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^{17}O NMR SPECTROSCOPY: ASSESSMENT OF STERIC PERTURBATION OF STRUCTURE IN ORGANIC COMPOUNDS

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CONTENTS

1. INTRODUCTION

The application of ^{17}O NMR spectroscopy to organic chemistry as a method for structure and conformation elucidation as well as a probe for assessing electronic distribution has begun to receive considerable attention.[1-3] The relatively limited number of earlier studies of ^{17}O NMR in organic chemistry could be attributed, in part, to the low natural abundance (0.037%) and to the quadrupolar properties of the ^{17}O nucleus.[1] The difficulties, broad lines and low signal to noise ratios (S/N), encountered previously have been greatly reduced by use of high field FT NMR spectrometers, by

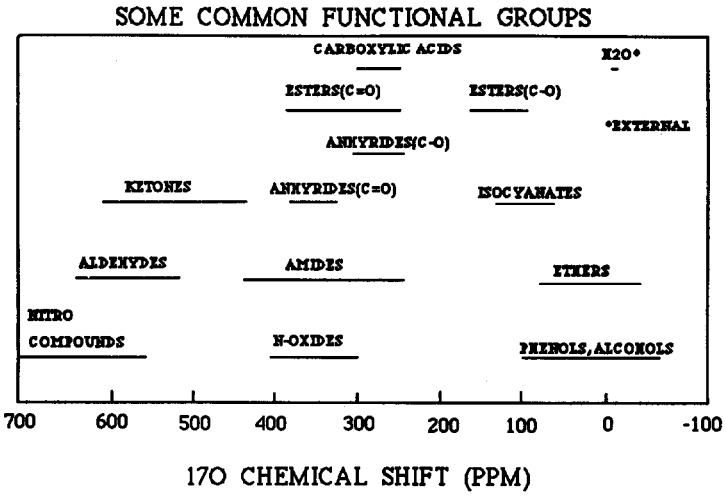


Fig. 1. ^{17}O chemical shift ranges for common functional groups.

carrying out measurements at higher temperatures at relatively low concentrations of solute and by use of low viscosity solvents.[1] Enrichment, when convenient, can also dramatically improve the ease of obtaining ^{17}O NMR spectra and may be accomplished by exchange or synthesis.[4]

The large chemical shift range and the widespread occurrence of oxygen in organic compounds makes ^{17}O an especially attractive nucleus for the study of structure and bonding. The NMR chemical shift ranges of some common functional groups are illustrated in Fig. 1. ^{17}O NMR chemical shifts have been found to be more sensitive to structural variation than those of ^{13}C and ^{15}N.[2] In addition to providing insights into molecular electronic distribution other important information is available from ^{17}O NMR data.

Heteronuclear NMR chemical shift data are dependent upon the paramagnetic (deshielding) σ_0^p and the diamagnetic (shielding) σ_0^d screening constants (Eqn. 1).[1,2,5] ^{17}O NMR chemical shifts are thought to be dependent essentially upon the paramagnetic term and are usually described by the Karplus–Pople[6] equation

$$\delta_0 = \sigma_0^p + \sigma_0^d \tag{1}$$

which is given as Eqn. 2 for an oxygen nucleus (O) bound to another nucleus (X):

$$\sigma_0^p = \frac{-e^2\hbar^2}{2m^2c^2\Delta E}(r^{-3})_{2p0}[\Sigma Q_{ox}] \tag{2}$$

ΔE is the 'average excitation energy,' often approximated by the wavelength of the 'lowest energy' maximum in the electronic spectra; $(r^{-3})_{2p0}$ is the inverse of the mean volume of $2p$ orbitals on oxygen and Q_{ox} is the charge density bond order matrix. These terms appear interrelated; however, a number of empirical correlations between ^{17}O NMR chemical shifts and other data taken to represent various terms in the Karplus–Pople expression have been reported.[1,2] For a detailed discussion of ^{17}O NMR chemical shift theory, the reader is referred to several reviews.[1-3]

1.1. *Scope*

Recent work from our laboratories has shown that ^{17}O NMR spectroscopy is a powerful method for detection and study of steric effects on molecular structure in organic systems. Our steric effect studies can be divided into two basic categories: systems in which steric interactions are characterized

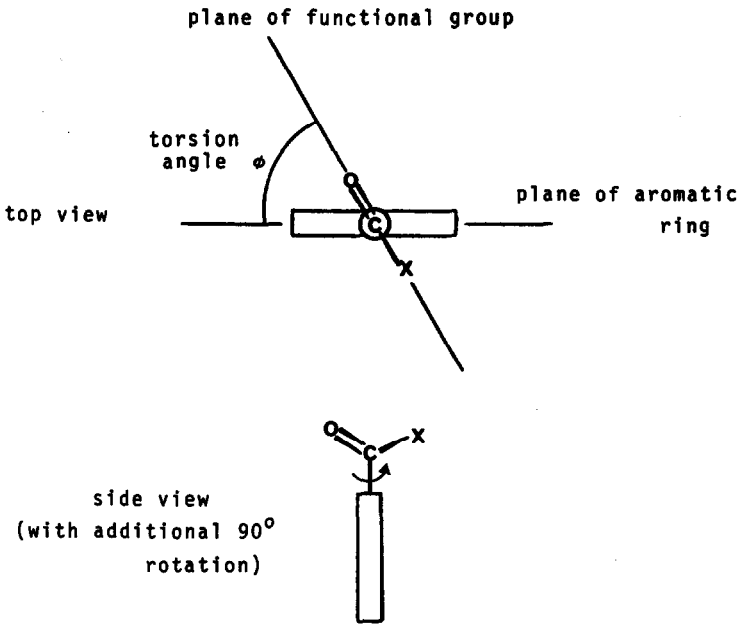


Fig. 2. Schematic representation of torsion angle for general carbonyl group.

by rotation of functional groups around single bonds to relieve van der Waals interactions and rigid systems in which steric interactions are partially accommodated by bond angle distortions.

Detailed treatments of electronic influences on ^{17}O NMR data have been extensively reviewed[1–3] and are beyond the scope of this report. An exhaustive review of the literature is not included; however, an attempt to include all pertinent references concerning steric effects and ^{17}O NMR chemical shifts appearing through 1987 has been made.

The relationships between ^{17}O NMR chemical shifts and the torsion angle between oxygen containing functional groups, carbonyl type oxygens, and aromatic rings in a number of systems are described in Section 2. These systems involve molecules in which van der Waals interactions are relieved by rotation around a single bond (Fig. 2). Isolated examples of the importance of steric effects on the ^{17}O NMR chemical shifts had been previously observed (*vide infra*); however, quantitative relationships between ^{17}O NMR chemical shifts and torsion angles have only been recently developed in our laboratories. The changes in chemical shift with torsion angle may be explained, in part, by changes in charge density on oxygen, which can be related to variations in the Q term of the Karplus–Pople equation[6] for the paramagnetic contribution to chemical shift results.

There are three conceivable consequences for the ^{17}O chemical shift of a functional group when torsion angle rotation occurs: (a) deshielding, (b) shielding and (c) no net change. The deshielding case is predicted when the rotated conformation leads to greater double bond character or reduced electron density on oxygen (an isolated carbonyl vs a conjugated carbonyl). The shielding case is expected for the situation in which the carbonyl assumes more single bond character or increased electron density on oxygen. No change in chemical shift occurring with rotation would be expected for the case in which one delocalizing system is exchanged for another of similar distribution. Examples of each of the three conceptual possibilities have been found.

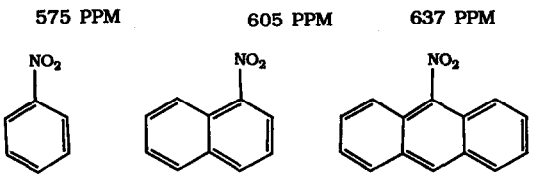
Section 3, on the other hand, concentrates on the ^{17}O NMR chemical shift studies of carbonyl groups of rigid, planar systems, work that was concurrent with our torsion angle studies. The effect of steric interactions on the ^{17}O NMR chemical shift data of N-oxides, as well as carbonyl functional

groups will be described. The ^{17}O NMR data for these sterically-hindered systems have been shown to correlate with in-plane bond angle distortions and repulsive van der Waals interactions (*vide infra*). Thus, the deshielding effects in these rigid planar systems are different fundamentally from those in which torsion angle changes occur.

