary carbon and CH_2 at δ 34.77. The ^{13}C resonances of the saturated analogue **7b** of **6b** were assigned similarly with the quaternary carbon absorptions each now appearing about 7 ppm upfield (δ 27.64 and 32.95) from the corresponding resonances of the alkene **6b**.

For the hydrocarbon **9c**, the CH and CH_2 resonances were distinguished by DEPT. Since the different CH_2 groups are present in a ratio of 4:2:1, these were readily distinguished by quantitative relative intensities under conditions of suppressed nuclear Overhauser enhancement, i.e., 30-s pulse delay, decoupler off during delay, and 1.5-s magnetic field spoiling pulse to enhance the rate of spin relaxation. For the unsaturated analogue **8c**, the different CH_2 groups are present in a ratio of 2:2:1. Therefore, the resonance at δ 30.50 was assigned to carbons 2 and 4 while that at δ 26.37 was assigned to carbons 6 and 7 on the basis of analogy with the relative positions for the resonances of the corresponding carbons in **9c**. This assignment is also consistent with the slight downfield shift expected for the

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(1) (a) Review: Klemperer, W. G. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 246. (b) Sardella, D. J.; Stothers, J. B. *Can. J. Chem.* **1969**, *47*, 3089. (c) Delseth, C.; Kintzinger, J.-P. *Helv. Chim. Acta* **1976**, *59*, 466. (d) Delseth, C.; Kintzinger, J.-P. *Helv. Chim. Acta* **1978**, *61*, 1327. (e) Sugawara, T.; Kawda, Y.; Iwamara, H. *Chem. Lett.* **1978**, 1371. (f) Iwamura, H.; Sugawara, T.; Kawada, Y. *Tetrahedron Lett.* **1979**, 3449. (g) Eliel, E. L.; Pietrusiewicz, K. M.; Jewell, L. M. *Tetrahedron Lett.* **1979**, 3649. (h) Crandall, J. K.; Centeno, M. A. *J. Org. Chem.* **1979**, *44*, 1183. (i) Crandall, J. K.; Centeno, M. A.; Borresen, S. *J. Org. Chem.* **1979**, *44*, 1184. (j) Sugawara, T.; Kawada, Y.; Morimatsu, K.; Iwamura, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3391. (k) Nguyen, T.-T.; Delseth, C.; Kintzinger, J.-P.; Corrupt, P.-A.; Vogel, P. *Tetrahedron* **1980**, *36*, 2793. (l) Beraldin, M.-T.; Vauthier, E.; Fliszar, S. *Can. J. Chem.* **1982**, *60*, 106. (m) Kalabin, G. A.; Kushnarev, D. F.; Valeyev, R. B.; Trofimov, B. A.; Fedotov, M. A. *Org. Magn. Reson.* **1982**, *18*, 1. (n) Kintzinger, J.-P. *NMR: Basic Princ. Prog.* **1981**, *17*, 1.

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(3) For recent work, see: van Dorp, D. A. In "Chemistry, Biochemistry, and Pharmacological Activity of Prostanoids"; Roberts, S. M., Scheinmann, F., Eds.; Pergamon Press: New York, 1979; pp 233–242 and references cited therein.

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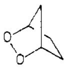
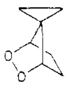
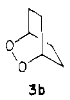
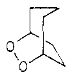
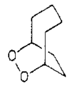
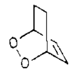
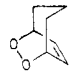
Table I. Solvent, Concentration, and Temperature Effects on ^{17}O Chemical Shifts

compd	solvent	conc, M	T, °C	LWHH,[a] Hz	chem shift,[b] ppm
 3a	CH_2Cl_2	1.5	23	184	303
	CH_2Cl_2	0.75	23	198	303
	benzene	0.75	20	168	303
 10	CH_2Cl_2	1.5	23	346	310
	CH_3OH	0.75	20	301	311
 3b	CH_2Cl_2	1.1	21	199	250
	CH_3OH	0.75	22	140	249
	benzene	1-4	24-25	200	250
 3c	CH_2Cl_2	1.5	21	125	261
	CH_3OH	0.75	22	154	260
	benzene	0.75	20	168	259
 4c	CH_2Cl_2	1.1	21	325	237
	benzene	1-4	24-25	100	232
 2b	CH_2Cl_2	1.5	23	214	265
	CH_2Cl_2	0.75	23	169	265
	CH_2Cl_2	1.5	15	258	265
 2c	CH_2Cl_2	1.5	23	287	277
	CH_2Cl_2	0.75	23	273	276
	CH_2Cl_2	1.5	15	387	278
	benzene	0.75	20	227	277
	CH_3OH	0.70	20	213	277

