4758 *J. Org. Chem.* **1989**, *54*, 4758–4767

a stirred solution of 1 (5 mL, 26.6 mmol) in 4 mL of xylene. Refluxing xylene was required for 3 h. The resulting mixture was then allowed to cool down and when the temperature was ca. 100 °C, 900 mg of S_8 (29 mmol) were added. Solvent was removed, leaving a yellow oil that was chromatographed with hexane/dichloromethane (20:80) as eluent. **8a*** was first eluted and, then, a mixture of **8a*** + **8b***. Pure **8a*** was crystallized in hexane (white crystals, mp = 156–158 °C); yield 50%. Overall yield of **8a*** + **8b*** was 75%.

8a*: ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 3 H, Me), 1.48 (d, ^4J(P–H) = 2.4 Hz, Me), 2.0 (s, 1 H, OH), 2.12–2.29 (m, 2 H, CH_2), 2.5–2.6 (m 1 H, H_α), 2.98 (d, $^3J(H_\alpha–H_\beta)$ = 6.1 Hz, 1 H, H_β), 3.8–4.2 (m, 2 H, CH_2OH), 7.06–7.45 ppm (m, 10 H, Ph × 2); ^{13}C NMR ($CDCl_3$) δ 15.8 (d, ^3J(P–C) = 12 Hz, Me), 19.4 (d, ^3J(P–C) = 16.6 Hz, Me), 46.7 (d, ^1J(P–C) = 45.8 Hz, C6), 50.1 (d, ^2J(P–C) = 20 Hz, C5), 52.5 (d, ^1J(P–C) = 54 Hz, C7), 54.4 (s, OCH_2 or C4), 60.7 (s, C4 or OCH_2), 126.0–138.0 (m, Ph × 2 + C2), 155.1 ppm (d, ^2J(P–C) = 14.1 Hz, C3); ^{31}P{^{1}H} NMR ($CDCl_3$) δ 55.3 ppm; MS, *m/z* (relative intensity) 354 (M, 30), 220 (M – cinnamyl alcohol, 100).

X-ray Structure Determination for 4a*. Crystals of **4a*** were obtained by slow diffusion of pentane into a dichloromethane solution of the compound. Data were collected at 18 ± 1° on an Enraf Nonius CAD 4 diffractometer. The crystal structure was solved and refined by using the Enraf Nonius supplied SDP package. The compound crystallizes in space group *P*-1, a = 7.434 (1) Å, b = 16.129 (2) Å, c = 17.509 (2) Å, α = 79.03 (1)°, β = 77.74 (1)°, γ = 76.67 (1)°, v = 1974.13 (54) Å^3; Z = 4; d_{calcd} = 1.266 g/cm^3; Mo K_α radiation (λ = 0.71013 Å) graphite monochromator; μ = 1.6 cm; $F(000)$ = 800. The asymmetric unit contains two independent molecules, corresponding to the *R* and *S* enantiomers. A total of 6909 unique reflections were recorded in the range 2° $\leq 2\theta \leq$ 50° of which 3422 were considered as unobserved ($F^2 < 3\sigma(F^2)$), leaving 3487 for solution and refinement. The structure was solved by direct methods, yielding a solution for 13 atoms. The hydrogen atoms were introduced as fixed contributors in the final stages of refinement while using anisotropic temperature factors for all other atoms. A non-Poisson weighting scheme was applied with a p factor equal to 0.08. The final R factors were R = 0.040, R_W = 0.056, G.O.F. = 1.17.

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Supplementary Material Available: Tables of atomic coordinates, thermal parameters, bond lengths, and bond angles for **4a*** (7 pages); structure factor tables for **4*** (19 pages). Ordering information is given on any current masthead page.

Correlations of Stereochemistry and Heteroatom Configurations with ^{17}O Chemical Shifts in Substituted 1-Hetera-4-cyclohexanones

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The ^{17}O chemical shifts for the oxygen atom of the carbonyl group [C=^{17}O] have been measured for several substituted 1-hetera-4-cyclohexanones and selected 3,7-diheterabicyclo[3.3.1]nonan-9-ones in D_3CCN/H_3CCN at 70 °C. The heteroatoms included N, O, S, Se, and P. Sharp trends in shielding and deshielding for C=^{17}O were observed with substituents at various positions. For example, deshielding effects are detected when phenyl or methyl groups are present at the 2,6-positions (α to the C=O). Increased deshielding was observed in the case of *trans*-2,6-diphenyl analogues as compared with the *cis*-2,6-diphenyl analogues. A *shielding* effect was seen when methyl groups were present at the 3,5-positions (β to the C=O). Negligible changes in C=^{17}O chemical shifts occurred in 1-aza and 1-oxa analogues as compared with cyclohexanone. In contrast, the sulfur, selenium, and phosphorus analogues showed a significant *downfield* shift for C=^{17}O as compared to cyclohexanone. For certain 3,7-diheterabicyclo[3.3.1]nonan-9-ones, a *shielding* effect on the C=^{17}O resonance was seen which was reminiscent of the effect elicited with substituents at the 3,5-positions (α to the C=O) in the 1-hetera-4-cyclohexanones. Interestingly, the related system tropinone, as compared to that in *N*-methyl-4-piperidinone, showed a *deshielding* for C=^{17}O which was quite similar to that found in 2,6-substituted (β to the C=O) 1-hetera-4-cyclohexanones compared to the corresponding parent 1-hetera-4-cyclohexanone. This suggests that the piperidinone ring in tropinone exists in a chair form in D_3CCN/H_3CCN at 70 °C.

Introduction

The use of ^{17}O NMR spectroscopy as a method to diagnose a variety of structural problems in oxygen-containing, organic systems is increasing rapidly.[1-4] In recent years, Boykin and co-workers[5-10] have shown that correlations exist between ^{17}O chemical shifts and an internal torsion angle [or perhaps van der Waals interactions] for aromatic nitro compounds,[5] acetophenones,[6] 3-substituted phthalic anhydrides,[7] aromatic carboxylic acids and derivatives,[8] certain aryl ketones,[9] and multisubstituted phthalimides.[10] Crandall and co-workers[11] reported C=^{17}O chemical shifts for several substituted cyclohexanones and indicated that substituent effects depended upon the di-

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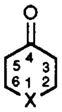
0022-3263/89/1954-4758\$01.50/0

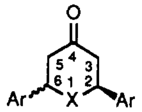
Table I. ^{17}O NMR Chemical Shifts (ppm, D_3CCN/H_3CCN) for 1–12



compd	X	δ ^{17}O (C=O)	$w_{1/2}$, Hz	other ^{17}O signals
1	CH_2	557.1	76.2	
2	NH	556.1	131.4	
3	NMe	560.3	135.6	
4	N-*i*-Pr	558.5	93.7	
5	NCH_2Ph	559.9	142.3	
6	NC(O)Ph	566.1	184.6	352.7 (223.2)[a]
7	O	560.4	85.1	10.3 (83.0)[a]
8	S	570.3	87.3	
9	Se	572.3	143.4	
10	PPh	564.5	146.9	
11	P(O)Ph	573.5	184.3	43.6 (156)[b]
12	P(S)Ph	574.5	210.6	

[a] $w_{1/2}$ in hertz. [b] $^1J_{PO}$ in hertz.

Table II. ^{17}O NMR Chemical Shifts (ppm, D_3CCN/H_3CCN) for 13–25

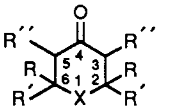


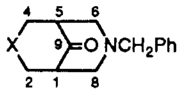
compd	X	Ar	δ ^{17}O (C=O)	$w_{1/2}$, Hz	other ^{17}O signals
13	CH_2	*cis*-Ph	562.2	317.1	
14	NH	*cis*-Ph	560.6	408.5	
15	NMe	*cis*-Ph	562.9	414.0	
16	O	*cis*-Ph	563.7	367.3	49.9 (507.8)[a]
17	S	*cis*-Ph	575.2	258.0	
18	Se	*cis*-*p*-Tol	578.7	201.4	
19	Se	*cis*-*p*-Anis	580.3	142.4	48.4 (596.3)[a]
20	PPh	*cis*-Ph	572.2	688.1	
21	O	*trans*-Ph	568.1	360.6	45.9 (328.4)[a]
22	S	*trans*-Ph	578.3	523.3	
23	PPh	*trans*-Ph	577.1	268.7	
24	P(O)Ph	*trans*-Ph	582.9	286.8	48.4 (130)[b]
25	$Ph_3P{\rightarrow}O$				49.22 (162)[b]

[a] $w_{1/2}$ in hertz. [b] $^1J_{PO}$ in hertz.

hedral angle between planes composed of CH_3–C(2)–C(1) and O–C(1)–C(2). Christ and co-workers[12] were the first to record C=^{17}O chemical shifts for cyclic ketones. Dahn and co-workers[13] observed large *upfield* shifts in the case of 8- and 9-membered 1-aza- and 1-oxacycloalkanones and attributed these *upfield* shifts to transannular interactions. It was noted that the 1-thia analogues did *not* exhibit such an effect.