2. TORSION ANGLE EFFECTS

2.1. *Carbonyl systems*

2.1.1. *Background.* In their pioneering compilation, Christ and Diehl observed that the ^{17}O NMR signal for *o*-nitrotoluene was downfield from that of *p*-nitrotoluene and attributed this deshielding shift to steric inhibition of resonance.[7] We noted that the nitro group signal for 3-methyl-4-nitropyridine-N-oxide **1** was 20 ppm downfield of that for 4-nitropyridine N-oxide **2** and the shift differences were discussed in terms of steric inhibition of resonance.[8] These observations led to the study of hindered aromatic nitro compounds in an effort to understand more fully the origin of these deshielding effects.[9]



The data for the aromatic nitro compounds yielded a quantitative relationship between the ^{17}O chemical shift of the nitro function and the torsional angle between the aromatic ring and the nitro groups.[9] Torsion angle values (from X-ray data) plotted vs ^{17}O chemical shifts resulted in a linear correlation for a series of seven nitro aromatic compounds. The solid state conformation apparently must also be the solution phase preference such that the torsion angle observed in the solid state is a remarkably good estimate of the average solution one. The symmetry of this system only allows dihedral angles (torsion angles) from 0° to 90°. At 0°, the charge density on conjugated nitro group oxygens is greater than on those of the 90° rotomer (non-conjugated nitro group). By simply considering charge density effects on chemical shift (Q term), the non-conjugated nitro group is expected to be deshielded relative to a conjugated one. Thus, the linear relationship observed is, in part, a consequence of change in charge density over this range of torsion angles.

The influence of electronic effects on the ^{17}O NMR chemical shifts of arylcarbonyl compounds have been extensively studied.[10–12] Sardella and Stothers[11] were the first to note the influence of steric factors on ^{17}O NMR chemical shifts of aryl ketones. Stothers and co-workers found that the ^{17}O NMR chemical shifts of *ortho*-substituted acetophenones were deshielded relative to unhindered derivatives and suggested steric inhibition of resonance as the origin of these shifts. In addition, examples of steric inhibition of conjugation on the ^{17}O NMR chemical shifts for *ortho*-substituted acetophenones and benzaldehydes had also been reported by Fiat *et al.*[12] However, quantitative relationships were not developed in these early reports.

2.1.2. *Aryl ketones and aldehydes.* The ^{17}O NMR chemical shifts of a number of hindered aryl ketones (**1–13**) in acetonitrile solution at 75°C have been reported[13,14] (Table 1). Qualitatively, the data showed that as the possibility for steric interactions between carbonyl group and alkyl groups of the acetophenones increased, the carbonyl ^{17}O NMR signal was deshielded; compare acetophenone (**1**), *o*-methylacetophenone (**2**), and 2,4,6-trimethylacetophenone (**7**) (Fig. 3). A similar trend was observed for the ^{17}O NMR chemical shifts for 1-acetylnaphthalene (**11**), 2-acetylnaphthalene (**12**), and 9-acetylanthracene (**13**). As *peri*-hydrogen interactions became important, substantial downfield shifts were observed; for (**12**) the chemical shift was δ 553 ppm; for (**11**) with

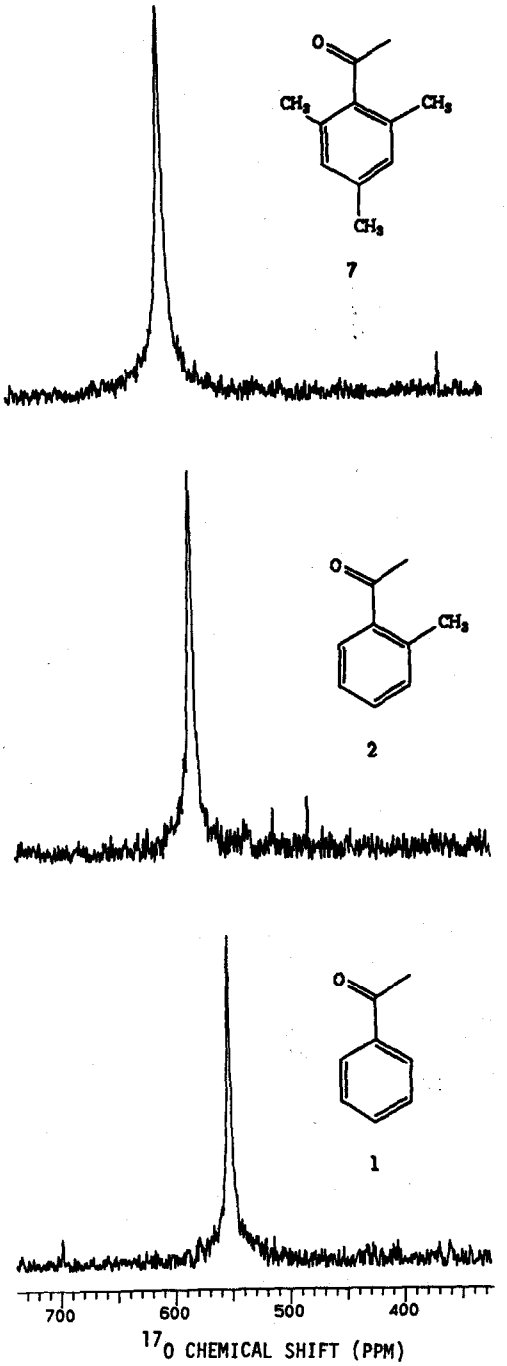


Fig. 3. Composite ^{17}O NMR spectra for acetophenones **1**, **2** and **7** in CH_3CN.

Table 1. ^{17}O chemical shift data (±1 ppm) and calculated torsion angles (deg) of aryl ketones

Compound No.	Name	Chemical Shift (ppm)	Torsion Angle deg. (±2°)
1	Acetophenone	552	1
2	o-Methylacetophenone	582	27
3	p-Methylacetophenone	546	1
4	2,4-Dimethylacetophenone	576	27
5	2,5-Dimethylacetophenone	582	26
6	3,4-Dimethylacetophenone	545	1
7	2,4,6-Trimethylacetophenone	601	57
8	2,4,5-Trimethylacetophenone	575	26
9	2,4,6-Tri-isopropylacetophenone	607	82
10	2,3,5,6-Tetramethylacetophenone	596	63
11	1-Acetylnaphthalene	585	38
12	2-Acetylnaphthalene	553	2
13	9-Acetylanthracene	613	69

one *peri*-hydrogen adjacent to the carbonyl group, the signal appears at δ 585 ppm and for (**13**) with two *peri*-hydrogens, the chemical shift was δ 613 ppm. As was observed for aromatic nitro compounds, the downfield shifts were consistent with steric inhibition of resonance; as the carbonyl group was rotated out of conjugation with the aromatic ring, greater double bond character was predicted for the carbon—oxygen bond. Most of the aryl ketones are liquids and consequently the possibilities for X-ray data are limited. Therefore, in order to estimate the torsion angles between the carbonyl group and the aromatic ring for the acetophenones (Table 1), a molecular mechanics approach was employed. A plot of the ^{17}O NMR chemical shift data vs the estimated torsion angles is shown in Fig. 4. The ^{17}O NMR data were plotted directly as obtained since very large chemical shift differences were noted and thus no correction for the small electronic effects of the alkyl groups was necessary.

The ^{17}O chemical shifts of hindered, electronically similar aromatic aldehydes (**14–20**) are listed in Table 2.[15] The general trend, similar to that described above for aryl ketones, of increasing chemical shift with increasing steric hindrance was evident. Methods previously reported for estimation of aldehyde torsion angles have suggested rotation of the carbonyl groups from the plane of the aromatic ring in hindered systems.[16a] In order to estimate aldehyde torsion angles, the slope obtained[13,14] for the aryl ketone chemical shift–torsion angle relationship (0.84 δ/angle in degrees) was used. Furthermore, a 0° torsion angle for benzaldehyde (**14**) and 4-methylbenzaldehyde (**15**) was assumed. The chemical shift difference between **14** or **15**, as appropriate, and the remaining aldehydes divided by the slope obtained from the ketone data[14] allowed the estimation of torsion