[a] Line width at half-height. [b] Relative to external water, presumed accurate to ±2 ppm.

carbons of the ethano bridge in **8c** vs. **9c** in analogy with that observed for the ethano bridge carbons in **6b** vs. **7b**.

For the hydrocarbon **9d**, a DEPT pulse sequence clearly shows that the δ 28.19 resonance corresponds with the bridgehead CH carbons. This assignment appears to be at odds with a previous assignment of the lowest field resonance (i.e., δ 39.7 in propane solution at −68 °C) to the bridgehead carbons 1 and 6 in **9c**.[10] Instead, we assign the lowest field resonance (δ 37.8 in $CDCl_3$) to the CH_2 groups at positions 2 and 5 in analogy with the lowest field resonance at δ 35.6 which corresponds to the CH_2 groups at positions 2 and 4 of **9c**. Quantitative analysis of relative intensities shows that the δ 24.5 resonance corresponds to the CH_2 groups at positions 7–10 of **9d**.

Oxygen-17 NMR Spectra. To explore the factors that might influence the chemical shifts of peroxidic oxygens, the ^{17}O NMR spectra of several peroxides were examined in various solvents at a variety of concentrations and temperatures (Table I). These data indicate that at most small changes in chemical shift are observed with variations in concentration within the range of 0.7–4 M and in temperature within the range of 15–25 °C, although line widths may increase somewhat at lower temperatures. Solvent effects are virtually absent. Thus ^{17}O NMR chemical shifts of dialkyl peroxides are insensitive to changes in solvent polarity. This observation is similar to the absence of a significant solvent effect on the ^{17}O NMR chemical shifts of various crown ethers observed previously in nitromethane, acetonitrile, pyridine, acetone, or chloroform solutions.[11]

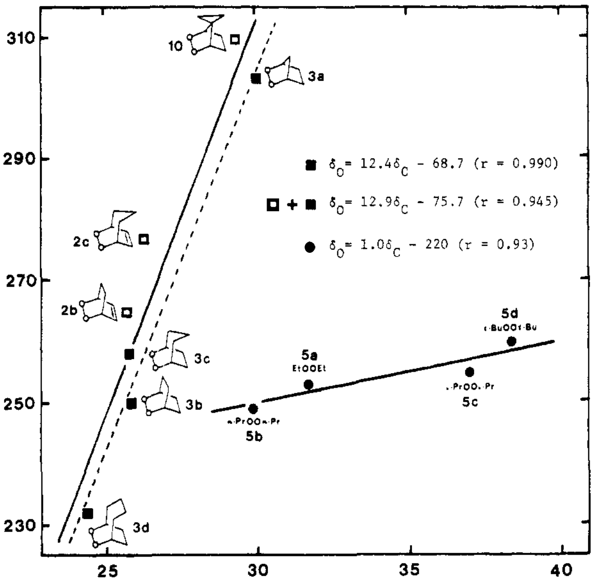


Figure 1. Linear correlation of ^{17}O chemical shifts of peroxides with ^{13}C chemical shifts of the corresponding hydrocarbons with CH_2 replacing O.

To determine the influence of substituents and structural features on the chemical shifts (δ_O) of oxygen atoms in peroxides, ^{17}O NMR spectra were recorded for 17 different dialkyl peroxides and one ozonide (Table II). For comparison also listed in Table II are: ^{13}C NMR chemical shifts (δ_C) for the corresponding carbon atom of a molecule in which O is replaced with CH_2, ^{15}N NMR chemical shifts (δ_N) for the corresponding nitrogen atom of a tetraalkyl hydrazine molecule in which O is replaced with NCH_3, adiabatic ionization potentials σ_o^- and n_o^- of the peroxide lone pairs, and $IP_{av} = (\sigma_o^- + n_o^-)/2$, which represents the lone pair energy with hypothetical absence of splitting between the lone pair combination orbitals.[12]