We have been interested in stereochemical and conformational aspects of substituted 1-hetera-4-cyclohexanones since they are important intermediates in the synthesis of certain bicyclic heterocycles.[14] We report herein a comprehensive study of C=^{17}O chemical shifts and the effects of various substituents for a large variety of 1-hetera-4-cyclohexanones. The heteroatoms include





N, O, P, S, and Se, and the substituents are *cis*-2,6-diphenyl, *trans*-2,6-diphenyl, *cis*-2,6-diphenyl-*trans*-3-methyl, *cis*-2,6-diphenyl-*trans*-3,5-dimethyl and 2,2,6,6-tetramethyl groups. With the nitrogen heterocycles, the substituents on nitrogen include methyl, isopropyl, benzyl, and benzoyl groups. Substituents on phosphorus in the phosphorus heterocycles include a phenyl group, along with the *P*-oxide and *P*-sulfide derivatives. Strong correlations appear to exist between the C=^{17}O chemical shifts and substituent effects within families and, to some degree, across related families with a different heteroatom. Moreover, a good correlation is apparent between the C=^{17}O chemical shifts in 1-hetera-4-cyclohexanone and the C=^{17}O chemical shifts observed for certain 3,7-diheterabicyclo[3.3.1]nonan-9-ones.

Results and Discussion

All ^{17}O chemical shifts and shift differences for ketones 1–47 are listed in Tables I–IX. Table I contains ^{17}O shift data for cyclohexanone and 1-hetera-4-cyclohexanones. The chemical shifts of certain *cis*- and *trans*-2,6-diphenyl analogues are given in Table II, while those of selected 2,6-diphenyl-3-methyl- and 2,6-diphenyl-3,5-dimethyl-1-hetera-4-cyclohexanones are provided in Table IV. Table VI has chemical shifts for 2,2,6,6-tetramethyl-substituted analogues. Certain bicyclic compounds are included in Table VIII. Linewidths at half height ($w_{1/2}$) or $^1J_{PO}$ values in hertz are given in Tables I, II, IV, VI, and VIII where appropriate. Differences in C=^{17}O chemical shifts between substituted 1-hetera-4-cyclohexanones and the corresponding parent compounds are in Tables III, V, VII, and IX.

In analyzing the results, it is useful to compare chemical shifts with a standard(s), which we selected to be the parent unsubstituted compound(s) listed in Table I. An extensive search of the literature revealed that only compounds **1**,[11–13,15] **7**,[13] **8**,[13] **25**,[16] and **36**[11] had been previously studied by ^{17}O NMR spectroscopy. Thus our work appears to be the first comprehensive investigation of several family members of 1-hetera-4-cyclohexanones via C=^{17}O NMR spectroscopy. Supporting data are found in Tables X–XII.[17–27]

Inspection of data in Table I reveals that the heteroatoms N and O do *not* cause a significant change in C=^{17}O chemical shift compared to that in cyclohexanone. However, within the family of isosteric heteroatoms, O, S and Se, a *downfield* trend is observed. This trend appears to be related to the C(2,6)–X bond length (Tables X–XII),

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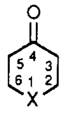
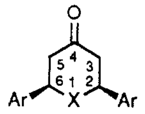
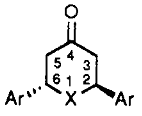
Table III. Shift Differences (ppm) between the 2,6-Substituted 1-Hetera-4-cyclohexanones and the Corresponding Unsubstituted Analogues ($\delta_E - \delta_A$, $\delta_B - \delta_A$, $\delta_C - \delta_A$, and $\delta_C - \delta_B$)



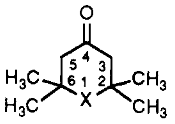
A



B



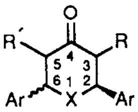
C



E

X	compds	$\delta_E - \delta_A$	Ar	$\delta_B - \delta_A$	$\delta_C - \delta_A$	$\delta_C - \delta_B$
CH_2	**13-1**	15.1	Ph	5.1	-	-
NH	**14-2**	12.9	Ph	4.5	-	-
NMe	**15-3**	-	Ph	2.6	-	-
O	**16-7**	-	Ph	3.3	7.7	4.4
S	**17-8**	16.2	Ph	4.9	8.0	3.1
Se	**18-9**	-	*p*-Tol	6.4	-	-
Se	**19-9**	-	*p*-Anis	8.0	-	-
PPh	**20-10**	21.2	Ph	7.7	12.6	5.0
P(O)Ph	**24-11**	18.8	Ph	-	9.4	-
P(S)Ph	**41-12**	20.5	-	-	-	-

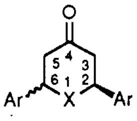
Table IV. ^{17}O NMR Chemical Shifts (ppm, D_3CCN/H_3CCN) for 26-35



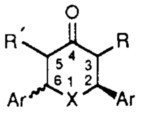
compd	X	Ar	R	R′	δ ^{17}O (C=O)	$w_{1/2}$, Hz	other ^{17}O signals
26	NH	*cis*-Ph	Me	H	553.8	593.3	-
27	NH	*cis*-Ph	Me	Me	542.9	500.7	-
28	O	*cis*-*p*-Anis	Me	H	556.0	532.8	62.3[a] (284.6)[b] 45.9[c] (678.3)[b]
29	O	*cis*-*p*-Anis	Me	Me	539.4	777.7	66.9[a] (379.3)[b] 46.2[c] (582.3)[b]
30	O	*cis*-*p*-Tol	Me	Me	541.6	485.1	70.3[a] (348.3)[b]
31	O	*cis*-Ph	Me	Me	537.8	786.0	67.8[a] (262.9)[b]
32	S	*trans*-Ph	H	Me	574.4	390.2	
33	S	*cis*-Ph	H	Me	565.1	594.9	
34	PPh	*cis*-Ph	Me	H	564.4	457.0	
35	P(O)Ph	*cis*-Ph	Me	H	575.5	451.4	30.5 (167)[d]

[a] Ring oxygen. [b] $w_{1/2}$ in hertz. [c] Anisole oxygen. [d] $^1J_{PO}$ in hertz.

Table V. Shift Differences (ppm) between the Methyl-Substituted 2,6-Diphenyl Heterocycles and 2,6-Diphenyl-1-hetera-4-cyclohexanones ($\delta_B - \delta_D$)



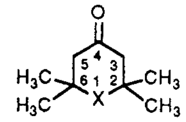
B



D

X	Ar	R	R′	compds	$\delta_B - \delta_D$
NH	*cis*-Ph	Me	H	**14-26**	6.8
NH	*cis*-Ph	Me	Me	**14-27**	17.7
O	*cis*-*p*-Anis	Me	H	**16-28**	7.7
O	*cis*-*p*-Anis	Me	Me	**16-29**	23.8
O	*cis*-*p*-Tol	Me	Me	**16-30**	22.1
O	*cis*-Ph	Me	Me	**16-31**	25.9
PPh	*cis*-Ph	Me	H	**20-34**	7.8
S	*cis*-Ph	H	Me	**17-33**	10.1
S	*trans*-Ph	H	Me	**22-32**	3.9

Table VI. ^{17}O Chemical Shifts (ppm, D_3CCN/H_3CCN) for 36-41

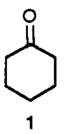


compd	X	δ ^{17}O (C=O)	$w_{1/2}$, Hz	other ^{17}O signals
36	CH_2	572.3	166.2	
37	NH	569.0	155.4	
38	S	586.5	173.1	
39	PPh	585.7	214.1	
40	P(O)Ph	592.3	260.6	27.4 (168)[a]
41	P(S)Ph	595.0	234.7	