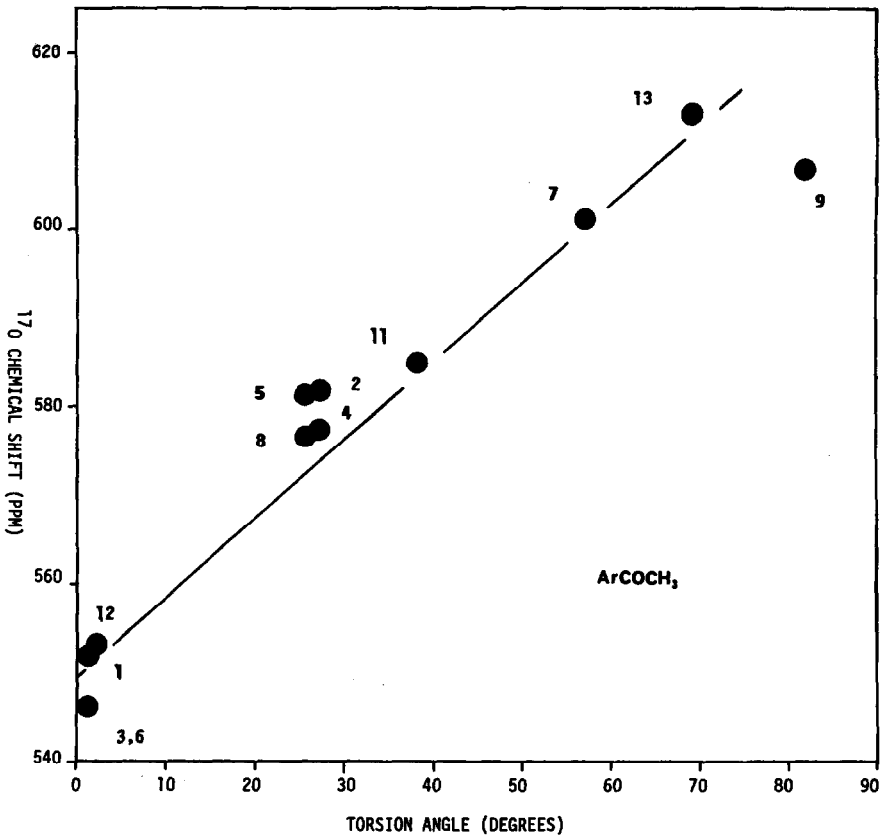
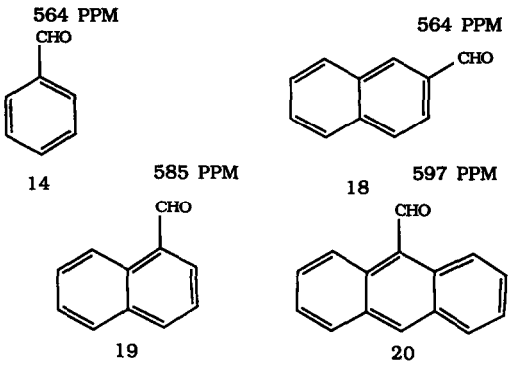


Fig. 4. Plot of ^{17}O chemical shift data vs calculated torsion angles for aryl methyl ketones.

Table 2. ^{17}O chemical shift data (± 1 ppm) and estimated torsion angles (deg) for aromatic aldehydes (ArCHO)

Compound No.	Ar	Chemical Shift (ppm)	Estimated Torsion Angle deg. (±4°)
14	Ph	564	0[a]
15	4-MeC_6H_4	557	0[a]
16	2-MeC_6H_4	575	21
17	2,4,6-$Me_3C_6H_2$	585	33
18	2-Naphthyl	564	0
19	1-Naphthyl	575	13
20	9-Anthryl	597	39

[a]Assumed value.



angles for **16–20** listed in Table 2. The torsion angle estimated for **16** by the ^{17}O NMR approach (21°) was identical with that obtained from UV data.[16b] The value obtained for **17** (33°) was in reasonable agreement with the literature value of 28° for a closely related analog, 2,6-dimethylbenzaldehyde,[16b] although different from the literature value[16b] (22°) obtained from UV data. The torsion angle for anthracene-9-carboxaldehyde (**20**) estimated by the ^{17}O NMR method (39°) was considerably higher than that found in the solid state (27°).[17] Simple molecular mechanics calculations for the aromatic aldehydes (**14–20**) were inconsistent.[15]

Tables 3 and 4 contain ^{17}O NMR data for a series of phenyl alkyl ketones (PhCOR) and methyl alkyl ketones (CH_3COR).[15] Only small changes in chemical shift were observed for these systems and therefore it was necessary to correct for electronic effects. The chemical shift data for the aryl ketones are influenced by both electronic effects and torsion angle rotation. The data for the aliphatic ketones were used to estimate the contribution of the electronic effects of alkyl groups on the aryl carbonyl chemical shift. Deviations from shifts predicted based on electronic factors were attributed to torsion angle rotation and the magnitude of the torsion angle was estimated by employing the slope determined previously[14,15] from torsion angle–^{17}O NMR chemical shift relationships for electronically similar aryl ketones.

Table 3. ^{17}O NMR chemical shift data (±1 ppm) for aryl alkyl ketones (PhCOR)

Compound No.	R	Chemical Shift (ppm)
21	Me	552
22	Et	540
23	nPr	543
24	i-Pr	535
25	t-Bu	565
26	Cyclopropyl	495
27	Cyclobutyl	530
28	Cyclopentyl	529
29	Cyclohexyl	538
30	Ph	552

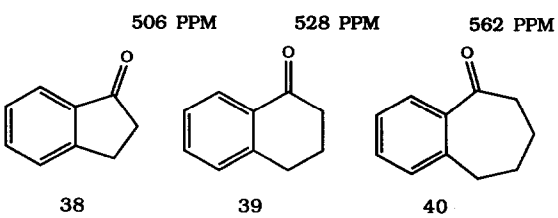
Table 4. ^{17}O NMR chemical shift data (±1 ppm) for methyl alkyl ketones (CH_3COR)

Compound No.	R	Chemical Shift (ppm)
31	Me	571
32	Et	558
33	n-Pr	563
34	i-Pr	557
35	t-Bu	560
36	Cyclopropyl	521
37	Cyclohexyl	560

The shielding trend exhibited for the phenyl alkyl ketones **21–24** was found to arise from the inductive effect of the alkyl group and/or any gamma or higher effects, rather than torsion angle rotation. Molecular mechanics calculations for **21–24** predicted little or no change in the torsion angles. The ^{17}O NMR datum for *t*-butyl phenyl ketone **25** showed significant deshielding due to large torsion angle rotation. The shift arising from torsion angle variation was estimated to be 24 ppm, allowing a prediction of a torsion angle of 29° for **25**. Dipole moment methodology estimated the torsion angle value to be 63°.[18] Molecular mechanics calculations yielded a value of 34°, in reasonable agreement with the ^{17}O NMR approach.

^{17}O NMR chemical shift data for several cycloalkyl phenyl ketones, **26–29**, were reported. The cyclobutyl and cyclopentyl phenyl ketones **27** and **28** exhibit similar chemical shifts which were slightly shielded compared with that of an acyclic branched-chained analog, isopropyl phenyl ketone **24**. The result for the cyclohexyl compound **31** was slightly deshielded compared with **24**. In contrast to **21–24**, the ^{17}O NMR resonance for phenyl cyclopropyl ketone **26** was substantially shielded, appearing at δ 495 ppm. This value corresponds to an upfield shift of 40 ppm when compared to the datum for its acyclic close-structural analog, isopropyl phenyl ketone **24**. This large shielding shift was viewed as an indication of substantial overlap between the carbonyl group and the cyclopropane ring. Such conjugation would be expected to increase the single bond character of the carbonyl group. A similar shielding result was found for methyl cyclopropyl ketone (**36**). The difference in the results[1] for methyl isopropyl ketone **34** and **36** is a 53 ppm shielding effect, which was greater than that of the analogous phenyl alkyl ketones **24** and **26**. The preferred conformation for maximum overlap of a cyclopropane ring and a conjugated π system has intrigued chemists for years.[19] It appears that ^{17}O NMR methodology should serve as a sensitive probe to test this point and explore its angular dependence.

The ^{17}O NMR spectral data for 1-indanone (**38**), 1-tetralone (**39**), and 1-benzosuberone (**40**) were reported and the chemical shifts showed significant sensitivity to ring size. The result of fusion



38 39 40

of a benzene ring on the cyclic ketones is an upfield shift compared to their acyclic counterparts. Using the previously described approach, ^{17}O NMR chemical shift values for cyclopentanone (δ 543 ppm), cyclohexanone (δ 558 ppm) and cycloheptanone (δ 566 ppm),[1] were employed to assess the electronic effects on ^{17}O NMR chemical shift of the different aliphatic rings. The difference values for the chemical shifts were used to estimate the torsion angles, based on the assumption that the torsion angle for 1-indanone **38** was zero degrees. This ^{17}O NMR approach for alkyl phenyl ketones yielded a torsion angle for **39** of 8° and for **40** of 39°. Molecular mechanics calculations yielded torsion angle values of 0°, 2°, and 34° for **38**, **39**, and **40**, respectively, which were in reasonable agreement with the ^{17}O NMR results. Earlier UV studies had predicted the torsion angle for **38** and **39** to be 0° and that for **40** to be 37°.[18]

The results from the aryl carbonyl systems showed that, in homologous series of compounds for which the deshielding shifts were relatively small, the contribution to ^{17}O NMR chemical shifts from steric factors could be deduced. Frequently, steric hindrance leads to torsion angle rotation, which can be estimated by using the previously developed ^{17}O NMR chemical shift correlations. This ^{17}O NMR method allows the facile estimation of the solution phase structure for a variety of carbonyl compounds.