Correlation of ^{17}O and ^{13}C Chemical Shifts. The ^{17}O NMR chemical shifts (δ_O) of dialkyl peroxides are listed in Table II in order, with the compounds absorbing at lowest field at the top of the table. Superficially the ^{13}C NMR chemical shifts of the corresponding hydrocarbons with O–O replaced by CH_2–CH_2 appear to vary randomly. However, correlations can be discerned if attention is focused on series of closely homologous molecules (Figure 1). An excellent linear correlation ($r = 0.990$) is found for the bicyclic secondary dialkyl peroxides **3a–d** which obeys the equation $\delta_O = 12.4\delta_C - 68.7$. A fair correlation ($r = 0.945$) is still observed if the unsaturated bicyclic secondary peroxides, **2b** and **2c**, and the spirocyclopropyl peroxide **10** are included. A remarkably different correlation, $\delta_O = 1.00\delta_C - 220$ ($r = 0.93$), is observed for four acyclic dialkyl peroxides **5a–d**. These very different correlations suggest that ^{17}O NMR chemical shifts are determined by at least two factors. The slope of the δ_O vs. δ_C correlation for the bicyclic peroxides shows that the factor which dominates here is 13 times more important for ^{17}O chemical shifts than for the ^{13}C chemical shifts of the corresponding hydrocarbons. In contrast, the factor that dominates for the series of acyclic peroxides exerts the same influence (slope = 1.00) on the ^{13}C chemical shifts of the corresponding hydrocarbons.

The acyclic peroxides all have quite similar conformations; e.g., C–O–O–C dihedral angles for **5c** and **5d** were

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[10] Dyllick-Brezinger, R.; Olsen, H. *J. Am. Chem. Soc.* **1981**, *103*, 704.

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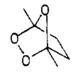
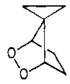
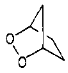
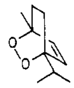
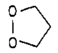
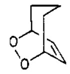
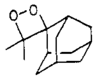
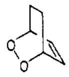
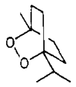
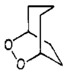
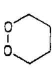
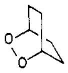
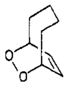
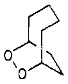
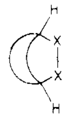
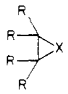
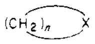
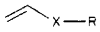
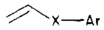
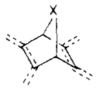
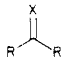
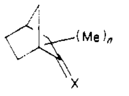
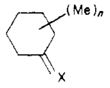
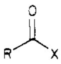
Table II. Comparison of ^{17}O Chemical Shifts with ^{13}C and ^{15}N Chemical Shifts and Lone Pair Ionization Potentials

		chem shifts			ionization potentials,[d] eV			
compd	LW[a]	δ_O	δ_C[b]	δ_N[c]	σ_O^-	n_O^-	IP_{av}	Θ[e]
 11	513 235	318[f] (perox) 169 (ether)						
 10	346	310[f]	29.4[h]		11.15	8.87	10.01	0
 3a	180	303[f,g]	30.1[i]	17.0	11.23	8.99	10.11	0
 12	701	283[f]	29.5 34.8		10.71	8.42	9.57	0
 4a	100	280[g]	26.5[i]	32.3	11.13	9.86	9.43	50
 2c	287	277[f,g]	26.4					
 13		275						
 2b	214	265[f]	25.8[j]		11.23	8.76	10.00	
 14	668	263[f]	28.4 33.6		10.63	8.50	9.43	32
t-BuOO-*t*-Bu 5d	340	260[g]	38.5		10.46	8.78	9.62	166
 3c	200	259[g]	25.9		10.37	8.97	9.67	51
i-PrOO-*i*-Pr 5c	360	255[g]	37.1	12.0	10.71	9.16	9.94	147
 4b	130	254[g]	27.3	19.2	10.20	10.00	10.10	88
EtOOEt 5a	300	253[g]	31.8					
 3b	200	250[f,g]	26.0[i]	18.5	10.84	8.82	9.83	21
n-PrOO-*n*-Pr 5b	300	249[g]	29.5					
 2d	244	247[f]			10.34	9.00	9.67	54
 3d	100	232[g]	24.5		10.03	9.05	9.54	65

[a] Line width at half-height. [b] $CDCl_3$ solutions. [c] Reference 13. [d] Data from ref 14. [e] COOC dihedral angle from ref 14. [f] CH_2Cl_2 solution. [g] Benzene solution. [h] Reference 15. [i] Reference 7a. [j] Reference 16.