[a] $^1J_{PO}$ in hertz.

i.e. as the bond length increases, the ^{17}O shift value also increases [average C(2)-Se > C(2)-S > C(2)-O].[17] The reverse is true in terms of electronegativity (Table X) of the heteroatom, i.e. as the electronegativity (χ) of the heteroatom decreases, the shift value increases [$\chi_O > \chi_S > \chi_{Se}$].[18]

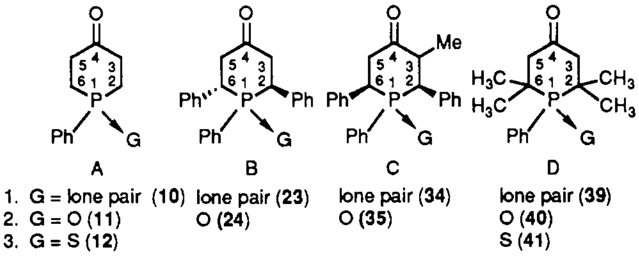
A similar correlation is observed in the family of isosteric heteroatoms N and P. The shift for **10** (X = PPh) is 4.2 ppm downfield from that of **3** (X = NCH_3) and 4.6 ppm downfield from that of **5** (X = NCH_2Ph) [(average C(2)-P > C(2)-N)[17] and ($\chi_N > \chi_P$)[18]]. This trend indicates that the C=^{17}O chemical shifts in 1-hetera-4-cyclohexanones may depend upon the electronegativity of the heteroatom and possibly upon the distance of the heteroatom from the carbonyl group. The chemical shift of cyclohexanone (**1**) does not fit in this trend since carbon is not isosteric with either O or N. However, it is possible that the C=^{17}O shift of **1** will correlate with 1-silicon analogues.[28] The trend



1

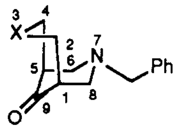
2-12

Table VII. Shift Differences (ppm) for C═^{17}O Resonances between Certain Substituted Phosporinanones

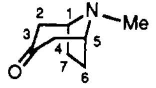


compd	$\delta_2 - \delta_1$	$\delta_3 - \delta_1$
A	9.0	10.0
B	5.8	–
C	11.1	–
D	6.6	9.3

Table VIII. ^{17}O NMR Chemical Shifts (ppm, D_3CCN/H_3CCN) for 42–47 and 49



42-47



49

compd	X	δ ^{17}O (C═O)	$w_{1/2}$, Hz	other ^{17}O signal
42	NMe	545.8	248.5	
43	N-*i*-Pr	542.0	318.4	
44	NCH_2Ph	545.0	431.5	
45	O	543.2	209.2	1.0 (173.3)[a]
46	S	559.9	246.5	
47	$CHCO_2Et$	547.2	799.7	339.5[b] (251.2)[a] 164.0[c] (543.9)[a]
49		573.9	139.2	

[a] $w_{1/2}$ in hertz. [b] C═O of ester. [c] C—O of ester.

Table IX. Shift Differences (ppm) between Bicyclic Ketones 42–47 and 49 and Their Monocyclic Constituents

MC compds[a]	$\bar{X}$ δ_I[b]	BC compd[c]	δ_{BC}[d]	$\Delta\delta_I - \delta_{BC}$
(**3** + **5**)/2	560.1	**42**	545.8	+14.3
(**4** + **5**)/2	559.2	**43**	542.0	+17.2
(**5** + **5**)/2	559.9	**44**	545.1	+14.8
(**7** + **5**)/2	560.2	**45**	543.2	+17.0
(**8** + **5**)/2	565.1	**46**	559.9	+5.2
(**1** + **5**)/2	558.5	**47**	547.2	+11.3
(**3** + **3**)/2	560.3	**49**	573.9	−13.6

[a] MC compds = monocyclic compounds. [b] $\bar{X}$ δ_I = average of the two C═^{17}O shifts for the monocyclic 1-hetera-4-cyclohexanones which constitute the bicyclo[3.3.1]nonan-9-one system. [c] BC compd = bicyclic compound. [d] δ_{BC} = C═^{17}O shift of bicyclic ketones.

Table X. Electronegativity (χ) Values[a] and Average C–X Bond Lengths (Å)[b]

X	χ	bond length, Å
H	2.1	1.086
C	2.5	1.370
N	3.0	1.285
O	3.5	1.290
P	2.1	1.870
S	2.5	1.680
Si	1.8	1.860
Se	2.4	1.845

[a] Values taken from ref 17. [b] Values taken from ref 18.

within the nitrogen heterocycles **3**–**5** (Table I) is also interesting as a 1.9 ppm upfield shift is observed for **4** (X = N-*i*-Pr) and only a 0.5 ppm upfield shift for **5** (X = NCH_2Ph) when compared with **3** (X = NCH_3). This observation further supports the contention that an increase in electron density on the heteroatom causes an *upfield* C═^{17}O shift, as, for example, with the system **3** (NCH_3, 560.34 ppm) versus the system **4** [$NCH(CH_3)_2$, 558.47 ppm] although the electron difference in the latter two systems is likely small. Substituting a benzoyl group for a benzyl group causes a *downfield* shift of 6.3 ppm, but this is not surprising in lieu of the trends observed since electron density on the nitrogen in **6** [X = $NC(O)C_6H_5$] is reduced via delocalization of electrons over the carbonyl group of the amide function as compared to electron density on the nitrogen in **5** (X = NCH_2Ph). Of course, a change in ring conformation could effect the C═^{17}O shift since a flattening of the ring would be expected.

That hydrogen-bonding influences the ^{17}O shift (Table I) has been well established,[4,29] and it is known that such interaction causes weakening of the carbonyl bond and induces an *upfield* shift by as much as about 50 ppm in aldehydes and ketones compared to standards.[29] We have observed an upfield C═^{17}O shift of 4.3 ppm in **2** (X = NH) as compared with **3** (X = NCH_3). This change is smaller than in most cases reported in literature.[29] For example, *N*-methylbenzamide exhibits an *upfield* shift of 32 ppm as compared with *N*,*N*-dimethylbenzamide.[29] Smaller changes observed in our case are possibly due to the concentrations of our test samples which are quite low (0.16 M) and perhaps less subject to intermolecular associations.

Phosphorus containing heterocycles **10**–**12** form another interesting series (Table I). In this family, large *downfield* C═^{17}O shifts are observed in oxide **11** (573.5 ppm) and sulfide **12** (574.4 ppm) as compared with **10** (564.5 ppm). These downfield shifts are not surprising since in **11** and **12** there is a partial positive charge on phosphorus, analogous to the case of nitrogen heterocycle **6**. It is noteworthy that sulfide **12** is more *deshielded* than the oxide **11**, since oxygen (in P→^{17}O) is more electronegative than sulfur S (in P→S). This might be due to $\sum\chi_{PO}(5.6) > \sum\chi_{PS}(4.6)$ and the different bond length of C(2)–P(S) in **12** (1.816 Å) compared to C(2)–P(O) in **11** (1.801 Å)[24] or to a slight change in conformation. It was observed that in phosphorus heterocycles **11** and **12** a large upfield shift occurs in ^{13}C═O resonance compared to that in phosphine **10**.[24] It has also been noted that a few substituents on phosphorus influence the ^{13}C shifts in a nonlinear fashion.[24]

Boykin[4] has suggested three conceivable explanations for the C═^{17}O chemical shift of a functional group. (1) There is predictable deshielding of ^{17}O when there is greater double bond character present in a C═O bond or there is reduced electron density on oxygen in the same group. (2) The case of increased shielding is reasonable when the carbonyl group assumes more single-bond character or there is increased electron density on oxygen. (3) A change in shielding on C═^{17}O can be caused by rotation of the C–C(O)–C groups to minimize the internal strain which might be offset (resulting in zero net change) by a contribution to the shielding of ^{17}O by a nearby group such as located at C(2,6). This type of rotation does not seem intuitively reasonable for our rigid system. Changes in chemical shifts were also attributed to changes in van der Waals interactions which are relieved by rotation of groups around a single bond. Thus, it is possible that in

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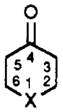
(28) Soderquist, J. A.; Shiau, F.-Y.; Lemesh, R. A. *J. Org. Chem.* **1984**, *49*, 2565. This work contains citation to 1,1-dimethyl-1-sila-4-cyclohexanone but no ^{17}O shift was reported.