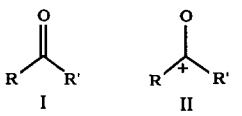
2.1.3. 1,2-*Diketones*. A recent study demonstrated the relationship of the inter-carbonyl dihedral angle in a series of 1,2-diketones to their ^{17}O NMR chemical shift.[20] The data for the 1,2-diketones **41–47** are shown in Table 5. Cerfontain and co-workers found that as the dihedral angle increased toward 90°, corresponding to a reduction of overlap between the two carbonyl groups, the chemical shift moved upfield and that on going from a dihedral angle of 90° to 180° a downfield shift was observed, yielding an approximate cosine relationship. The chemical shift change for the diketones as a function of dihedral angle (0°–90°) is in the opposite direction of that noted for aryl carbonyl compounds discussed above.

The 1,2-diketone chemical shifts paralleled the MNDO calculated π-electron density at oxygen (Q_0^π) for glyoxal which was used as a model; π-electron density at oxygen increased as the overlap between the two π systems decreased. The mean excitation energy, ΔE^{-1}, for the diketones was also found to vary with dihedral angle and a linear relationship was noted for the ^{17}O NMR chemical shift and the product of $\Delta E^{-1} \cdot Q_0^\pi$. The observed upfield shift was attributed to an expansion of the $2p$ orbitals, resulting from the increase in Q_0^π, which would cause a reduction in the r^{-3} term of the Pople–Karplus equation and result in a reduction in the magnitude of the paramagnetic term (σ_N^P). The change in ΔE^{-1} also affects σ_N^P in the same direction.

Table 5. Reported ^{17}O chemical shift values (ppm) for 1,2-diketones[20]

Compound No.	Name	Chemical Shift (ppm)
41	3,3,5,5-tetramethylcyclopentane-1,2-dione	573
42	homoadamantane-4,5-dione	572
43	3,3,6,6-tetramethylcyclohexane-1,2-dione	564
44	3,3,7,7-tetramethylcycloheptane-1,2-dione	557
45	2,2,5,5-tetramethylhexane-3,4-dione	558
46	butane-2,3-dione	569
47	cyclododecane-1,2-dione	576

The opposite direction of the chemical shift change on rotation of a carbonyl group from coplanarity for the diketones and the aryl ketones requires additional comment. An interpretation is that for coplanar aryl carbonyl compounds the electron density on the carbonyl oxygen is greater (larger r^{-3}) because of participation of aryl ring electron density. When the dihedral angle is increased in the aryl ketone system, the carbonyl group becomes more like an isolated carbonyl and assumes more double bond character (lower charge density on oxygen). In contrast to aryl ketones, for the 1,2-diketones the planar conformation more closely resembles an isolated carbonyl. Alternatively the explanation can be expressed in a valence-bond representation for carbonyls by noting that the canonical form I is favored in the planar conformer for the diketone and in the rotated conformer for the aryl ketone, whereas form II is expected to be favored in the rotated conformer



of the diketone and the planar conformer of the aryl ketone. Additional examples of an upfield shift of a carbonyl group signal on rotation from conjugation are described in the section on N-arylacetamides and anhydrides.

2.1.4. *Carboxylic acids.* The ^{17}O NMR chemical shift data for representative aliphatic[21] and aromatic carboxylic acids[22] have been shown to be sensitive to electronic effects of substituents. Table 6 contains the ^{17}O NMR chemical shift values for a series of hindered but electronically similar aromatic carboxylic acids **48–56**. It has been previously noted for carboxylic acids[21] that only one ^{17}O NMR signal for this functional group could be detected. The equivalence of the two oxygens was attributed to fast proton exchange[21] in dimeric or higher aggregates. Qualitatively for **48–56**, it was clear that as steric hindrance to coplanarity of the carboxylic function and the aromatic ring was increased, the magnitude of the carboxyl chemical shift increased. The direction of the shift

Table 6. ^{17}O chemical shift data (± 1 ppm) and torsion angles (deg) for aromatic carboxylic acids

Compound No.	Ar-CO_2H	Chemical Shift	Torsion Angle deg.[a]
48	Ph	250.5	2
49	4-MeC_6H_4	249	2
50	2-MeC_6H_4	265	29
51	2,3-$Me_2C_6H_3$	269	29
52	2,6-$Me_2C_6H_3$	280	55
53	2,4,6-$Me_3C_6H_2$	280	55
54	1-Naphthyl	267	35
55	2-Naphthyl	251.5	2
56	9-Anthryl	287	67

[a]Both oxygens. [b]Calculated by molecular mechanics method (MM2).

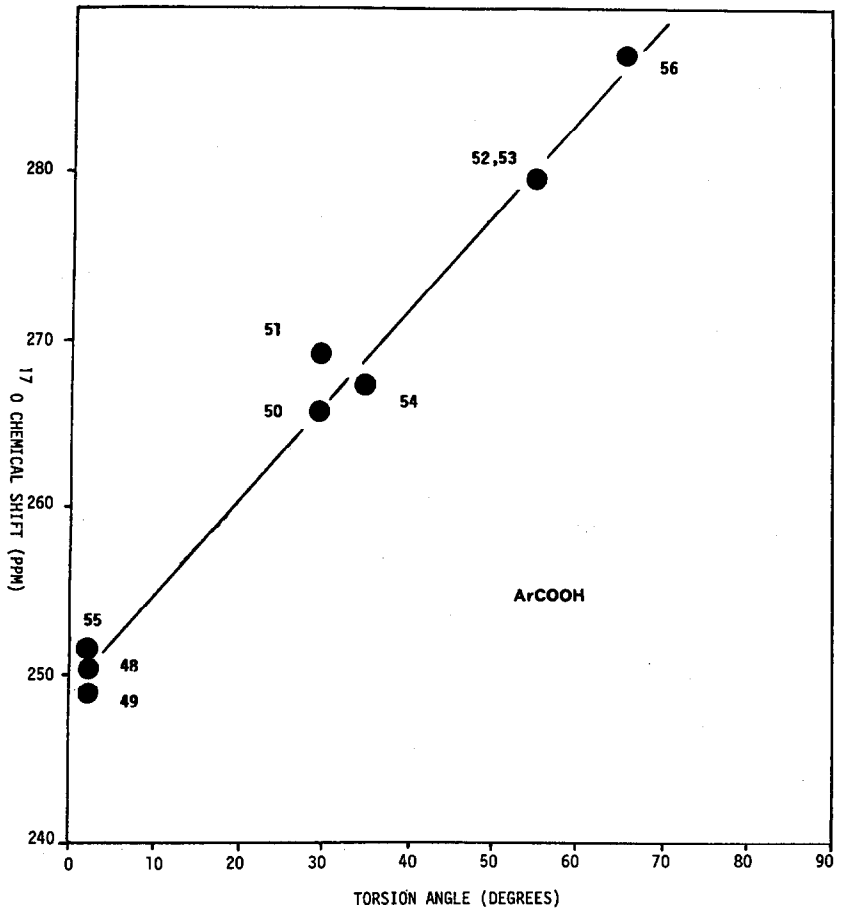


Fig. 5. Plot of ^{17}O chemical shift data vs calculated torsion angles of aryl carboxylic acids.

was consistent with the rotation of the carboxyl group from the plane of the aromatic ring. A clear correlation between estimated torsion angle and ^{17}O NMR chemical shift is reflected in Fig. 5. Torsion angle data appear in the literature for two compounds included in the study. The torsion angle estimated by the MM2 method for **52** (55°) was in good agreement with the X-ray value[23] (51.5°) and the value (50.7°) estimated by ^{13}C NMR methods.[24] The calculated value for **51** (29°) did not agree with the X-ray data[23] (10°) but was reasonably consistent with the value obtained from a ^{13}C NMR approach (25°).[24]

2.1.5. *Carboxylic esters.* The ^{17}O NMR chemical shift data for variously hindered aromatic methyl esters are listed in Table 7.[14] In carlier studies, the ^{17}O NMR chemical shifts of esters have been shown to be influenced by both substituents attached to the carbonyl carbon[22,25] and to the single-bonded oxygen.[26,27] Variation of the size of the alkyl group attached to single-bonded oxygen significantly influences the chemical shift of the single-bonded oxygen, and although less pronounced, a readily detected effect is observed on the carbonyl oxygen resonance.[27] However, in the series listed in Table 7 chemical shift differences arising from electronic effects were small and were negligible.

