Table I. ^{1}H NMR Chemical Shift and Coupling Constant Data

	δ (ppm)							J (Hz)				
compd	H-2	H-3	H-4	H-5	H-5′	$C(CH_3)_2$	OCH_3	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$
2[a]	4.72	4.62	4.31			1.25, 1.29, 1.35 (×2)		5.6	3.2			
3[a]	4.75		4.46	4.02		1.28, 1.36				7.2		
5[b]	4.60	4.79	4.27	3.89		1.30, 1.44		5.9	3.7			
6[b]	4.66	4.80	4.10–4.46			1.32, 1.46		5.8	3.2			
7	4.87		4.59	3.97		1.38, 1.46						
8[c]	4.82		4.70	4.40	4.27	1.36, 1.38			1.9	4.5	7.1	11.2
9	4.73	4.12	3.01	2.80	2.69	1.39, 1.63	3.80	7.2	5.8	4.0	2.6	5.1
10	4.72	3.80	2.83	2.52	2.29	1.37, 1.64	3.80	6.8	8.7	6.1	5.0	1.5
11[d]	4.67	4.64	4.12	4.35		1.40, 1.50		4.9	0.6	4.5		
12[e]	4.66	4.45	3.84–3.90					4.4	1.2			
16	4.78	4.07	3.00	2.81	2.72	1.40, 1.62	3.80	6.9	6.4	3.9	2.5	5.1
17	4.73	3.88	2.86	2.42	2.23	1.38, 1.64	3.80	7.1	8.5	6.4	5.3	1.5
18[d]	4.69	4.77	4.24	4.63	4.39	1.39, 1.46		4.6	4.2	6.0	8.3	11.3
19[e]	4.62	4.57	4.15	4.07	3.89			4.0	3.1	6.3	8.0	11.4

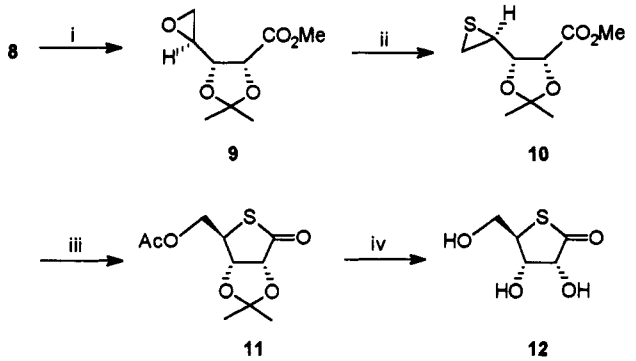
[a] Resonances for H-6, H-6′ appeared at 3.71 and 4.11 ppm (for 2), and 3.69 and 3.78 ppm (for 3). [b] Resonances for H-1 appeared at 5.42 ppm, $J_{1,2} < 0.5$ Hz (for 5), and 6.14, $J_{1,2} < 0.5$ Hz (for 6). [c] It showed a singlet (3 H) at 2.47 ppm due to the $CH_3C_6H_4$. [d] It showed a singlet (3H) at 2.10 ppm due to CH_3CO. [e] Recorded in ^2H_2O.

Table II. ^{13}C NMR Chemical Shift Data (δ, ppm)

compd	C-1	C-2	C-3	C-4	C-5	$C(CH_3)_2$	$C(CH_3)_2$
2[b]	173.5	76.1[a]	75.8[a]	80.9	75.3[a]	114.7, 110.5	26.8, 26.7, 25.9, 25.3
3[c]	173.2	76.5[a]	76.1[a]	79.4	70.9	114.7	26.8, 25.9
5	100.5	85.4	79.9	79.9	60.8	112.4	25.7, 24.4
6	100.7	85.0	79.9[a]	79.4[a]	62.4	113.4	26.2, 25.0
7	174.2	76.0	76.0	79.7	60.4	113.9	26.5, 25.5
8	172.4	75.8[a]	75.6[a]	75.2[a]	66.7	114.4	26.5, 25.6
9	169.5	75.3	78.2	50.0	43.7	111.5	26.6, 25.3
10	169.4	76.9	82.7	30.5	22.7	111.4	27.0, 25.5
11	203.6	83.4	78.6	47.5	65.1	112.6	27.5, 25.9
12[d]	210.1	78.7	71.7	54.6	63.3		
16	169.4	76.2	77.7	49.5	45.0	111.6	26.9, 25.4
17	169.2	76.8	82.3	32.8	21.3	110.0	26.5, 25.3
18	203.3	85.0	75.4	44.5	63.7	113.0	27.2, 25.9
19[d]	209.5	81.3	70.9	50.3	61.8		