(29) (a) Klemperer, W. G. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 246. (b) Burgar, M. I.; St. Armour, T. E.; Fiat, D. *J. Phys. Chem.* **1981**, *85*, 502.

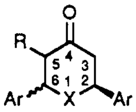
Table XI. Selected Bond Lengths (Å), Bond Angles (deg), and Torsion Angles (deg) for Certain 1-Hetera-4-cyclohexanones



	compd, X =						
	1, CH$_2$[a]	7, O[b]	8, S[c]	9, Se[d]	10, PPh[e]	11, P(O)Ph[f]	12, P(S)Ph[f]
bond lengths, Å							
C(2)-X(1)	1.55	1.41	1.80	1.93	1.84	1.80	1.82
bond angles, deg							
∠C(2)X(1)C(6)	110.8	113.0	97.0	95.0	98.2	101.2	99.8
∠C(2)C(3)C(4)	111.5	110.5	112.5	115.8	114.7	113.1	108.9
∠C(3)C(4)C(5)	115.3	116.0	118.9	118.2	117.7	117.4	117.4
∠C(3)C(2)X(1)	110.8	113.5	113.2	112.2	117.0	109.3	108.9
torsion angles, deg							
X(1)C(2)C(3)C(4)	53.0	-	57.1	57.0	57.0	59.8	59.2

[a] Electron diffraction: ref 19. [b] Microwave: ref 20. [c] Electron diffraction: ref 21. [d] X-ray diffraction: ref 22. [e] X-ray diffraction: ref 23. [f] X-ray diffraction: ref 24.

Table XII. Selected Bond Lengths (Å), Bond Angles (deg), and Torsion Angles (deg) for Certain Substituted 1-Hetera-4-cyclohexanones



	A[a]	B[a]	C[b]	D[b]	E[c]
X	O (16)	O (21)	S (32)	S	PPh (34)
Ar	*cis*-Ph	*trans*-Ph	*trans*-Ph	*trans*-Ph	*cis*-Ph
R	H	H	Me	Et	Me
bond lengths, Å					
C(2)-X(1)	1.44	1.43	1.83	1.83	1.85
bond angles, deg					
∠C(2)X(1)C(6)	113	112	99	100	100
∠C(2)C(3)C(4)	114	112	114	113	118
∠C(3)C(4)C(5)	114	114	117	118	119
∠C(3)C(2)X(1)	110	110	111	112	108
torsion angles, deg					
X(1)C(2)C(3)C(4)	48	52	57	55	62
X(1)C(6)C(5)C(4)	52	53	58	58	58

[a] X-ray diffraction: ref 25. [b] X-ray diffraction: ref 26. [c] X-ray diffraction: ref 27.

our 1-hetera-4-cyclohexanones (where a *deshielding* trend has been observed in the same vertical group, namely with S and Se compared with O heterocycles and with P compared with N heterocycles) there is a significant change in van der Waals interactions or that there is increased double-bond character for the C=O bond. The van der Waals interactions which could be increasingly significant in the series O to S to Se are those involving the heteroatom and the α protons [H(2,6)]. The S- and Se-containing rings are flattened, and the C–S or C–Se bonds are lengthened in the cyclic systems (compared to simple acyclic systems) to minimize such internal repulsive forces. Of course, such changes could be reflected in the ^{17}O shift.

Inspection of data in Table II reveals that *cis*-2,6-diphenyl groups cause significant downfield C=^{17}O shifts (~5 ppm) [compared with that for unsubstituted 1-hetera-4-cyclohexanones in Table I], and appropriate shift differences are listed in Table III. In this family of *cis*-2,6-diphenyl-1-hetera-4-cyclohexanones, a trend towards a *downfield* shift is seen within the isosteric families of O, S, and Se (11.5 and 3.3 ppm, respectively, between **16**, **17** and **17**, **18**) and of N and P (9.2 ppm between **15** and **20**). This is analogous to the trend previously described for the unsubstituted 1-hetera-4-cyclohexanones. The effect (Table III) of *cis*-2,6-diphenyl substituents on the C=^{17}O chemical shift causes an average downfield shift of 4.9 ± 1.6 ppm in **13**–**20** compared with the respective unsubstituted analogues (Table I). This change is significantly greater than the effect of *cis*-dimethyl groups in equivalent positions in cyclohexanone (a downfield shift of 1.3 ppm) as observed by Crandall and co-workers.[11] The larger phenyl groups will almost surely cause increased repulsive forces around the heteroatom and possibly some conformational changes which likely influence the ^{17}O shift. Recently Li and Chesnut[30] found a good correlation between local van der Waals energies and observed ^{13}C chemical shifts in several substituted cyclohexanes and were able to predict with a good degree of accuracy the ^{13}C chemical shifts. The work of Boykin[4] and Li and Chesnut[30] seems to suggest that local van der Waals interactions form an important factor which govern the chemical shifts. Thus, such repulsive van der Waals interactions may be more pronounced in systems with large substituents such as in *cis*-2,6-diphenyl-1-hetera-4-cyclohexanones compared to that in *cis*-3,5-dimethylcyclohexanone.

The C=^{17}O resonances are shifted *downfield* in the *trans*-2,6-diphenyl-substituted systems by about 9.4 ppm in **21**, **22**, **23**, and **24** compared to **7**, **8**, **10**, and **11** and are listed in Table II. Interestingly, this deshielding effect is close in value to that for *trans*-3,5-dimethylcyclohexanone, which is 11.4 ppm downfield from cyclohexanone.[11]

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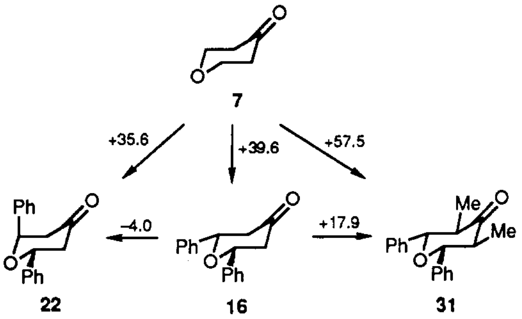
(30) (a) Li, S.; Chesnut, D. B. *Magn. Reson. Chem.* **1985**, *23*, 625. (b) Li, S.; Chesnut, D. B. *Magn. Reson. Chem.* **1986**, *24*, 93.

Crandall and co-workers[11] reasoned that the large deshielding $C{=}^{17}O$ shift induced by an axial C(3)–CH_3 bond in 3-methylcyclohexanone, as compared to cyclohexanone (1), is possibly due to a through-space interaction involving the $CH_{3_{axial}}$—C(3) bond and the C=O groups. They suggested that the substituent axial carbon–carbon bond [CH_3–C(3)] in such compounds is reasonably proximate and roughly parallel to the axis of the p orbital on carbon of the C=O group. In our work, this conclusion is further supported by X-ray data[26] which indicates that one ortho hydrogen atom in the axial phenyl group is in close proximity to the carbonyl group in crystalline **32** (Table IV). Moreover, in our examples **21**–**24** the downfield $C{=}^{17}O$ shift (Table II) presumably is due to the *deshielding* effect (compared with the cis analogues) by the axial Ar–C bond which produces greater repulsive interactions compared to the cis isomer. An average *downfield* effect of 9.4 ± 2.0 ppm is seen for **21**–**24** with respect to the unsubstituted 1-hetera-4-cyclohexanones (Table I) and 4.2 ± 0.8 ppm compared with the *cis*-2,6-diphenyl analogues (Table II). These shift differences are listed in Table III.