The signals for both the carbonyl oxygen and the single-bonded oxygen of the aromatic esters were both substantially deshielded in compounds which have greater steric interactions (Fig. 6).

Table 7. ^{17}O chemical shift data (±1 ppm) and calculated torsion angles (deg) for aromatic esters

Compound No.	Ar-CO_2Me	δ(C=O)	Chemical Shifts δ(-O-)	Torsion Angle deg. (±2°)
57	Ph	340	128	2
58	4-MeC_6H_4	339	127	2
59	2-MeC_6H_4	359	138.5	29
60	2,3-$Me_2C_6H_3$	363	141	29
61	2,6-$Me_2C_6H_3$	377	150	54
62	2,4,6-$Me_3C_6H_2$	376	149	54
63	1-Naphthyl	361	139	33
64	2-Naphthyl	341	129	2
65	9-Anthryl	385	154	67
66	2,4,6-t-BuC_6H_2	392	162	76

Consistent with previous findings, rotation of the functional group from the plane of the aromatic ring was expected to increase the double-bond character of both oxygen atoms and result in deshielding of both oxygen NMR signals. Molecular mechanics (MM2) calculations were carried out on the aromatic esters with the OCH_3 group in the *s*-Z conformation. The calculated torsion angles for **57** and **62** (2 and 54°, respectively) are in reasonable agreement with the torsion angles predicted by dipole moment studies[28] (0° and 47°). A plot of the calculated torsion angles vs the chemical shift for both the double- and single-bonded oxygen is shown in Fig. 7; excellent correlations were obtained for data from both oxygen resonances. The slope from linear regression analysis of the single-bonded oxygen results is approximately one-half that of the slope for the carbonyl oxygen data; the average value of which was approximately the value noted for carboxylic acids. This is in agreement with the concept that the carboxylic acid data are a consequence of proton exchange between the oxygen atoms.

2.1.6. *Carboxylic amides.* Extensive studies on simple amides and peptides have appeared and the role of solvent, electronic factors and hydrogen bonding on their ^{17}O NMR chemical shifts has been reported.[29–33] The ^{17}O NMR chemical shift data reported for electronically similar hindered aromatic amides **67–73** are listed in Table 8.[14] The chemical shift range for the amides is substantially compressed compared to that of the ketone and ester carbonyl data described previously. The reduction in range was attributed to the fact that for the least hindered amide, benzamide **67**, the amide–aromatic ring torsion angle was not zero, as in the case for acetophenone and methyl benzoate, but was 26° as determined by X-ray analysis (MM2 value 28°).[34] In addition, the quality of the correlation for the simple amides (Fig. 8) was not as good as that obtained for ketones and esters. A linear relationship is depicted in Fig. 8, even though the data for the simple amides ($ArCONH_2$) appeared to exhibit scatter or curvature which may be attributed to hydrogen-bonding interactions and/or changes in the partial pyramidal structure of the amides.

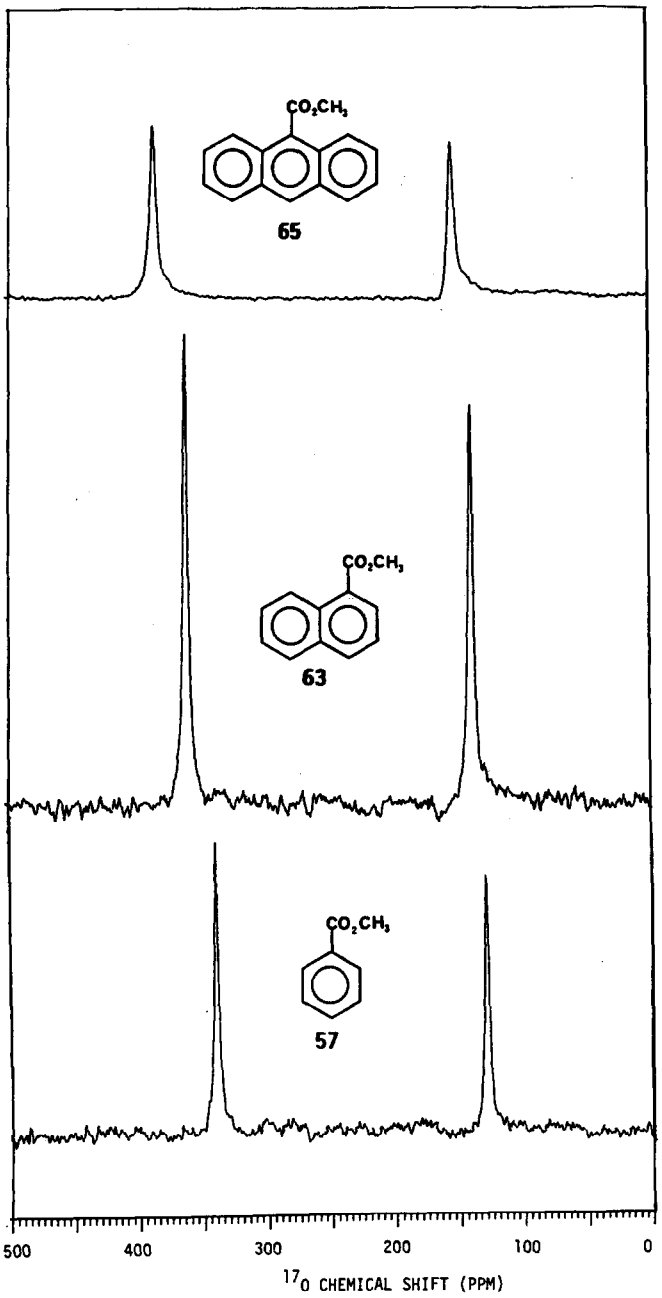


Fig. 6. Representative ^{17}O NMR spectra for aryl esters.

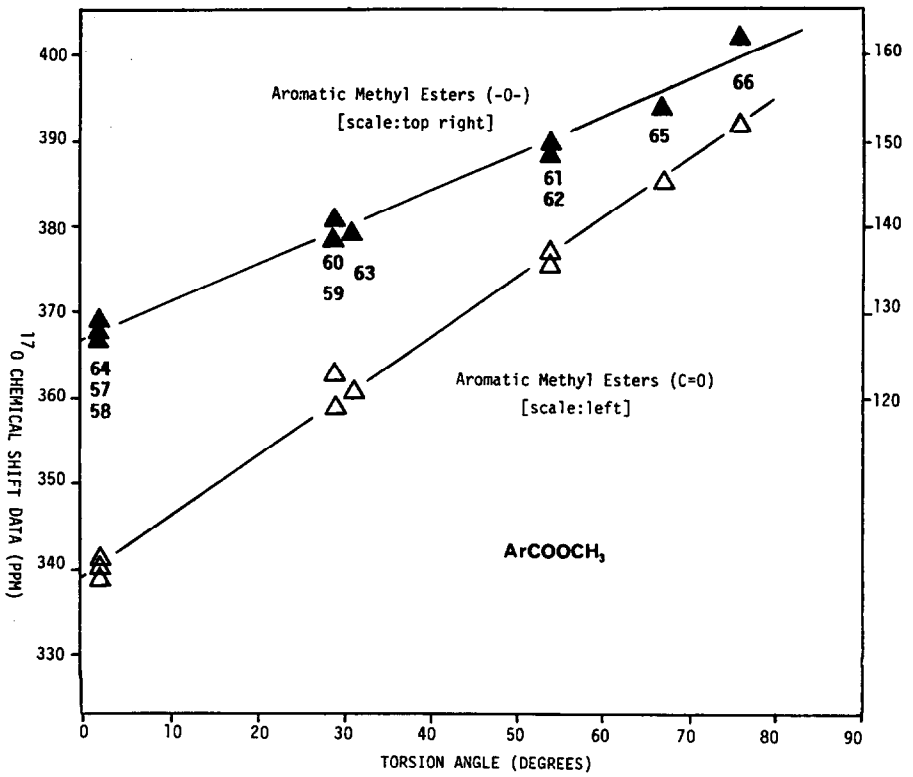
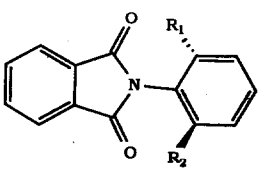


Fig. 7. Plots of ^{17}O chemical shift data vs calculated torsion angles for aromatic methyl esters.