[a] Signals may be interchanged. [b] C-6 appeared at 65.3 ppm. [c] C-6 appeared at 62.5 ppm. [d] Recorded in ^2H_2O. Data for compound 4, see Experimental Section.

Scheme III[a]

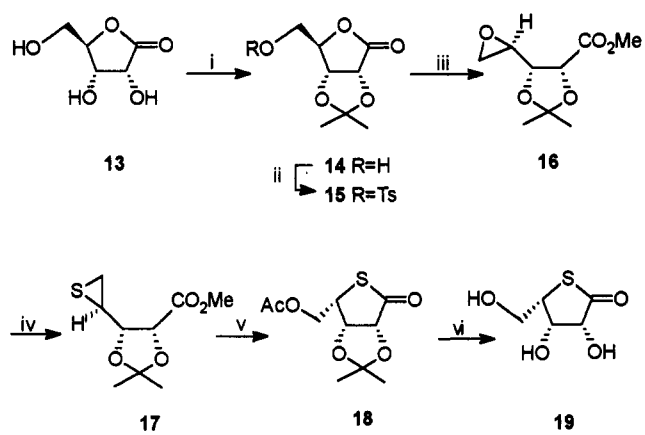


[a] (i) NaOMe, MeOH; (ii) $(NH_2)_2CS$, MeOH; (iii) KOAc, HOAc, DMF; (iv) 2% HCl in 2:1 THF–H_2O.

the sulfur atom hockey sticks effect,[24] which will operate in the other possible conformations.

Thiirane ring opening and thiolactonization took place by heating 17 at reflux with KOAc in HOAc–DMF. The 5-*O*-acetyl-2,3-*O*-isopropylidene-4-thio-L-lyxono-1,4-lactone (18) was obtained in crystalline form after chromatographic purification. The ^{13}C NMR spectrum of 18 showed the characteristic signal for the thiolactone carbon at 203.3 ppm. Acid removal of the acetyl and isopropylidene protecting groups of 18 afforded crystalline 4-thio-L-lyxono-1,4-lactone (19). The presence of a sulfur atom within the ring was again evidenced in the ^{13}C NMR spectrum of 19, by the large shift of the signals corresponding to the carbons bonded to sulfur (δ_{C-1} 209.5 and δ_{C-4} 50.3).

Scheme IV[a]



[a] (i) Me_2CO, H_2SO_4; (ii) TsCl, pyridine, $CHCl_3$; (iii) NaOMe, MeOH; (iv) $(NH_2)_2CS$, MeOH; (v) KOAc, HOAc, DMF; (vi) 2% HCl in 2:1 THF–H_2O.

The synthetic routes described herein constitute efficient procedures for the preparation of aldono-1,4-thiolactones having D-*ribo* (12) and L-*lyxo* (19) configurations [the overall yield for 12 was 20% from 1 (37% from 7), and for 19, 32% from 13]. This methodology can also be applied to the synthesis of other aldopentonothiolactones having different configurations.