Analysis of data presented in Table IV reveals a significant *upfield* shift upon introduction of methyl groups at the 3,5-positions (β to C=O; compared with *cis*-2,6-diphenyl analogues). As a reference, the parent compounds for systems listed in Table IV are the corresponding 2,6-diphenyl analogues listed in Table II. Shift differences between the nonmethylated and methylated compounds are listed in Table V. An introduction of one methyl group (Table IV) at the 3-position (β position to C=O) in **26**, **28**, **33**, and **34** causes an average ^{17}O *upfield* shift of 8.1 ± 1.2 ppm compared with that for **14**, **16**, **17**, and **20**, while the introduction of second methyl group at the 5-position (α to C=O) causes an upfield shift of 10.9 ± 1.7 ppm in the 3,5-dimethyl analogues compared also to **14**, **16**, **17**, and **20**. This shielding trend is analogous to that observed in 2-methyl-substituted (−11.0 ppm; positions α to C=O) and in 2,6-dimethyl-substituted (−8.0 ppm) cyclohexanones (as compared with cyclohexanone) and in 2-methyl-4-*tert*-butylcyclohexanone (−8.1 ppm; 2-position is α to C=O) compared with 4-*tert*-butylcyclohexanone.[11]

The $C{=}^{17}O$ resonances are shifted downfield by about 17.5 ppm in tetramethylated systems **36**–**41** (Table VI) compared with unsubstituted systems **1**, **2**, **8**, and **10**–**12**, respectively. The shift differences are listed in Table III. In a similar situation involving cyclohexanone as the standard, where methyl groups were successively substituted at the 3- and 5-positions, the following trends were observed:[11] 3(e)-CH_3 (+1.9), 3(e),5(e)-$(CH_3)_2$ (+1.3), 3,3-$(CH_3)_2$ (+12.4), 3(e),5(a)-$(CH_3)_2$ (+11.4), 3,3,5(e)-$(CH_3)_3$ (+10.1), and 3,3,5,5-$(CH_3)_4$ (+16.6) [values in parentheses are downfield shifts from cyclohexanone]. Thus, it can be seen that the large downfield shifts observed in the tetramethyl analogues are mainly due to the methyl groups in axial positions. This large *deshielding* of $C{=}^{17}O$ shifts induced by axial C(2) and C(6) methyl groups in 1-hetera-4-cyclohexanones seems to follow trends found with δ substituted, simple ketones.[1,2,11] Perhaps, it is similar to the case of *trans*-2,6-diphenyl analogues. It is also conceivable that a rotation of the carbonyl group around the single bonds to relieve van der Waals interactions[4] might induce a conformational change and result in a significant downfield ^{17}O shift. The effect on $C{=}^{17}O$ shift by the tetramethyl groups appears to be an average *deshielding* of 17.5 ± 3.0 ppm for six systems (Table III). The deviations from the mean are not very large when considering the different parameters that might be influencing ^{17}O shifts and the linewidths of ^{17}O signals which limit reproducibility of data to within ±1 ppm. Delseth and Kintzinger[15] measured ^{17}O chemical shifts for several aliphatic aldehydes and ketones and concluded that the shift data for various groups was additive with a standard deviation of 2.5 ppm.

Scheme I



We have observed interesting trends for the chemical shifts of *ether oxygen* atom in each substituted tetrahydro-4-pyranones (Scheme I) in this work. Values above the arrows are for shielding (−) or deshielding (+) effects due to substituents. When compared to standard **7**, *cis*-phenyl groups in the 2- and 6-positions caused a deshielding effect of 39.6 ppm as found in **16**. Whereas, when the phenyl groups are trans oriented, a slightly diminished deshielding effect of 35.6 ppm is noted (in **22**). A similar situation has been observed by Eliel and co-workers[31] in certain 1,3-dioxanes. Ether oxygen in *cis*-4,6-dimethyl-1,3-dioxane is deshielded by 22.7 ppm whereas in *trans*-4,6-dimethyl-1,3-dioxane, C–^{17}O–C is deshielded by 17.1 ppm (compared with 1,3-dioxane). Increased deshielding for C–^{17}O is observed in the dimethyl analogue **31** compared to **7** (+57.5 ppm) or to **16** (+17.9 ppm). Unfortunately, no related model systems could be found in the literature. However, we note that in tetrahydro-4-pyranones with equatorial substituents at the 2-, 3-, 5-, and 6-positions, a deshielding effect occurs for $C{=}^{17}O$ which proved helpful in the study of conformations in bicyclo[3.3.1]nonan-9-ones containing a tetrahydropyran ring system which will be discussed shortly.

We have observed the ^{17}O chemical shift of the oxygen in $P{\rightarrow}^{17}O$ of 4-phosphorinanone oxides (Tables I–III and VI), and we were also able to detect the $P{\rightarrow}^{17}O$ coupling in these systems. The $P{\rightarrow}^{17}O$ signal in triphenylphosphine oxide (**25**) is at 49.2 ppm (Table II) with $^1J_{PO}$ = 162 Hz, (lit.[16] J = 160 Hz), while 1-phenyl-4-phosphorinanone 1-oxide (**11**) has a $P{\rightarrow}^{17}O$ shift of 43.6 ppm (Table I) with $^1J_{PO}$ = 156 Hz. The chemical shift in **24**, which has *trans*-phenyl groups in the 2- and 6-positions, is 48.4 ppm with $^1J_{PO}$ = 130 Hz. The oxygen atom of $P{\rightarrow}^{17}O$ in **24** is deshielded by 4.8 ppm (compared to that in **11**) and is accompanied by a decrease in the $^1J_{PO}$ value (156 Hz in **11** and 130 Hz in **24**), which is not unreasonable because of the drastic difference in environment around the $P{\rightarrow}^{17}O$ bond in the two systems. There is a greater change in the $P{\rightarrow}^{17}O$ shift and the $^1J_{PO}$ value in **35** (Table IV) compared to **11** and **24**, the values for **35** being 30.5 ppm and 167 Hz, respectively. The 2,6-phenyl groups in **24** are in a trans arrangement, while in **35** the 2,6-phenyl groups are syn to one another; however, there is a methyl group in the 3-position in **35** which appears to shield the $P{\rightarrow}^{17}O$ group and change the $^1J_{PO}$ value. In the 2,2,6,6-tetramethyl analogue **40** (Table VI), the oxygen in $P{\rightarrow}^{17}O$ is even more

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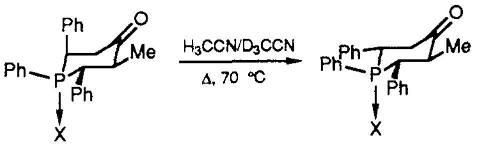
[31] Eliel, E. L.; Pietrusiewicz, K. M.; Jewell, L. M.; Kenan, W. R. *Tetrahedron Lett.* **1979**, *38*, 3649.

Scheme II



34′, X = lone pair
35′, X = O

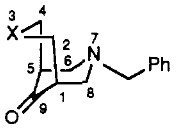
34, X = lone pair
35, X = O

shielded at 27.4 ppm (compared to **11**, **25**, and **35**, see Table IV) and has a $^1J_{\mathrm{PO}}$ value of 167 Hz. This seems to suggest that as steric effects increase around $\mathrm{P}\rightarrow\mathrm{O}$ groups, there is a shielding effect with concomitant increase in the $^1J_{\mathrm{PO}}$ value. Unfortunately, the *r*-1,*trans*-2,6(e)-triphenyl-4-phosphorinanone 1-oxide was not available for comparison.

We have observed a novel case of isomerization in two members of the 4-phosphorinanone family under the conditions of our experiment, and this is outlined in Scheme II. Using an authentic sample[32] of trans isomer **34′**, heating in the solvents shown for 16 h produced a $\mathrm{C{=}^{17}O}$ resonance at 564.60 ppm which persisted even after 24 h. However, with authentic sample[32] of cis isomer **34**, a signal for $\mathrm{C{=}^{17}O}$ appeared at 564.44 ppm within 20 h. Thus, it was concluded that only the $\mathrm{C{=}^{17}O}$ signal for **34** was observed in both experiments which was supported by the $w_{1/2}$ of 460 and 457 Hz for the two signals, respectively. The differences in δ and $w_{1/2}$ values are within experimental error. A similar situation was observed for *trans*-oxide **35′** and *cis*-oxide **35**, i.e. heating **35′** in the system gave only **35** for which a $\mathrm{C{=}^{17}O}$ signal occurred at 575.53 ppm with an $^{17}\mathrm{O}$ signal from $\mathrm{P}\rightarrow{}^{17}\mathrm{O}$ at 30.48 ppm ($^1J_{\mathrm{P}\rightarrow\mathrm{O}}$ = 167 Hz). The data for the product from heating **35′** was essentially identical. These observations were not totally unexpected, as we had reported a similar case of isomerization in this family under different conditions,[32] namely where the trans isomer **34′** isomerized to the cis isomer **34** when the former was heated in a sealed glass tube under N_2 to a temperature of 200–210 °C for 2 h. Although heating of keto phosphine **34′** to 70 °C seems modest, possibly inherent strain induced by steric congestion around the P atom is sufficient to promote the isomerization at the lower temperature in acetonitrile.