Table III. Linear Correlation of ^{17}O and ^{13}C Chemical Shifts

compd type	slope[a]	intercept, ppm	correlation coefficient	no. of compounds	ref[b]
R-X-X-R	1.00	220	0.931	4	*c*
	12.9	−75.7	0.945	7	*c*
RXH	3.83	−49.3	0.979	22	1h
	3.83	−29.9	0.936	11	1f
	3.64	−22.4	0.944	8	1k
	1.99	−43.0	0.953	5	1j, 17
R-X-R^2 (acyclic)	2.96	−93.6	0.983	31	1d
Ar-X-R	2.69	−24.9	0.971	5	1m
	2.50	2.4	0.982	8	1m
	4.55	−310	0.90	7	1m
	2.84	−25.7	0.996	7	1k
	4.74	38.7	0.957	23	1c
	6.58	−148	0.960	7	18
	4.59	71.9	0.989	8	18
	1.96	78.1	0.990	6	18

[a] For the equation $\delta_O = (\text{slope})\delta_C + \text{intercept}$. [b] Source of values listed or data from which values were calculated. [c] This work.

estimated to be 147° and 166°, respectively.[14] The acyclic peroxides **5a–d** differ primarily in the extent of alkyl substitution, and both δ_O and δ_C occur at lower field for R–X–X–R as R varies from primary to secondary to tertiary. Since this order corresponds with the electron-donating abilities of the alkyl groups, the downfield shift indicates dominance of the paramagnetic over the diamagnetic contribution to the total screening constant. It is interesting to compare the influence of this electronic factor on δ_O for dialkyl peroxides vs. dialkyl ethers or alcohols (Table III). Thus, for a series of acyclic dialkyl ethers and the corresponding hydrocarbons RXR′, both δ_O and δ_C occur at lower field as R varies from primary to secondary to tertiary, but δ_O is 3 times *more* sensitive to the substituent effect than δ_C. Similarly, δ_O for alcohols (RXH with X = O) are about 4 times *more* sensitive than δ_C of the corresponding hydrocarbons (with X = CH_2) to *the electron-donating ability of R (Table III). In contrast,* δ_O of peroxides are 3 times *less* sensitive to electronic changes in R than δ_O of ethers relative to δ_C of the corresponding hydrocarbons. A theoretical study[11] of dialkyl ethers has shown that the calculated net atomic charge, q_o, at the oxygen atom increases as expected in the order Me < Et < *i*-Pr < *t*-Bu. Moreover, a comparison of δ_O with q_o reveals an excellent linear correlation which obeys the equation $\delta_O = -3.30q_o - 1033$ ($r = 0.997$). Since the adiabatic ionization potentials of the ethers (IP) are linearly correlated with q_o according to IP = $0.0274q_o + 18.16$ eV ($r = 0.9914$),[11] it is understandable that linear correlations are found between δ_O and IP for dialkyl ethers.[1d,j]

The situation is more complicated for dialkyl peroxides since two ionization potentials, σ_o^- and n_o^-, are associated with the oxygen lone pair electrons. These potentials as well as an average value, IP_{av}, are listed in Table II for the peroxides. As might be expected n_o^- decreases in the order primary (**4a,b**) > secondary (**2b,d**, **3a–d**, **5c**, **10**) > tertiary (**12**, **14**) with n_o^- of **5d** being slightly higher than expected. Notably, while δ_O varies from 232 to 310 ppm for the bicyclic secondary dialkyl peroxides (**2b,d**, **3a–d**, **5c**, and **10**), n_o^- is relatively constant at 8.76–9.05 eV. Thus, some factor other than variations in net atomic charge seems to be of paramount importance in determining δ_O for these bicyclic peroxides.