Experimental Section

General Procedures. Melting points were determined in a Thomas-Hoover apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. ^{1}H NMR spectra were determined with a Varian XL-100 or a Bruker 500 spectrometer at 100 or 500 MHz, respectively. ^{13}C NMR spectra were recorded with a Varian XL-100 at 25.2 MHz. Unless otherwise indicated the spectra were determined in $CDCl_3$ solutions and with tetramethylsilane (0.00 ppm) as an internal reference. Signal assignments for the ^{13}C NMR spectra were made on the basis of selective heteronuclear decoupling experiments. Data are shown in Tables I and II. Analytical thin-layer chromatography (TLC) was performed on 0.25-mm silica gel 60 F_{254} (Merck) aluminum-supported plates with A, EtOAc; B, 1:1

(24) Zefirov, N. S.; Blagoveshchensky, V. S.; Kazimirchik, I. V.; Surova, N. S. *Tetrahedron* **1971**, *27*, 3111.

hexane–EtOAc; C, 3:1 toluene–EtOAc; and D, 6:1 hexane–EtOAc. Detection was affected by exposure to UV light or charring with 10% H_2SO_4 (v/v) in EtOH. Column chromatography was performed on silica gel 60 (230–400 Mesh, Merck). The following solvents were distilled before use: MeOH (from I_2/Mg), THF (from Na/benzophenone), acetone (from $KMnO_4$ and K_2CO_3), and acetic acid[25] (from Ac_2O and CrO_3). DMF was purified by sequential drying[26] with 3-Å molecular sieves and distillation. The GC-MS of the TMS derivatives of **12** and **19** were performed with a Varian Aerograph 1400 chromatograph coupled to a mass spectrometer Varian MAT CH7 A (70 eV), employing a SP-2330 column.

2,3-*O*-Isopropylidene-D-gulono-1,4-lactone (3). Compound **3** was prepared from D-gulono-1,4-lactone (**1**) *via* the 2,3:5,6-di-*O*-isopropylidene-D-gulono-1,4-lactone (**2**) as previously described.[14]

2,3-*O*-Isopropylidene-α-L-lyxose (5). To a solution of compound **3** (2.28 g, 10.4 mmol) in water (28 mL) was added a 1 M solution of aqueous $NaIO_4$ (10.5 mmol). After 20 min of stirring in the dark at room temperature, the starting material **3** (R_f 0.32, solvent A) was not detected by TLC. The solution was freeze-dried and the residue extracted with CH_2Cl_2 and concentrated. The homogeneous (R_f 0.57, solvent A) syrupy product obtained, characterized as **3,4-*O*-isopropylidene-L-arabinuronic acid 2,5-lactone** (**4**, 1.94 g, 99% yield) showed to be a mixture of the aldehyde and its hydrated form: ^{13}C NMR ($CDCl_3$) aldehyde δ 195.0 (C-5, *C*HO), 174.8 (C-1), 114.1 (*C*Me_2), 81.2 (C-4), 76.4, 76.2 (C-2,3), 26.7, 25.7 (C(*C*H_3)$_2$); hydrated form δ (*inter alia*) 173.4 (C-1), 114.9 (*C*Me_2), 88.7 (*C*H(OH)$_2$).

To a solution of crude **4** (124 mg, 0.57 mmol) in ethanol (5 mL) was added $NaBH_4$ (22 mg, 0.58 mmol). After 40 min of stirring at 0 °C, monitoring by TLC showed the formation of a single spot (R_f 0.55, solvent A) slower moving than **4**. The solution was made neutral by addition of 10% aqueous HOAc and then concentrated. The residue was filtered through a short column of silica gel with 1:1 hexane–EtOAc as solvent, affording **5** (66 mg, 62%): mp 78–80 °C (lit.[16] mp 80–82 °C for the enantiomer).

1,5-Di-*O*-acetyl-2,3-*O*-isopropylidene-α-L-lyxofuranose (6). Acetylation of **5** (35 mg, 0.18 mmol) with acetic anhydride (0.5 mL) and pyridine (0.5 mL) for 2 h afforded, after evaporation, compound **6** (42 mg, 84% yield) which had mp 47–49 °C; $[\alpha]_D$ −53.4° (*c* 1.1, $CHCl_3$) (lit.[16] mp 48–50 °C; $[\alpha]_D$ +59.5° for the enantiomer).