In Table VII, we listed all phosphorus heterocycles examined. We recognized that **10–12**, **23**, **24**, and **39**, and **40** are likely dynamic systems in solution in contrast to **34** and **35** which are likely biased. Consequently, the $^{17}\mathrm{O}$ shifts for the former molecules must be considered average values for $\mathrm{C{=}^{17}O}$. It is clear in all families that $^{17}\mathrm{O}$ shifts in $\mathrm{C{=}^{17}O}$ for all *P*-oxides and *P*-sulfides occur *downfield* compared to the corresponding phosphines, with the signals for *P*-sulfides being at lowest field. It is noteworthy that as substitution on phosphorus occurs, as observed in phosphine **34** versus phosphine oxide **35**, a large deshielding of $^{17}\mathrm{O}$ in $\mathrm{C{=}^{17}O}$ is noted. As steric congestion increases around phosphorus, as in **40** versus **41**, the shift differences in the $^{17}\mathrm{O}$ resonances in the $\mathrm{C{=}^{17}O}$ groups are quite large. We suspect that the larger size of the S atom is not compensated sufficiently by the longer $\mathrm{P}\rightarrow\mathrm{S}$ bond in **41** (compared to the $\mathrm{P}\rightarrow\mathrm{O}$ bond in **40**) with the result being a marked *downfield* effect on the $^{17}\mathrm{O}$ resonance in $\mathrm{C{=}^{17}O}$. Possibly, in **41** there is some ring distortion because of crowding around phosphorus. It has been presumed[32] that $\mathrm{P}\rightarrow\mathrm{G}$ (G = O, S, etc.) bonds in systems like **10–12**, **23**, **24**, **34**, **35**, and **39–41** have a propensity to occupy predominantly an axial position. Therefore, it is tempting to speculate that the large sulfur causes a *deshielding effect* on the $\mathrm{C{=}^{17}O}$ resonance because of nonbonding, through-space interactions such as dipole–dipole interactions or changes in local van der Waals interactions.[4,30] Moreover, even in an axial position, the $\mathrm{P}\rightarrow\mathrm{S}$ group may induce a slight twist in the ring to relieve the strain in **41**. This is turn might result in a closer position of S in the $\mathrm{P}\rightarrow\mathrm{S}$ groups to the C in C=O.

Table XIII. Selected Bond Lengths (Å), Bond Angles (deg), and Torsion Angles (deg) for Certain 3,7-Diheterabicyclo[3.3.1]nonan-9-ones



	X		
	NMe[a] (**42**)	S[b] (**46**)	Se[c]
bond length, Å			
C(2)X(3)	1.43	1.81	1.95
C(6)N(7)	1.46	1.46	1.45
bond angles, deg			
∠C(2)X(3)C(4)	110.4	98	95.3
∠C(6)N(7)C(8)	111.2	112.7	110.8
∠C(2)C(1)C(9)	108.6	111.7	113.3
∠C(8)C(1)C(9)	106.0	106.4	105.5
torsion angles, deg			
X(3)C(2)C(1)C(9)	1.9	2.9	46.3
N(9)C(8)C(1)C(9)	59.8	58.9	68.2

[a] X-ray diffraction: ref 34. [b] X-ray diffraction: ref 33b. [c] X-ray diffraction: ref 33a.

We have an interest in the conformational analysis of 3,7-diheterabicyclo[3.3.1]nonanes and their derivatives as potential antiarrhythmic agents.[33] Present in these bicyclic ketones are two 1-hetera-4-cyclohexanone moieties. It will be recalled that some trends on $\mathrm{C{=}^{17}O}$ shifts induced by substituents were visible in the 1-hetera-4-cyclohexanones examined (Tables I, IV, and V). Substituting methyl groups at the 3(e)- and 5(e)-positions (α to C=O) in cyclohexanones resulted in an *upfield* shift of about 20 ppm (Table V). Crandall and co-workers[11] noted that substituting methyl groups in the 2(a)-position in cyclohexanone and related cyclohexanones resulted in *downfield* shifts of 2-6 ppm in $\mathrm{C{=}^{17}O}$. In analogy, bicyclic systems **42** and **46** (Table VIII) have *axial* C—C bonds at positions α to the C=O group. Single-crystal X-ray analyses have been reported for **42**[34] and **46**,[33b] and selected data for these compounds are listed in Table XIII. Both compounds exist in a chair–boat conformation with the ring containing the *N*-benzyl group in the chair conformation in the solid state. The C(1)–C(2) and C(4)–C(5) bonds are *axially* oriented to the *N*-benzyl-4-piperidinone ring.

The $^{17}\mathrm{O}$ chemical shifts of bicyclic ketones **42–47** are listed in Table VIII. The shift differences between these bicyclic ketones and their monocyclic counterparts are listed in Table IX and are calculated as follows. The chemical shifts of the $\mathrm{C{=}^{17}O}$ bicyclic ketone were subtracted from the average of the chemical shifts of the

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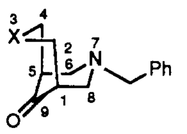
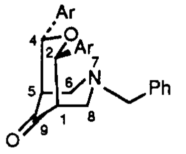
carbonyl oxygens for the two 1-hetera-4-cyclohexanones making up the bicyclic ketone skeleton. For example, in ketone **42** which contains both *N*-methyl and an *N*-benzyl-4-piperdinone rings, the ^{17}O shift of carbonyl oxygen was subtracted from the *average* of the C=^{17}O shift for *N*-methyl- and *N*-benzyl-4-piperidinones. These differences reveal an *upfield* shift compared with the monocyclic ketones. In analogy with the observation of Crandall and co-workers,[11] we expected a *downfield* shift of about 2–6 ppm, contrary to a significant *upfield* shift of about 5–17 ppm observed in these bicyclic ketones with axially oriented substituents which are also α to the carbonyl group. Such upfield shifts seem possible only if there is significant interaction between the lone pair on the heteroatom and the p orbital of the carbon of the C=^{17}O carbonyl group (transannular interaction), a result which could cause increased electron density on the carbonyl oxygen or increased single bond character in C=O. Thus, in ketone **42** (X = NCH_3) an upfield shift of 14.28 ppm is noted, while in ketone **46** (X = S) an upfield shift of only 5.15 ppm is observed. Similar trends in a few monocyclic heterocycles has been noted by Dahn and co-workers.[13] The torsion angles X(3)–C(2)–C(1)–C(9) [1.9° (**42**)[34] and 2.9° (**46**)[33b]] and X(3)–C(4)–C(5)–C(9) [–0.4° (**42**)[34] and –2.6° (**46**)[33b]] (Table XIII) are not significantly different in these two compounds. However, the bond lengths C(2)–X(3) and C(4)–X(3) are different (1.46 and 1.81 Å in **42**[34] and **46**,[33b] respectively). Thus the lone pair on the nitrogen of NCH_3 group in **42** may be closer to the carbonyl group than is the lone pair on sulfur in **46** which also is in a flattened ring. In **42**, a boat–chair seems plausible to cause significant shielding of the carbonyl group, whereas in **46** we observe a diminished upfield ^{17}O shift.