As noted above, the magnitudes of the two factors that contribute to ^{17}O chemical shifts of dialkyl peroxides, revealed by the correlations in Figure 1, are remarkably different relative to the effects of these factors on the ^{13}C chemical shifts of the corresponding hydrocarbons. This dichotomy is all the more remarkable when the magnitudes of the two factors are compared with those revealed by

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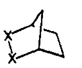
slopes for the linear correlations of ^{17}O and ^{13}C chemical shifts for other oxygen containing functional groups (Table III). Thus, the factor (presumably electronic) predominating for the series of acyclic peroxides has the smallest influence on δ_O relative to δ_C (slope = 1.00) compared to the factors influencing ^{17}O chemical shifts for alcohols, ethers, ketones, or esters. In striking contrast, the factor predominating for the series of bicyclic secondary dialkyl peroxides exerts the largest influence (slope = 12.9) compared to these other functional groups. A conformational effect provides a plausible explanation for this factor since conformations vary widely among these bicyclic peroxides with C–O–O–C dihedral angles, Θ, between 0° and 65°.[14] The extraordinarily low field position of the peroxide ^{17}O resonances of the bicyclo[2.2.1] compounds **3a**, **10**, and **11** might result from very strong interactions of vicinal lone pairs which are constrained to be coplanar or from compression of the C–O–O bond angles in this strained ring system. The somewhat smaller downfield shift for dioxetane **13** is understandable if the former effect predominates. Thus, while very great compression of the C–O–O bond angles is incorporated in the dioxetane ring system, puckering of the ring can diminish vicinal lone pair interactions by allowing a C–O–O–C dihedral angle greater than 0°.[19] Other observations also suggest that differences in the ^{17}O chemical shifts of the homologous series of bicyclic peroxides **2** or **3** cannot be explained solely in terms of the effect of compressing the C–O–O bond angles. Thus, while the C–O–O angles in **3b** are certainly more compressed than those of **3c** or **3d**, δ_O for **3b** falls *between* that for **3c** or **3d**. A similar order of ^{17}O chemical shifts is found for **2b–d**. For the corresponding hydrocarbons with CH_2–CH_2 replacing the peroxide oxygens, interactions of vicinal C–H bonds replace interactions of vicinal nonbonding electron pairs. It seems reasonable that (1) the dependence of the later interactions on the C–CH_2–CH_2–C dihedral angle could parallel that of the peroxide lone pair interactions as a function of C–O–O–C dihedral angle and (2) the conformations of the peroxides and corresponding hydrocarbons would vary similarly through the two homologous series.

Although the conformations of **2b** and **2d** are very different, the influence of their allylic unsaturation on δ_O relative to the saturated peroxides **3b** and **3d** is identical, a 15 ppm downfield shift. Since homoconjugation of the oxygen lone pairs with the allylic unsaturation should be subject to strict geometrical requirements, the observed influence of unsaturation upon δ_O cannot be the result of such an interaction.[20] Downfield shifts of similar magnitude are also found for δ_O of **2c** and **14** relative to their saturated counterparts **3c** and **12**, respectively. Downfield shifts of 13–18 ppm for δ_O of **12** and **14**, relative to **2b** and **3b**, respectively, are understandable in terms of electronic effects of the bridgehead alkyl substituents on the paramagnetic contribution to the total screening constant.

The ^{17}O chemical shifts (δ_O) of dialkyl peroxides show no obvious correlation with the ^{15}N chemical shifts (δ_N) of the corresponding tetraalkyl hydrazine molecule in which O–O is replaced by H_3CN–NCH_3 (see Table II). Thus, while δ_O for **3a** occurs significantly downfield (δ 303) from that for **3b** (δ 250), δ_N for **15a** occurs slightly upfield (δ 17.0) from that for **15b** (δ 18.5). Although these hydrazines possess vicinal nonbonding electron pairs on nitrogen, the lone pairs in **15a** are not constrained to be coplanar in contrast with the lone pairs in the peroxide **3a**. Instead, a lone pair–N–N–lone pair dihedral angle >120° is adopted.[13]



3a, X=O
15a, X=NCH$_3$

3b, X=O
15b, X=NCH$_3$

Experimental Section

Materials. Benzene was distilled under dry nitrogen from sodium benzophenone ketyl, then stirred over Na_2EDTA, and redistilled. Methylene chloride was distilled from P_2O_5, then stirred over Na_2EDTA, and redistilled. Spectral grade methanol and NMR grade $CDCl_3$ were used without further purification.