2,3-*O*-Isopropylidene-L-lyxono-1,4-lactone (7). The crude aldehyde derivative **4** (1.94 g) was dissolved in methanol (16 mL) containing a trace of bromocresol green. To this solution was added $NaBH_3CN$ (1.7 g, 26 mmol), and the yellow color (pH 4) was maintained by dropwise addition of 0.4 N methanolic HCl. After 6 h of stirring at room temperature, the solution was concentrated. The residue was extracted with CH_2Cl_2, and the extract was washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated. The resulting syrupy product (R_f 0.51, solvent A) was purified by flash chromatography (3:1 hexane–EtOAc). Compound **7** crystallized from hexane–EtOAc (1.46 g, 74%); recrystallized from the same solvent it gave mp 96–98 °C, $[\alpha]_D$ −85° (*c* 1.1, acetone). The analogous derivative in the D series had[17] mp 99–100 °C, $[\alpha]_D$ +106°, and[18] mp 88–93 °C, $[\alpha]_D$ +108°. Anal. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.43. Found: C, 50.90; H, 6.27.

2,3-*O*-Isopropylidene-5-*O*-(*p*-tolylsulfonyl)-L-lyxono-1,4-lactone (8). (A) To a solution of **7** (0.70 g, 3.70 mmol) in dry pyridine was added tosyl chloride (1.50 g, 7.90 mmol). The mixture was kept at 0 °C for 24 h and then poured into ice–water to yield compound **8** as a chromatographically homogeneous solid (R_f 0.56, solvent B), which was recrystallized from EtOH (0.76 g, 60%). After recrystallization from the same solvent, **8** had mp 121–123 °C; $[\alpha]_D$ −66.8° (*c* 0.4, $CHCl_3$). Anal. Calcd for $C_{15}H_{18}O_7S$: C, 52.62; H, 5.29. Found: C, 52.47; H, 5.24.

(B) To a stirring solution of **7** (0.96 g, 5.1 mmol) in dry $CHCl_3$ (5 mL), cooled at 0 °C, were added pyridine (0.82 mL, 10.1 mmol) and tosyl chloride (1.44 g, 7.6 mmol). After 4 h of stirring at 0 °C was added water (5 mL) dropwise, and the stirring was maintained for 0.5 h. The mixture was diluted with CH_2Cl_2 (60 mL) and it was successively washed with 2 N aqueous HCl, saturated aqueous $NaHCO_3$, and water. The organic extract was dried ($MgSO_4$) and concentrated. Compound **8** crystallized upon addition of EtOH (1.36 g, 78%); it showed the same physical constants as those described in A.

Methyl 4,5-epoxy-2,3-*O*-isopropylidene-L-lyxonate (9). Compound **8** was added to a stirring solution prepared by dissolving sodium (40 mg) in anhydrous methanol (6.5 mL). After 20 min of stirring at room temperature, a single spot, migrating faster than **8** (R_f 0.60, solvent B) was detected by TLC. Evaporation of the solvent afforded a residue which was extracted with ether. The extract was concentrated and the resulting syrup dissolved in hexane and filtered. Upon evaporation of the solvent, compound **9** was obtained as a chromatographically homogeneous oil (0.30 g, 85%): $[\alpha]_D$ −13.1° (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_9H_{14}O_5$: C, 53.45; H, 6.98. Found: C, 53.22; H, 6.98.

Methyl 4,5-Dideoxy-4,5-epithio-2,3-*O*-isopropylidene-D-ribonate (10). To a stirring solution of **9** (0.13 g, 0.64 mmol) in anhydrous methanol (7.7 mL) was added thiourea (83 mg, 1.1 mmol). After 48 h of stirring at room temperature, TLC showed a single spot (R_f 0.74, solvent C). The solution was concentrated, and the resulting residue was treated as described for **9**, to afford compound **10** as a clear oil (0.13 g, 93%): $[\alpha]_D$ −84.4° (*c* 1.2, $CHCl_3$). Anal. Calcd for $C_9H_{14}O_4S$: C, 49.52; H, 6.46; S, 14.60. Found: C, 49.64; H, 6.36; S, 14.82.