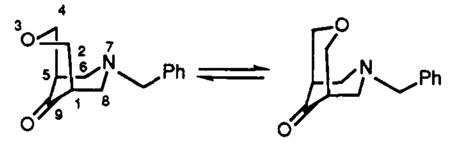
42-47



48 (Ar = *o*-ClC$_6$C$_4$)

It appears that a boat–chair conformation is preferred in acetonitrile at 70 °C for **42** and probably for **46** although the latter has less influence by S on altering charge in C=^{17}O because of the flattened ring and long C—S bonds. Three other members of this family, namely **43–45**, also follow the same trend and hence appear to be in a boat–chair (BC) conformation with the ring containing the *N*-benzyl group in a chair conformation. An average upfield shift for C=^{17}O in ketones **42–45** is 15.8 ± 1.3 ppm as determined by the method in Table IX and discussed previously. We presume that C(2)–X and C(4)–X bond lengths are comparable in **42–45**. Moreover, we assume in **43**, where X = O, the C(2,4)–X bonds are of comparable length as found in **7**[20] (1.41 Å) and in 7-benzyl-2,4-bis(2-chlorophenyl)-7-aza-3-oxabicyclo[3.3.1]nonan-9-one (1.42 Å) (**48**).[35]

Another interesting observation was made in detecting the chemical shift of *ether oxygen* in the ketone **45** (Table VIII). The ther C–^{17}O shift is at 1.0 ppm and is shielded by 9.3 ppm as compared with tetrahydro-4-pyranone (**7**, Table I). This upfield C–^{17}O shift in **45** is contrary to the *downfield* shift of 17.9 ppm observed for the methylated tetrahydro-4-pyranone (**31**, Scheme I) and a downfield shift of 1.5 ppm observed in 3-methyltetrahydropyran.[31] While accounting for this observation, the differences in conformation, electronic environment, and steric factors should be considered. The tetrahydropyran ring in the compounds outlined in Scheme I and in 3-methyltetrahydropyran[31] exist in a chair conformation, while in ketone **45**, the ^{17}O data suggest that a *boat* conformation or perhaps a boat $\rightleftharpoons$ chair equilibrium is present. A chair–boat $\rightleftharpoons$ boat–chair equilibrium has been observed, via dynamic NMR studies, in a related system with phenyl groups at the 1,5-positions.[36] Moreover, there is probably a significant interaction between a lone pair on oxygen in the tetrahydropyran ring of **45** and the p orbital of the π system in C=^{17}O. The chair–chair conformer **45′** might be less stable due to nonbonding repulsive interactions between the lone pairs on nitrogen and oxygen. Moreover, solvation of the system in boat–chair conformation might be more facile as compared with the chair–chair conformer, thus leading to greater stabilization of the boat–chair conformer in acetonitrile. It is possible that both of these factors can cause a *downfield* C=^{17}O shift, but solvation may be the more important factor. Taken on the whole, the above observations support a boat–chair (BC, X = O) conformation for **45** in D_3CCN/H_3CCN.



45-BC **45′**-CC

Ketone **47** also appears to be in boat–chair (BC, X = $CHCO_2Et$) conformation. For certain related bicyclic ketones, a boat–chair conformation has been suggested by Speckamp and Peters based on ^{1}H and ^{13}C NMR analyses.[37] The C=^{17}O shift in ketone **47** is 547.17 ppm, which is upfield by 11.33 ppm from the average of the ^{17}O shifts of both *N*-benzyl-4-piperidinone (**5**) and cyclohexanone (**1**). This shift difference value is slightly smaller than those observed for ketones **42–45**. Speckamp and Peters suggested that the carboethoxy group is in the endo position (as in **47**-BC) and that the ring bearing the carbethoxy group is in boat conformation in related systems.[37] If their observations hold for keto ester **47**, then the ketone C=^{17}O should experience a *downfield* shift and not an upfield shift as observed for ketones **42–46**. However, there is no heteroatom or group present in the 7-exo-position of **47** which could produce a shielding effect (via transannular interaction) on the ketone C=^{17}O (the carbethoxy group in an endo position cannot cause such an effect—compare **47** with **42–46**). Thus, it is possible that there is an boat–chair (**47**-BC) $\rightleftharpoons$ chair–boat (**47′**-CB) equilibrium in this system. Consequently, this C=^{17}O NMR study seems to suggest that 7-benzyl-7-aza-3-heterabicyclo[3.3.1]nonan-9-ones **42–47** exist in boat–chair (BC) conformations in acetonitrile at 70 °C.

An interesting model system related to **42–47** is tropinone (**49**). The ^{17}O chemical shift of tropinone (**49**) is 573.91 ppm, which is *downfield* by 13.57 ppm compared with *N*-methyl-4-piperidinone (**3**). An analogous effect was observed in the study of several cyclohexanones with methyl groups in the 3(a)- and 5(a)-positions (downfield shift of 15.3 ppm)[11] whereas when the methyl groups were in the 3(e)- and 5(e)-positions, a downfield shift of only 1.3 ppm was detected.[11] This seems to suggest that the

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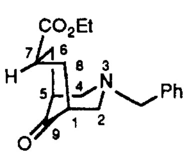
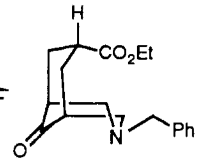
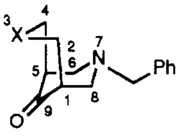


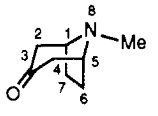
47-BC



47′-CB



42-46



49

6-membered ring in **49** is in the *chair* conformation with the ethylene bridge axially oriented. The solid-state conformation of **49** has not been established.

Summary

Forty-one 1-hetera-4-cyclohexanones have been examined via ^{17}O NMR spectroscopy for the purpose of determining whether or not a correlation exists between δ ^{17}O in C=^{17}O and stereochemical and electronic properties of the systems. Correlation between the ^{17}O shifts and the electronegativity of heteroatoms and the C–X bond lengths have been observed. Substituents at the 2- and 6-positions in the ring result in *downfield* shifts, while equatorial substituents at the 3- and 5-positions result in *upfield* shifts. The C=^{17}O chemical shifts of 3,7-diheterabicyclo[3.3.1]nonan-9-ones **42–47** suggest that these systems may exist in boat–chair (BC) conformations in acetonitrile. Thus, the trends observed for δ ^{17}O from analysis of C=^{17}O strongly suggest that such data can be most instructive in diagnosing stereochemical features in 1-hetera-4-cyclohexanones.