To test for the probable complications arising from hydrogen-bonding, a limited number of N,N-dimethylcarboxamides **74–76** (Table 8) were examined. The enhanced steric interactions arising from the N,N-dimethyl group substantially contributed to the torsion angle in this system as noted in Table 8. The predicted (MM2) torsion angle for N,N-dimethylbenzamide **74** was 62°. Because of the additional steric hindrance due to N-substitution, the range of torsion angles was greatly reduced and the chemical shift range was expected to be correspondingly smaller. Although the number of compounds studied was limited, the slope of the line for the N,N-dimethylamide data was clearly reduced from that of the corresponding unsubstituted amides.

2.1.7. N-*Phenylphthalimides.* A study of steric interactions in hindered N-substituted imides (**77a–c**) found an interesting torsion angle relationship between the two ring systems of N-aryl phthalimides[35] and the carbonyl oxygen chemical shifts. The N-aryl phthalimide system differs from those previously studied since in this case the carbonyl functional group is locked in a specific



77a R1 = R2 = H
78b R1 = H, R2 = ME
79c R1 = R2 = ME

Table 8. ^{17}O chemical shift data (±1 ppm) and calculated torsion angles (deg) for aromatic amides

Compound No.	Ar-$CONH_2$	Chemical Shift	Torsion Angele deg. (±1°)
67	Ph	329	28
68	4-MeC_6H_4	327	28
69	2-MeC_6H_4	350	44
70	2,6-$Me_2C_6H_3$	353	60
71	1-Naphthyl	359	51
72	2-Naphthyl	331	27
73	9-Anthryl	365	71
	AR-$CONMe_2$		
74	Ph	348	62
75	1-Naphthyl	352	71
76	9-Anthryl	357	78

geometry and the conjugated aryl ring is allowed to rotate to relieve van der Waals interactions. Molecular mechanics calculations for **77a–c** predicted dihedral angles (torsion angles) for the aryl ring with the phthalimide system of 50°, 64° and 75°, respectively. The X-ray structure of **77a** showed a dihedral angle of 56° in reasonable agreement with the calculations. A plot of ^{17}O NMR chemical shift vs calculated dihedral angle for **77a–c** is shown in Fig. 9. The reasonable correlation seen suggests that the ^{17}O NMR shifts for the N-aryl phthalimides arise primarily from reduction of van der Waals repulsions by torsion angle rotation (loss of overlap) of the N-aryl group. However, the ^{17}O NMR data showed some sensitivity to electronic effects. It was also concluded that minimization of van der Waals repulsion was not complete and that some conjugation between the two systems was retained at the expense of complete minimization of van der Waals interactions. The ^{17}O NMR results were consistent with the IR[36] and ^{13}C NMR[37] results; however, they were not in agreement with dipole moment studies[38] which had suggested that the two rings of N-aryl phthalimides were coplanar.

2.1.8. N-*Aryl acetamides.* A study of N-aryl acetamides **78–82** (Table 9) showed that introduction of steric hindrance causes shielding of the carbonyl ^{17}O NMR chemical shifts.[39] This result, exactly the opposite of that obtained for the other hindered aryl carbonyl systems discussed above, for which steric hindrance caused deshielding shifts is consistent with the results found for 1,2-diketones. Molecular mechanics calculations for the N-aryl acetamides showed a large change of torsion angle with substituents (Table 9) which paralleled their ^{17}O NMR chemical shift values. A quantitative torsion angle–^{17}O NMR chemical shift relationship was also developed (Fig. 10) for the N-aryl acetamide data.

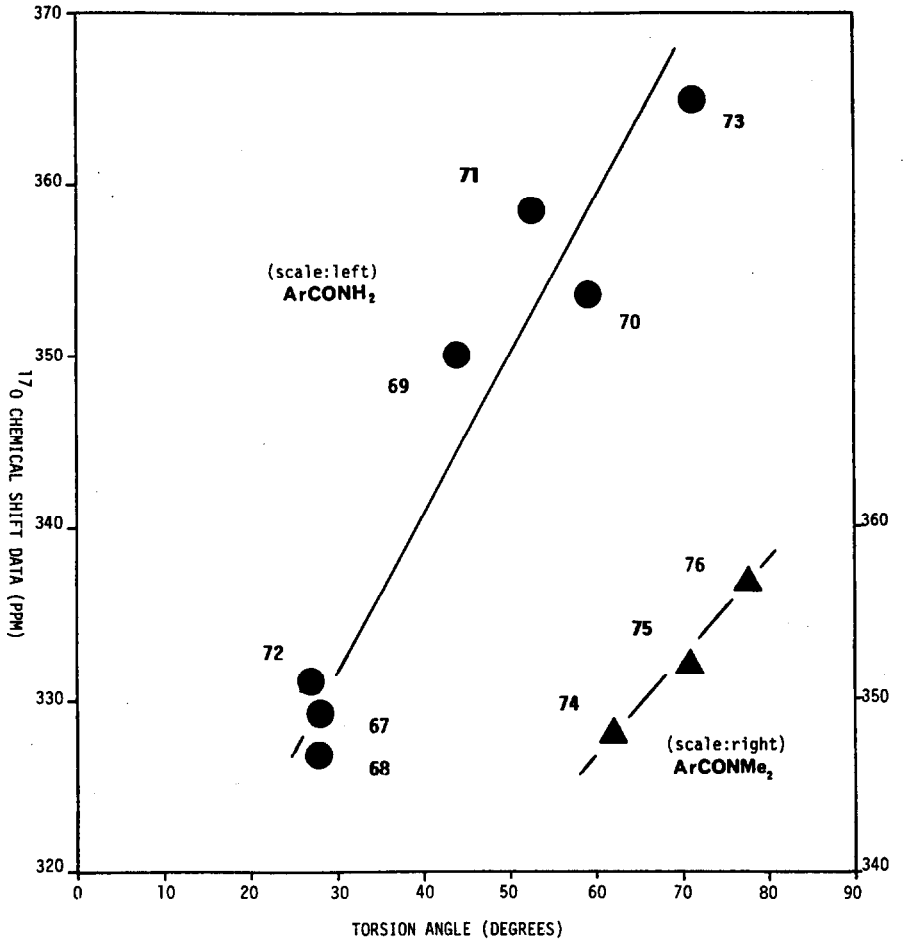


Fig. 8. Plots of ^{17}O chemical shift data vs calculated torsion angles for aryl amides.

Table 9. ^{17}O chemical shift data (±1 ppm) and calculated torsion angles (deg) for substituted acetanilides

Compound No.	ArNHCOME	Torsion Angle deg. (±2°)	δ(C=O)
78	Ph	21	355.3
79	2-MeC_6H_4	34	349.0
80	2,6-$Me_2C_6H_3$	58	343.0
81	1-naphthyl	38	350.5
82	2-naphthyl	19	358.1

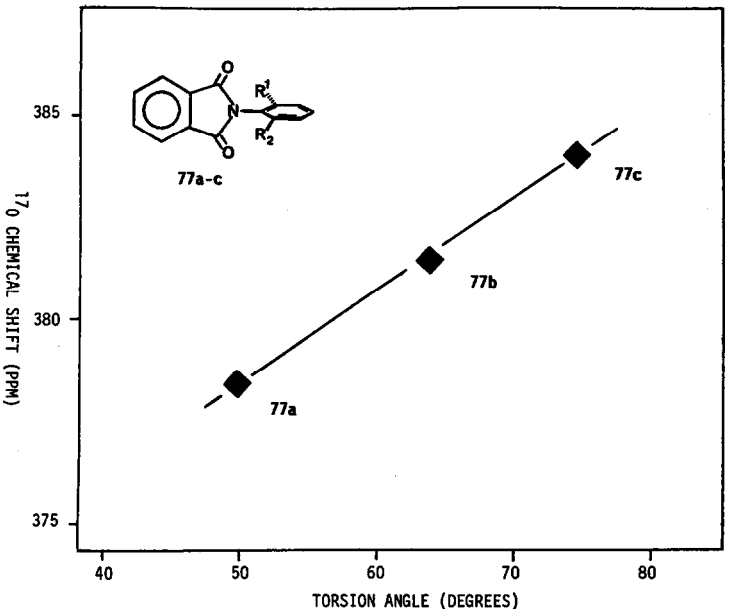


Fig. 9. Plot of ^{17}O chemical shift data vs calculated torsion angle for N-aryl phthalimides.