5-*O*-Acetyl-2,3-*O*-isopropylidene-4-thio-D-ribono-1,4-lactone (11). Compound **10** (0.16 g, 0.73 mmol) was dissolved in a mixture of anhydrous DMF (6 mL), glacial HOAc (6 mL), and KOAc (0.75 g, 7.6 mmol). The solution was heated at the reflux temperature for 16 h, under nitrogen, when a main spot (R_f 0.50, solvent C) was detected by TLC. The reaction mixture was diluted with CH_2Cl_2 (60 mL) and washed with aqueous KOAc and water. The organic extract was dried ($MgSO_4$) and concentrated to a syrup, which was chromatographed using 5:1 hexane–EtOAc. From the column, unreacted starting **10** (24 mg) was recovered, and the fractions containing the product of R_f 0.50 were pooled and evaporated affording the thiolactone **11** (0.11 g, 70% yield, based on reacted **10**); $[\alpha]_D$ +23.5° (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{10}H_{14}O_5S$: C, 48.77; H, 5.73. Found: C, 48.50; H, 5.56.

4-Thio-D-ribono-1,4-lactone (12). Compound **11** (165 mg, 0.67 mmol) dissolved in a mixture of THF (5 mL) and 6% aqueous HCl (2.5 mL) was stirred for 16 h at room temperature. Evaporation afforded a clear oil, which was filtered through a silica gel column with EtOAc as eluent. Fractions containing the product of R_f 0.22 (solvent A) were evaporated, and compound **12** slowly crystallized upon standing (95 mg, 86%). It had mp 112–114 °C; $[\alpha]_D$ +60.3° (*c* 0.9, methanol). Anal. Calcd for $C_5H_8O_4S$: C, 36.58; H, 4.91; S, 19.53. Found: C, 37.03; H, 5.19; S, 19.51.

Compound **12** was conventionally silylated with Sylon HTP. The GC-MS of the silylated derivative was performed: MS *m/z* (rel inten) 380 (0.6), 365 (11), 290 (6), 262 (13), 260 (11), 219 (10), 218 (40), 217 (41), 204 (8), 191 (9), 147 (41), 146 (14), 133 (13), 103 (16), 75 (13), 74 (11), 73 (100).

2,3-*O*-Isopropylidene-5-*O*-(*p*-tolylsulfonyl)-D-ribono-1,4-lactone (15). To a solution of 2,3-*O*-isopropylidene-D-ribono-1,4-lactone[27] (**14**, 3.0 g, 15.9 mmol) in pyridine (2.6 mL, 32 mmol) and $CHCl_3$ (16 mL) was added tosyl chloride (4.57 g, 24 mmol) at 0 °C. The mixture was stirred for 6 h at 0 °C, when water was added dropwise, and the stirring was maintained for 0.5 h. TLC examination showed a single spot of R_f 0.71 (solvent A). The product was isolated as described for **8**, method B, affording a syrup, which crystallized upon addition of methanol (4.8 g, 88%); mp 116–118 °C; $[\alpha]_D$ −15.5° (*c* 2.4, acetone) (lit.[28] mp 117.5–118 °C, $[\alpha]_D$ −15.8°).

Methyl 4,5-epoxy-2,3-*O*-isopropylidene-D-ribonate (16). It was prepared as described for **9**, starting from **15** (0.67 g, 1.9 mmol). Compound **16** was obtained as a syrup (0.36 g, 93%), $[\alpha]_D$ −10.7° (*c* 4.7, $CHCl_3$) (lit.[29] $[\alpha]_D$ −11.7°).

Methyl 4,5-Dideoxy-4,5-epithio-2,3-*O*-isopropylidene-L-lyxonate (17). To a solution of **16** (0.12 g, 0.6 mmol) in dry

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methanol (8 mL) was added thiourea (92 mg, 1.2 mmol). The solution was stirred for 48 h at room temperature, when TLC showed a single spot (R_f 0.65, solvent C). The residue was treated as described for **9**, to afford compound **10** as a clear oil (0.12 g, 88%); $[\alpha]_D$ −84.4° (*c* 1.2, $CHCl_3$). Anal. Calcd for $C_5H_{14}O_4S$: C, 49.52; H, 6.46. Found: C, 49.45; H, 6.19.