The unsaturated bicyclic peroxides **2b–d** and **12** were prepared as described previously[21] by cycloaddition of singlet oxygen (sensitized photooxygenation). These were selectively reduced with diimide[4a] to provide the corresponding saturated peroxides **3b–d** and **14**, and the bicyclo[2.2.1] peroxides **3a** and **10** were prepared similarly.[4] The dioxetane **13** was prepared by tris(*o*,*p*-dibromophenyl)ammonium hexachloroantimonate catalyzed oxygenation of isopropylideneadamantane as described previously.[22] The monocyclic peroxides **4a** and **4b** and the acyclic peroxides **5a** and **5c** were prepared by the peroxide transfer reaction.[5c] Di-*n*-propyl peroxide (**5b**) was prepared by alkylation of hydrogen peroxide.[23] Di-*tert*-butyl peroxide (**5d**) was commercial product from Matheson, Coleman, and Bell. The ozonide **11** was prepared as described previously.[24] The alkenes **6b**,[25] **8c**,[26] and bicyclo[4.2.2]deca-3,7,9-triene[27] and alkanes **7b**,[25] **9c**,[26] and **9d**[10] which were prepared as described previously were characterized by ^{13}C NMR.

1-Isopropyl-4-methylbicyclo[2.2.2]oct-2-ene (6b): ^{13}C NMR ($CDCl_3$) δ 138.55 (vinyl CH), 135.24 (vinyl CH), 40.58 (C), 34.77 (C), 34.77 (2 CH_2), 33.68 (CH), 29.52 (2 CH_2), 25.38 (CH_3), 18.18 (2 CH_3).

Bicyclo[3.2.2]non-6-ene (8c): ^{13}C NMR ($CDCl_3$) δ 134.34 (2 vinyl CH), 31.75 (2 CH), 30.50 (2 CH_2), 26.37 (2 CH_2), 23.49 (1 CH_2).

Bicyclo[4.2.2]deca-3,7,9-triene: ^{13}C NMR ($CDCl_3$) δ 131.3 (4 vinyl CH), 123.4 (2 vinyl CH), 41.8, 35.3.

1-Isopropyl-4-methylbicyclo[2.2.2]octane (7b): ^{13}C NMR ($CDCl_3$) δ 35.69 (CH), 33.59 (3 CH_2), 32.95 (C), 28.41 (3 CH_2), 28.24 (CH_3), 27.64 (C), 17.39 (2 CH_3).

Bicyclo[3.2.2]nonane (9c): ^{13}C NMR ($CDCl_3$) δ 35.64 (2 CH_2), 28.95 (2 CH), 25.91 (4 CH_2), 22.21 (1 CH_2).

Bicyclo[4.2.2]decane (9d): ^{13}C NMR ($CDCl_3$) δ 24.52 (4 CH_2), 26.07 (2 CH_2), 28.19 (2 CH), 37.79 (2 CH_2).

NMR Measurements. The NMR spectra were recorded on a JEOL FX270, a Varian XL-100, or a Varian XL-200 spectrometer. The JEOL instrument was operated at 36.54 MHz for recording ^{17}O NMR spectra. A total of 4096 points were collected over a spectral width of 30 030 Hz, by utilizing a pulse delay of 50 ms. Sensitivity enhancement was utilized to improve the signal to noise ratio, but this also leads to a 50-Hz artificial broadening of the ^{17}O peaks. With the XL-100 NMR spectrometer at 13.56 MHz, a spectral width of 10 000 Hz, acquisition time of 0.04–0.06 s, 90° pulse corresponding to about 50 s, and weighting factor (sensitivity enhancement) of 0.02 s were employed, whereas a spectral width of 20 000 Hz, acquisition time of 0.05 s, 90° pulse corresponding to 16.5 s, and sensitivity enhancement of 0.06 s were the parameters used on the XL-200 NMR spectrometer at 27.12 MHz. Considerable base line distortions occurred for each of the spectra obtained, probably due to incomplete spectrometer recovery following each rf pulse.[28] This caused a residual "tail"