Experimental Section

All compounds used in this study were commercially available or were prepared via literature procedures. The following commercially available compounds were purified by distillation prior to use under conditions described: acetonitrile (dried over CaH_2, 83–84 °C, stored over molecular sieves, 3A, Fisher), cyclohexanone (**1**) (154–156 °C, Aldrich), *N*-methyl-4-piperidinone (**3**) (49–50 °C/0.3 mmHg, Aldrich), *N*-isopropyl-4-piperidinone (**4**) (38–41 °C/0.5 mmHg, Aldrich), *N*-benzyl-4-piperidinone (**5**) (111–112 °C/0.3 mmHg, Aldrich), and tetrahydro-4*H*-pyran-4-one (**7**) (166–167 °C, Aldrich). Tropinone (**48**, Aldrich) was recrystallized (hexanes, mp 44–44.5 °C). 4-Piperidinone (**2**) and 2,2,6,6-tetramethyl-4-piperidinone (**37**) were purchased (Aldrich) as hydrochlorides and then dissolved in H_2O to give a solution which was made basic to pH 12 (10% aqueous NaOH solution). The free amines were extracted (ether) from the basic solution, and after drying (Na_2SO_4), the extracts were subjected to evaporation (rotary evaporator). The crude amines were oils and were used without further purification. The following materials were obtained from commercial sources and were also used without further purification: acetonitrile-d_3 (99 atom % D, Aldrich), 1-benzoyl-4-piperidinone (**6**) (mp 55–59 °C, Aldrich), triphenylphosphine oxide (**25**, Aldrich), and 3,3,5,5-tetramethylcyclohexanone (**36**, Aldrich). The following compounds were prepared previously and fully identified: tetrahydro-4*H*-thiopyran-4-one (**8**),[38,39] 4-selenanone (**9**),[23] 1-phenyl-4-phosphorinanone (**10**),[40] 1-phenyl-4-phosphorinanone 1-oxide (**11**),[41] 1-phenyl-4-phosphorinanone 1-sulfide (**12**),[24] *cis*-3,5-diphenylcyclohexanone (**13**),[38,42] *cis*-2,6-diphenyl-4-piperidinone (**14**),[38,43] *r*-2,*cis*-6(e)-diphenyl-1(e)-*trans*-methyl-4-piperidinone (**15**),[38,43] *cis*-2,6-diphenyltetrahydro-4*H*-pyran-4-one (**16**),[38,44] *cis*-2,6-diphenyltetrahydro-4*H*-thiopyran-4-one (**17**),[38,45] *cis*-2,6-bis(4-methylphenyl)-4-selenanone (**18**),[46] *cis*-2,6-bis(4-methoxyphenyl)-4-selenanone (**19**),[46,47] *r*-1,-*trans*-2(e),6(e)-triphenyl-4-phosphorinanone (**20**),[32,48] *trans*-2,6-diphenyltetrahydro-4*H*-pyran-4-one (**22**),[38,44] *trans*-2,6-diphenyltetrahydro-4*H*-thiopyran-4-one (**23**),[38,49] *r*-1,*trans*-2(e),-*cis*-6(a)-triphenyl-4-phosphorinanone (**24**),[32,48] *r*-1,*trans*-2(e),*cis*-6(e)-triphenyl-4-phosphorinanone 1-oxide (**25**),[27,32] *r*-2,*cis*-6(e)-diphenyl-*trans*-3(e)-methyl-4-piperidinone (**26**),[38,43] *r*-2,*cis*-6-(e)-diphenyl-*trans*-3(e),5(e)-dimethyl-4-piperidinone (**27**),[38,43] *r*-2,*cis*-6(e)-bis(4-methoxyphenyl)-*trans*-3(e)-methyltetrahydro-4*H*-pyran-4-one (**28**),[50] *r*-2,*cis*-6(e)-bis(4-methoxyphenyl)-*trans*-3(e),5(e)-dimethyltetrahydro-4*H*-pyran-4-one (**29**),[50] *r*-2,*cis*-6-(e)-bis(4-methylphenyl)-*trans*-3(e),5(e)-dimethyltetrahydro-4*H*-pyran-4-one (**30**),[50] *r*-2,*cis*-6(e)-diphenyl-*trans*-3(e),5(e)-dimethyltetrahydro-4*H*-pyran-4-one (**31**),[38,51] *r*-2,*trans*-6(a)-diphenyl-*cis*-3(e)-methyltetrahydro-4*H*-thiopyran-4-one (**32**),[38] *r*-2,*cis*-6(e)-diphenyl-*trans*-3(e)-methyltetrahydro-4*H*-thiopyran-4-one (**33**),[38] *r*-1,*trans*-2(e),*cis*-6(e)-triphenyl-*cis*-3(e)-methyl-4-phosphorinanone (**34**),[52] *r*-1,*trans*-2(e),*cis*-6(e)-triphenyl-*cis*-3-(e)-methyl-4-phosphorinanone 1-oxide (**35**),[52] 2,2,6,6-tetramethyltetrahydro-4*H*-thiopyran-4-one (**38**),[38,53] 1-phenyl-2,2,6,6-tetramethyl-4-phosphorinanone (**39**),[27] 1-phenyl-2,2,6,6-tetramethyl-4-phosphorinanone 1-oxide (**40**),[54] 1-phenyl-2,2,6,6-tetramethyl-4-phosphorinanone 1-sulfide (**41**),[55] 3-benzyl-7-methyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**42**),[56] 7-benzyl-3-isopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**43**),[57] 3,7-dibenzyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**44**),[58,59] 7-benzyl-7-aza-3-oxabicyclo[3.3.1]nonan-9-one (**45**),[35] 7-benzyl-7-aza-3-thiabicyclo-[3.3.1]nonan-9-one (**46**),[60] and ethyl 3-benzyl-9-oxo-3-azabicyclo[3.3.1]nonan-7-carboxylate (**47**).[59]

The ^{17}O NMR spectra were recorded on a Varian XL-400 spectrometer equipped with a 10-mm, broad-band, variable-temperature probe operating at 54.2 MHz. All spectra were acquired at natural abundance ^{17}O at 70 °C in a 2:1 (v/v) mixture of acetonitrile (H_3CCN) and acetonitrile-d_3 (D_3CCN, 99 atom % D). The concentration of the ketones examined was 0.16 M, except for the selenium- and phosphorus-containing systems **18**, **19**, **20**, **24**, **25**, **34**, and **35**. The latter were examined as saturated solutions at 70 °C (due to poor solubility in the H_3CCN–D_3CCN mixture; the concentration is estimated to be about 0.05–0.10 M). Distilled, deionized water was used as an external reference in a 5-mm tube, placed concentrically within a sample tube of 10-mm o.d. containing 2:1 mixture of H_3CCN–D_3CCN. The oxygen of water was referenced to 0 ppm. The spectra of ketones were added to the spectrum of water using an add–subtract routine. The instrumental settings were as follows: spectral width 44 248 Hz, 1024 data points, 40-μs pulse width (PW: 90° at 50 μs), 1-ms acquisition delay, 0.012-s acquisition time and 1×10^5 to 4×10^6 scans. The spectra were recorded with sample spinning and deuterium lock.

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The signal-to-noise ratio was improved by applying a 20-Hz exponential broadening factor to the FID prior to Fourier transformation. The digital resolution was improved to ±1.4 Hz by zero filling to 16K data points prior to Fourier transformation. The reproducibility of the chemical shift data is estimated to be greater than ±1.0 ppm.

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Aminolysis of 2,2,2-Trichloro-1-arylethanones in Aprotic Solvents

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The kinetics of the reaction of the title substrate with various alkylamines was studied in *n*-heptane, dichloromethane, dioxane, tetrahydrofuran, and acetonitrile. The reaction was third-order in amine when the solvent was *n*-heptane or dichloromethane. In the other solvents a second-order dependence on $[RNH_2]$ was observed. The fourth-order rate constants for the reaction of *n*-butylamine with various 2,2,2-trichloro-1-arylethanones in dichloromethane yielded a ρ value of 3.0. In all solvents the observed rate constants decreased with a temperature increase. Two mechanistic possibilities were suggested, the first one in solvents of low donicity, involving a T^0 intermediate formed in a concerted process with the participation of an amine dimer; and the second one, a stepwise process in more basic solvents which takes place via a $T^{\pm}$ intermediate. Base-catalyzed collapse of the tetrahedral intermediates is the rate-determining step in both pathways.

Introduction

The 2,2,2-trichloro-1-arylethanones (1) are an interesting class of compounds which share the chemical behavior of both carboxylic acid derivatives and ketones. Like simple esters, for example, they have long been known to undergo basic hydrolysis to yield arylcarboxylic salts.[1] This observation has led to the use of these compounds as carboxylating agents in a number of scattered reports. Preparation of heterocyclic acids,[2] esters,[3] amides,[4] and sulfonamides[5] from substrates 1 have been reported. On the other hand, *O*-alkyl oximes are obtained when compounds 1 react with *O*-(pentafluorobenzyl)hydroxylamine,[6] in a behavior which is characteristic of ketones.

Table I. Third- and Fourth-Order Rate Constants for the Aminolysis of 2,2,2-Trichloro-1-phenylethanone (1a) in Various Solvents

solvent	order of the reaction in RNH_2	k^a	
		n-propylamine	*n*-decylamine
n-heptane	3	1.32	1.68
dichloromethane	3	0.84	1.40
1,4-dioxane	2	–	5.16
tetrahydrofuran	2	10.24	11.88
acetonitrile	2	17.50	27.70

[a] Fourth-order rate constants in heptane and dichloromethane in $M^{-3}\ s^{-1}$, third-order rate constants in dioxane, THF, and acetonitrile in $M^{-2}\ s^{-1}$.

We have studied the alcoholysis of these substrates and shown that it proceeds via intermediate hemiketals.[7] These hemiketals are stable in neutral or acidic solutions but collapse to the corresponding esters in the presence of basic catalysts. Hydrated species are intermediates in the basic hydrolysis of 1, but in this case the reaction occurs via two tetrahedral intermediates, a mono- and a dianionic species.[8] In all cases, however, basic catalysis is present. Since in neutral or acidic media a reversible equilibrium between the ketone and a tetrahedral intermediate is established, compounds 1 will only act as acylating agents in the presence of a basic catalyst. This fact may be exploited and these substrates utilized as selective benzoylating reagents under suitable conditions.[9] The formation of an amide by the reaction of 2,2,2-trichloro-1-phenylethanone with an amine in hexane was first reported nearly 40 years ago.[10] We have investigated in more detail the scope of this conversion, which is a smooth reaction generally proceeding in high yields.[9] We now present a detailed kinetic study of this conversion, which

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