5-*O*-Acetyl-2,3-*O*-isopropylidene-4-thio-L-lyxono-1,4-lactone (18). Compound **17** (0.20 g, 0.9 mmol) was dissolved in a mixture of DMF (7 mL), HOAc (7 mL), and KOAc (0.9 g, 9.1 mmol) and refluxed, under nitrogen, for 18 h. TLC showed a main spot (R_f 0.52, solvent C) which was isolated and purified (column chromatography with 5:1 hexane–EtOAc) as described for **11**. The thiolactone **18** (0.14 g, 57%) gave mp 56–58 °C, $[\alpha]_D$ −114° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{10}H_{14}O_5S$: C, 48.77; H, 5.73; S, 13.02. Found: C, 48.96; H, 5.63; S, 13.36.

4-Thio-L-lyxono-1,4-lactone (19). Compound **18** (0.30 g, 1.2 mmol) was dissolved in a mixture of THF (9 mL) and 6% HCl (4.5 mL), and the resulting solution was stirred for 18 h at room temperature. The reaction mixture, which showed by TLC a main spot of R_f 0.26 (solvent A), was concentrated. The resulting syrup was purified through a short column of silica gel with EtOAc as eluent. Upon evaporation of the solvent, crystalline **19** (0.17 g, 86%) was obtained. After recrystallization from acetone, **19** gave mp 146–148 °C; $[\alpha]_D$ −136° (*c* 1, methanol). Anal. Calcd for $C_5H_8O_4S$: C, 36.58; H, 4.91; S, 19.53. Found: C, 36.71; H, 4.71; S, 19.49.

Compound **19** was conventionally silylated with Sylon HTP. The GC-MS of the silylated derivative was performed: MS *m/z* (rel inten) 380 (3), 365 (33), 290 (11), 262 (26), 219 (18), 218 (68), 217 (100), 204 (16), 191 (11), 147 (41), 146 (14), 133 (11), 103 (7), 75 (4), 73 (47).

Acknowledgment. We are indebted to CONICET (Consejo Nacional de Investigaciones Científicas y Técnicas) and the University of Buenos Aires for financial support and to UMYMFOR (CONICET-FCEN, UBA) for the microanalyses and MS. O.V. is a Research Member of CONICET.

Axial/Equatorial Proportions for 2-Substituted Cyclohexanones

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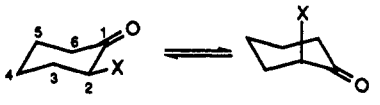
Received July 16, 1993•

Axial–equatorial conformational proportions have been measured for 2-substituted cyclohexanones in chloroform by the Eliel method for F, Cl, Br, I, MeO, MeS, Me_2N, MeSe, and Me. For the first seven of these, at least five experimentally independent measurables were used and the resulting conformational preferences appear to be accurate to within 10%. Systematic errors degraded the results for MeSe and Me. For Me_2N, the conformational preference also was measured for the first time at slow exchange in the low-temperature ^{13}C spectrum in several solvents. In chloroform, steric and polar effects contribute to the conformational preferences, with steric effects dominant for large groups such as I and MeS.

The conformational analysis of six-membered rings has provided the foundation for modern stereochemistry. Investigations of the factors that determine conformational preferences of substituents on saturated six-membered rings (*A* values) have enriched our understanding of how atoms and functional groups interact with hydrocarbon fragments.[2] The introduction of unsaturation into the ring has a profound effect on conformational properties. An endocyclic double bond changes the fundamental conformational family from chair to half-chair,[3] and the interactions of substituents at the 3 and 4 positions respond to the new steric milieu. An exocyclic double bond may be illustrated by either the exomethylene group (C=CH_2) or the carbonyl group (C=O), and substituents may be introduced at the 2, 3, or 4 positions. We have previously studied in depth the case of the 3-substituted exomethylene system.[4] Herein we provide a comprehensive study of 2-substituted cyclohexanones in an effort to understand how polar and nonpolar substituents interact with the carbonyl group.