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signal from each pulse, superimposed on the first part of the FID. Fortunately, these base line distortions could be almost entirely eliminated by selectively removing the few pulse breakthrough data points from the beginning of the FID.[29] Oxygen-17 chemical shifts referenced to internal (1.0–4.0 M) or external acetone gave the same value in ppm (±1 ppm). Thus, changes in the ^{17}O resonance due to a solvent effect is negligible. Chemical shifts are presented in Table II relative to external water (acetone resonates 572 ppm downfield of external water). The proton and ^{13}C NMR spectra are referenced to tetramethylsilane.

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Registry No. **2b**, 6671-70-1; **2c**, 6786-21-6; **2d**, 52148-56-8; **3a**, 279-35-6; **3b**, 280-53-5; **3c**, 283-35-2; **3d**, 52965-57-8; **4a**, 4362-13-4; **4b**, 5703-46-8; **5a**, 628-37-5; **5b**, 29914-92-9; **5c**, 16642-57-2; **5d**, 110-05-4; **6b**, 1127-11-3; **7b**, 1127-10-2; **8c**, 7124-86-9; **9c**, 283-19-2; **9d**, 284-26-4; **10**, 67105-55-9; **11**, 19077-73-7; **12**, 512-85-6; **13**, 88510-82-1; **14**, 5718-73-0; bicyclo[4.2.2]deca-3,7,9-triene, 35733-48-3.

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Computer-Assisted Mechanistic Evaluation of Organic Reactions. 11. Electrophilic Aromatic Substitution

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CAMEO, an interactive computer program which predicts the products of organic reactions primarily through mechanistic reasoning, has been expanded to treat electrophilic aromatic substitution (EAS). The major types of EAS reactions, i.e., nitration, sulfonation, alkylation, acylation, and halogenation, have been implemented for substituted benzenes, polycyclic aromatic hydrocarbons, and heteroaromatic systems. Key considerations include perception and classification of electrophiles, determining the relative reactivities of aromatic compounds and the most reactive sites, and matching electrophile and substitution site reactivity. Integral to the treatment is the development of a structure/reactivity correlation equation for EAS reactions. The paper begins with a brief review of the important facets of EAS chemistry. A discussion of the implementation of EAS in CAMEO follows including sample EAS reaction sequences produced by the program.

I. Introduction

An interactive computer program, CAMEO, that predicts the products of organic reactions given starting materials and reaction conditions is under continued development. Algorithms have been implemented to cover base-catalyzed and nucleophilic processes[1] including some organometallic reactions,[2] organosilicon chemistry,[3] pericyclic reactions,[4] nucleophilic aromatic substitution,[5] and acid-catalyzed reactions.[6] The program has also been expanded to treat electrophilic aromatic substitution (EAS) reactions as described here. Naturally, this has required analysis of the key features governing reactivity for this class of processes. Therefore, attention has been focused on perception and classification of electrophiles and identification of the most reactive rings and of the most reactive sites for a given electrophile. Substituent effects are considered in detail and relative reactivity is gauged via structure/activity relationships. To begin, a brief overview of electrophilic aromatic substitution is provided followed by a discussion of the implementation of EAS chemistry in CAMEO. The paper concludes with a presentation and discussion of sample EAS sequences predicted by the program.

Table I. Examples from the Three Classes of Electrophiles

I (weak)	II (moderate)	III (strong)
$HC{\equiv}NH^+$	R_3C^+	NO_2^+
NO^+	RCH_2X	Br_2
ArN_2^+	RCO^+	Cl_2
$H_2C{=}NR_2^+$	$RCOX$	$BrOH_2^+$
	$R_2C{=}OH^+$	$ClOH_2^+$
	$RN{=}C{=}O$	SO_3
		RSO_2^+

II. Key Aspects of EAS

Electrophilic aromatic substitution is a class of reactions that has been particularly well studied, so only a brief review of the major points of EAS chemistry is presented here. The discussion focuses on electrophiles for EAS, relative reactivity of different aromatic systems, and identification of the most reactive sites of aromatic compounds. For a more detailed coverage of EAS chemistry, several excellent sources may be consulted.[7,8]

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