Unlike the other aryl carbonyl systems, increasing steric hindrance caused a decrease in chemical shift of the carbonyl ^{17}O NMR signal for the N-aryl acetamides. This upfield shift was explained in terms of the varying importance of the canonical forms **III** and **IV** as a function of substituents *ortho* to the NHAc group. In the absence of sterically large *ortho* substituents, contributions from **III** were considered important. It is interesting to note the similarity in structure between **III** and

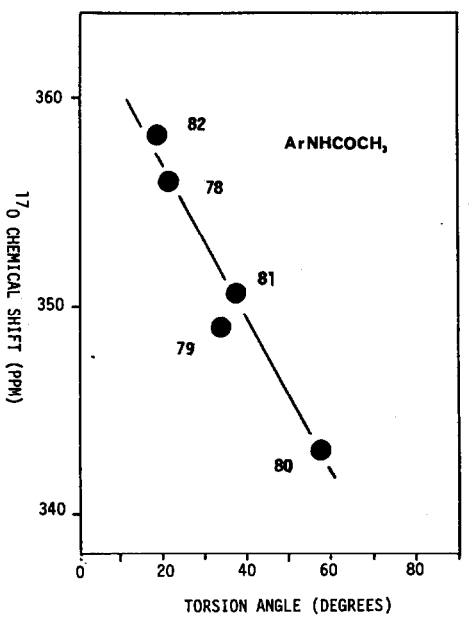
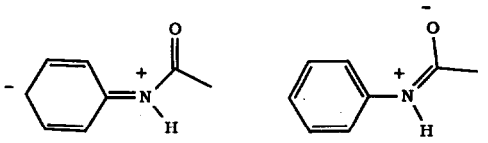


Fig. 10. Plot of ^{17}O chemical shift data vs calculated torsion angle for aryl acetamides.



III IV

that of the 1,2-diketones. *ortho* Substituents would be expected to reduce the overlap between the amide function and the aromatic ring because of torsional rotation to reduce van der Waals interactions. A decrease in the contribution of **III** and concomitantly an increase in the importance of **IV** was expected to result from such an interaction. On increasing the importance of the contribution from **IV**, the chemical shift of the amide carbonyl was expected to decrease. The observed upfield shift is also consistent with a charge density argument since as the torsion angle increases, the structure approaches that of an isolated amide function (*cf* N-methylacetamide), the chemical shift of which is upfield of that of conjugated N-aryl acetamides. The results and the explanation for the change of chemical shift for the N-arylacetamides with increasing steric interaction are consistent with those noted for the 1,2-diketones.[20]

Additional support for the argument developed to explain the upfield shift observed for the hindered N-arylacetamides is available from the chemical shift value for N-methyl-N-phenylacetamide **83**, δ 350 ppm. Molecular mechanics calculations predicted a large torsion angle (62°) for **83**. Increased steric hindrance by introduction of an N-methyl group was expected to cause an increased torsion angle and consequently increased contribution of canonical form **IV**. The ^{17}O NMR chemical shift of **83** was upfield of **77** by 6 ppm, which is consistent with this argument.

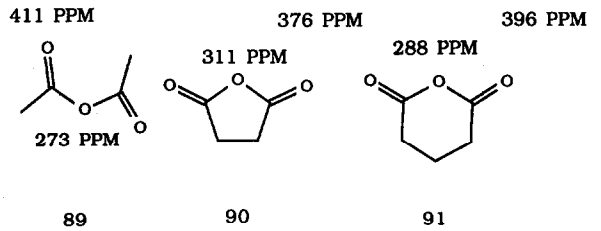
2.1.9. *Aryl acetates.* A series of aryl acetates **84–88** was studied (Table 10) and small changes in their ^{17}O NMR chemical shifts were noted with increasing steric hindrance.[39] The insensitivity of carbonyl chemical shift for these compounds was partially attributed to the large calculated (MM2) torsion angles and the relatively small changes in torsion angle predicted with increasing steric hindrance. Further complicating the interpretation of the results for the aryl acetates is the competition between overlap of the aromatic ring orbitals and one or the other of the lone pair orbitals of the single bonded oxygen and maintenance of overlap of the carbonyl orbitals and the other lone pair orbital of the single bonded oxygen. The interaction of these two independent overlap networks appears to maintain the electron density on the carbonyl oxygen essentially constant as steric hindrance is altered. The chemical shift range for the singly bonded oxygen is substantially less than was noted for similarly substituted anisoles (*vide infra*), which is consistent with the cross-conjugation

Table 10. ^{17}O chemical shift data (±1 ppm) and calculated torsion angles (deg) for substituted phenylacetates

Compound No.	ArOCOMe	Torsion Angle deg. (±2°)	δ(C=O)	δ (-O-)
84	Ph	64	370.0	201.3
85	2-MeC_6H_4	68	371.0	199.6
86	2,6-Me$_2C_6H_3$	73	371.0	196.6
87	1-naphthyl	76	371.6	195.3
88	2-naphthyl	66	371.3	201.3

argument. The aryl acetates appear to be an example of the case in which no change in ^{17}O NMR chemical shift would be noted on change of torsion angle.

2.1.10. *Anhydrides.* An earlier study of several different series of anhydrides[40] found that the chemical shifts for both types of anhydride oxygens were sensitive to structural changes as illustrated by **89**, **90** and **91**. The single-bonded oxygen was deshielded in the cyclic structures **90** and **91** compared to the one in acetic anhydride **89**, which corresponds to greater π overlap with the carbonyl system in the cyclic structures. In contrast, the chemical shift data for the carbonyl oxygens were shielded in the cyclic systems on comparison with those of acetic anhydride which reflects



89 90 91

greater single bond character for these carbonyl groups. The benzoic anhydride data (δ 398 and δ 242 ppm) suggested that delocalization influences both types of oxygens in the same manner; both are shielded compared to acetic anhydride. The trend in chemical shifts for **89–91** parallels their O=C—O—C dihedral angle. The planar systems **90** and **91** are shielded relative to the rotated acetic anhydride **89**; this system provides a case analogous to the 1,2-diketones[20] and the N-aryl acetamides.[39]

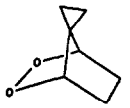
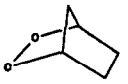
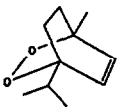
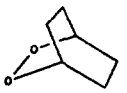
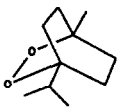
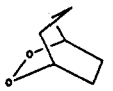
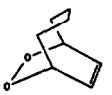
2.2. *Miscellaneous systems*

2.2.1. *Cyclic peroxides.* A ^{17}O NMR study for several series of cyclic peroxides (**92–101**) was reported by Salomon, Clennan *et al.*[41] The chemical shifts of the cyclic peroxides were shown to be insensitive to solvent changes. Chemical shift data for these compounds are listed in Table 11. The chemical shift range for the cyclic peroxides was rather large, from δ 232 to 318 ppm. Unlike alkyl ethers,[42] no apparent correlation between ^{17}O NMR chemical shifts and ionization potentials, relatable to the Q term of the Karplus–Pople expression, was established for the cyclic peroxides.[41] This case seems to be more complex since two ionization potentials (η_0- and σ_0-) are associated with the lone-pair of electrons of the peroxide oxygens.[41] No straightforward relationship between atomic charge and ^{17}O NMR chemical shifts for the cyclic peroxides was apparent. It was suggested that conformational changes contributed to the variation in ^{17}O NMR chemical shifts. The C—O—O—C dihedral angles for the compounds listed in Table 11 varied from 0° to approximately 90°. No quantitative relationship between dihedral angle and ^{17}O NMR chemical shift was found. However, the general trend seems to indicate that as the dihedral angle increases, the chemical shift decreases. The large chemical shift of **92–94** was attributed to the interaction of neighboring lone-pair electrons arising from their co-planar arrangement. This interaction, presumably, results in an increase in the r^{-3} term which would be expected to result in a downfield position of the oxygen signal relative to those of the other cyclic peroxides. It seems likely that changes in the C—O—O—C dihedral angle play a role in determining the chemical shifts of cyclic peroxides. However, the chemical shift values for these systems apparently result from the interaction of several factors which cannot be readily resolved at this time.

2.3. *Summary*

The magnitude of ^{17}O NMR chemical shift changes with torsion angle can be very large for a variety of functional groups—up to 60 ppm or more—and thereby provides a sensitive and direct

Table 11. Reported ^{17}O chemical shift data (ppm) and dihedral angle (deg) for cyclic peroxides[41]

Compound No.	Compound	Chemical Shift	Dihedral Angle
92		310	0
93		303	0
94		283	0
95		250	21
96		263	32
97		280	50
98		259	51
99		247	54
100		232	65
101		254	88

method of detection of the consequences of steric interactions. It is clear from the studies cited that ^{17}O NMR spectroscopy is an extremely sensitive and valuable method for assessing solution phase geometries for molecules containing any one of a number of different functional groups. Table 12 summarizes the quantitative relationships between ^{17}O NMR chemical shift and torsion angles which have been developed to date. These results coupled with ^{17}O NMR chemical shift measurements should allow for the rapid estimation of torsion angles for a wide variety of compounds.