There are significant differences between the ring shapes of cyclohexane and cyclohexanone. Whereas the C–C–C angle is 111° in cyclohexane,[5] it is about 116° for the C–(CO)–C portion in cyclohexanone.[6] The C1–C2 bond length of 1.510 Å and the C2–C3 bond length of 1.545 Å in cyclohexanone compare with 1.530 Å in cyclohexane.[6] These differences cause the carbonyl portion of cyclohexanone to be flattened in comparison with cyclohexane. The barrier to rotation about a $C(sp^3)$–$C(sp^2)$ bond as in cyclohexanone is generally lower than that about a $C(sp^3)$–$C(sp^3)$ bond. The more flattened ring and the lower barrier cause ring reversal, the process that interconverts axial and equatorial positions, to be more rapid for cyclohexanone than for cyclohexane. For this reason it is more difficult with cyclohexanones to obtain slow-exchange NMR spectra, which provide distinct resonances for axial and equatorial groups. The barrier typically is 10 kcal mol^{-1} for cyclohexanes and 5 kcal mol^{-1} for cyclohexanones.[7] To date, there are no examples of conformational populations measured directly at slow exchange for substituted cyclohexanones, whereas the experiment is commonplace for cyclohexanes.

The conformational preference of a monosubstituted cyclohexane is determined largely by the interaction of the substituent with the syn-axial protons and the carbons to which the latter are attached. For 2-substituted cyclohexanones, such interactions still are important, but in addition the interaction of the substituent with the carbonyl group must be taken into consideration, eq 1. For



(1)

a nonpolar substituent X, there are simple nonbonded interactions with the carbonyl group, which are clearly larger in the equatorial conformation. Such interactions, first recognized for alkyl groups by Robins and Walker[8] and later referred to as the 2-alkyl ketone effect,[9] proved to be relatively small. Polar interactions have proved to be more important (except with alkyl substituents). The dipole of an equatorial, electronegative substituent is nearly parallel to that of the carbonyl group and results

• Abstract published in *Advance ACS Abstracts*, December 1, 1993.
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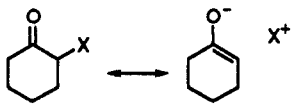
in a repulsive interaction, whereas that of an axial, electronegative substituent is approximately orthogonal to that of the carbonyl group and results in little interaction. An equatorial arrangement thus is repulsive and should decrease the dipole of the carbonyl group. Reduction in the dipolar contribution to the resonance hybrid in fact is documented by a 20-cm^{-1} increase in the carbonyl stretching frequency.[6]

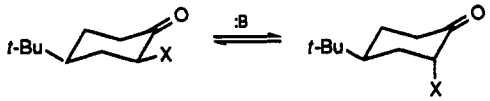
The interaction between a 2 substituent and the carbonyl group also may be described in terms of the generalized anomeric effect or hyperconjugation.[10] A number of orbital interactions have been suggested, such as donation of electrons from the C–X σ bond or from the lone pairs on X to the σ^* or π^* orbital of the carbonyl group.[11,12] These interactions may be exemplified by the valence bond structures of eq 2. The orbitals are aligned for better



(2)

overlap in the axial conformation, so that orbital considerations favor the axial form.

There have been numerous studies aimed at determining the conformational preferences of 2-substituted cyclohexanones. The importance of solvent is clear from these studies. Irrespective of whether dipole–dipole or orbital interactions provide the dominant factor, the more-polar equatorial form is favored by increased polarity of the solvent. Methods to determine axial/equatorial equilibrium constants include isomer equilibration, dipole moments, infrared, ultraviolet, and proton NMR spectroscopies. When the time scale of observation is relatively long, the two forms equilibrate and render measurements of distinct conformations impossible. Allinger and Allinger[13] introduced the use of the 4-*tert*-butyl group to bias conformational forms. A 2-X-4-*tert*-butylcyclohexanone exists in two forms (eq 3),which may be equilibrated



(3)

by a suitable base. Provided that the *tert*-butyl group does not perturb the system, such equilibration experiments can provide conformational preferences. Alternatively, a physical property may be measured separately for the two *tert*-butyl isomers and compared with that for the simple 2-substituted system of eq 1. The property for the simple system should be intermediate between those for the two conformational extremes of eq 1, and the precise value is determined by the mole fractions N, as in eq 4 for

$$R = N_{ax}R_{ax} + N_{eq}R_{eq} \quad (4)$$

a general property R. If the unmeasurable R_{ax} and R_{eq} for eq 1 can be approximated by the measurable values for the distinct isomers of eq 3, the conformer populations N_{ax} and N_{eq} may be calculated from eq 5 and the fact that

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Table I. Axial Percentages of 2-Substituted Cyclohexanones

X	solvent	^{1}H (δ)	^{1}H (J)	infrared	ultraviolet
F	cyclohexane	56[a]	30[a]		
	CCl_4	34[a]	34[a]		
	$CHCl_3$	24[a]	13[a]		
	1,4-dioxane	20[a]	23[a]		
Cl	cyclohexane	77[a]	70[a]	73[b]	63[b]
	CCl_4	72[a]	65[a]		
	$CHCl_3$	56[a]	49[a]		
	1,4-dioxane	50[a]	36[a]	25[b]	37[b]
Br	cyclohexane	87[a]	89[a]	45[c]	
	CCl_4	84[a]	87[a]	74[c]	
	$CHCl_3$	79[a]	70[a]	68[c]	
	1,4-dioxane	70[a]	69[a]	57[c]	
I	hexane	95[d]			
OCD_3	CH_3CN	20[e]			
SCH_3	$CHCl_3$			70[f]	
CH_3	$CDCl_3$	5[g]			

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$$N_{ax} = \frac{R - R_{eq}}{R_{ax} - R_{eq}} \quad (5)$$

$N_{ax} + N_{eq} = 1$. This approach is attributed to Eliel[6,14] and was first applied to cyclohexanones by Garbisch.[15]

We have gathered in Table I some previous spectroscopic determinations of conformational preferences of 2-substituted cyclohexanones. The pronounced solvent effect clearly supports the importance of a polar component to the substituent–carbonyl interaction. The objectives of this study were to apply high-field proton techniques to the problem, to use carbon-13 resonances to determine conformational preferences, and to obtain slow-exchange spectra for the direct measurement of the preferences.

Results

All the monosubstituted cyclohexanones were known compounds, but some of our syntheses were novel and all are described in the Experimental Section. For each 2-substituent but one, we prepared the monosubstituted molecule (eq 1) and the 4-*tert*-butyl systems in both cis and trans stereochemistries (eq 3). In some cases the two stereoisomers were obtained separately, in others as binary mixtures. It was not necessary to separate the two isomers of eq 3 in order to obtain their spectral parameters as models for those of the pure 2-axial and 2-equatorial forms. In this study, the X groups of eq 1 and 3 were H (**1**, **12**), F (**2**, **13**), Cl (**3**, **14**), Br (**4**, **15**), I (**5**, **16**), OMe (**6**, **17**), SMe (**7**, **18**), SeMe (**8**, **19**), NMe_2 (**9**, **20**), Me (**10**, **21**), and *tert*-Bu (**11**, **22**) (for each case, the first compound number refers to the monosubstituted systems of eq 1 and the second number to the *tert*-butyl systems of eq 3; the latter are further distinguished as the 2-axial or 2-equatorial isomer, i.e., **12a**, **12e**). Spectral assignments of the 2-protons were unambiguous by inspection except for the hydrocarbons (X = Me, *tert*-Bu). In the latter cases assignments were assisted by HETCOR spectra (two

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