The three possible consequences of ^{17}O NMR chemical shift for torsion angle rotation have been observed. It was apparent that the direction of the shift depends, in part, upon the charge density change at oxygen upon rotation of the functional group.[20] Previously, for systems under discussion here it was suggested that repulsive van der Waals interactions were minimized by rotation of the functional group from the plane of conjugation.[14] As expected, molecular mechanics estimated total steric energies of a number of different compounds did not correlate with ^{17}O NMR chemical

Table 12. Correlations of ^{17}O chemical shift data with calculated torsion angles (MM2)

series	slope (δ/angle deg)[a]	r[b]	intercept	n[c]
ketones (C=O)	0.84 ± 0.14	0.979	553 ± 6	10
esters (C=O)	0.70 ± 0.04[a]	0.997	339 ± 2	10
esters (-O-)	0.43 ± 0.03	0.992	127 ± 2	10
acids	0.56 ± 0.05	0.994	249 ± 2	9
amides (C=O)	0.84 ± 0.5	0.942	308 ± 16	7
N,N-dimethylamides (C=O)	0.6[d]	0.991	313[d]	3
nitro compounds (NO_2)	0.76 ± 0.14	0.987	574 ± 16	7

a) Error limits shown are 95% confidence limits

b) Correlation coefficient

c) Number of data points

d) Limited number of data points

shift.[3] In an effort to clarify the nature of the steric interaction, we have estimated repulsive van der Waals energies by a molecular mechanics approach. On comparing the difference in the calculated van der Waals energy for isomeric hindered and non-hindered ketones and esters, little or no differences were found. For example, the naphthalene series α and β isomers were contrasted, for the *ortho* substituted compounds *para* isomers were used, for the 2,6-disubstituted systems their 3,5-disubstituted isomers were used and for the 9-anthryl compounds the 2-anthryl isomers were used. The result suggests that for these systems repulsive van der Waals interactions have been essentially minimized by torsion angle rotation. Nevertheless, it was noted above that the ^{17}O NMR chemical shift data for the same set of isomeric hindered and non-hindered ketones, esters and N-aryl acetamides exhibited large differences in their chemical shift values. A plot (Fig. 11) of the estimated repulsive van der Waals energies for a wide range of structurally different aryl ketones, esters and N-aryl acetamides versus the ^{17}O NMR chemical shift difference values (δ hindered isomer-δ unhindered isomer) in their chemical shifts shows a large variation of chemical shift, yet all systems show essentially zero net repulsive van der Waals steric energies. Despite the fact that there is considerable error in this approximation of repulsive van der Waals energies, this result provides strong support for the minimization of repulsive steric interactions in these series. Consequently, the chemical shift changes with torsion angle should be attributed, in large part, to changes in charge density at the oxygen atom arising, indirectly, from minimization of van der Waals interactions. The ΔE^{-1}-torsion angle relationship is clearly important since a linear relationship between the product $\Delta E^{-1} \cdot Q$ and ^{17}O NMR chemical shifts for 1,2-diketones was found.[20] The results from these conformationally rotatable systems indicate a distinctly different origin for the shift differences than that observed for rigid systems[35,43,44] (Section 3) where deshielding shifts are shown to correlate directly with the magnitude of the repulsive van der Waals interactions.

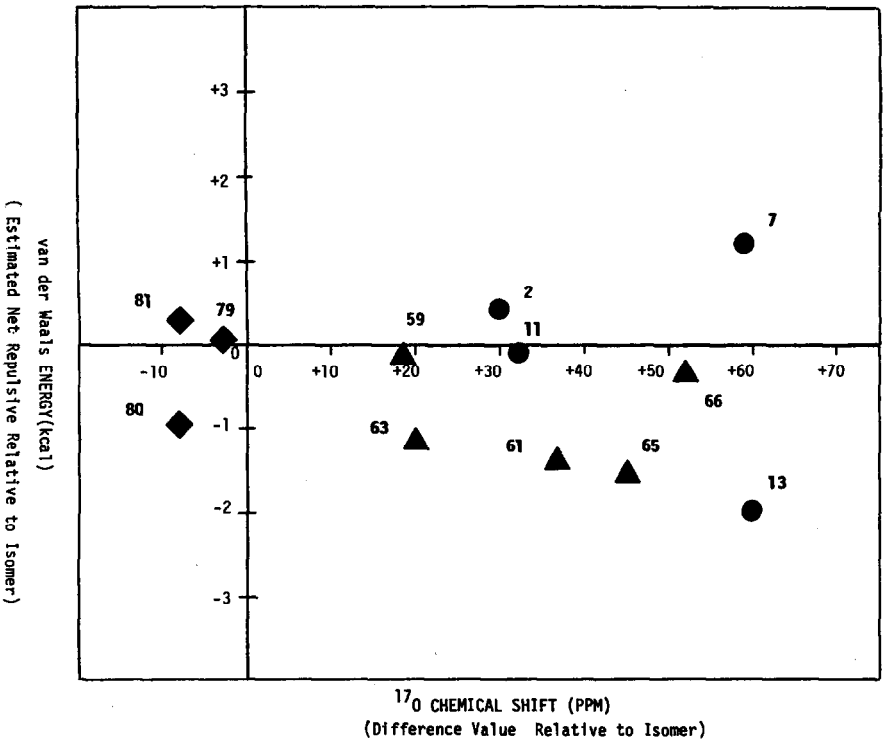


Fig. 11. Plot of net repulsive van der Waals energy vs ^{17}O difference chemical shifts for torsion angle systems.

3. NON-TORSIONAL EFFECTS

3.1. N-*Oxides*

3.1.1. *Background.* Prior to 1985 little was known about steric effects on ^{17}O NMR chemical shifts in general; only studies on saturated carbocyclic and heterocyclic systems[45] and the effect of *ortho* substituents for benzaldehydes and acetophenones[11,12] had been reported. No studies had explored the influence of steric hindrance on ^{17}O NMR data in rigid, planar systems. Pyridine N-oxides and related heterocyclic N-oxides appeared to be excellent systems for the study of steric interactions since rotation of the functional group out of the plane of the aromatic ring was not probable. In addition, we had earlier shown that the ^{17}O NMR chemical shifts of the N-oxide group for pyridine N-oxides were remarkably sensitive to electronic and solvent effects.[46,47] This sensitivity to structural changes[46] made the N-oxide group an important system in which to examine the effect of changing steric environments on ^{17}O NMR chemical shifts.

3.1.2. *Pyridine* N-*oxides.* A series of electronically similar 2-substituted pyridine N-oxides were chosen to assess the effect of changing steric environment on the N-oxide ^{17}O NMR chemical shift.[8] The ^{17}O NMR data for 2- and 4-substituted pyridine N-oxides (**102–111**) in acetonitrile at 75°C, are listed in Table 13. Comparison of the chemical shift data of the 2-alkylpyridine N-oxides with their 4-alkyl isomers showed that the 2-alkyl isomers were deshielded[8] relative to the 4-alkyl isomers. The chemical shift data for the 4-substituted pyridine N-oxides (shielded relative to pyridine N-oxide) were consistent with normal electronic effects. Representative spectra for pyridine N-oxide and 2-*t*-butylpyridine N-oxide are shown in Fig. 12. Since electronic effects of alkyl groups in the 2- and 4-positions are comparable, the deshielding (6–14 ppm) observed for the ^{17}O NMR signals

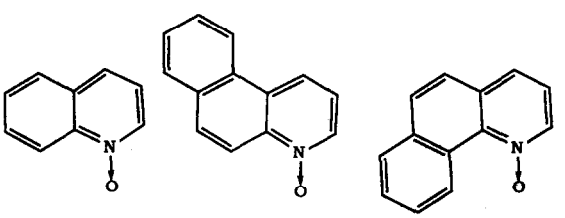
Table 13. ^{17}O NMR data (±1 ppm) for alkyl-substituted pyridine N-oxides[17] in acetonitrile at 75°

Compound No.	R	δ(ppm)	$\Delta(\delta_{2R}-\delta_{4R})$
102	H	349	--
103	2-Me	350	14
104	4-Me	336	
105	2-Et	346	10
106	4-Et	336	
107	2-n-Pr	342	6
108	2-i-Pr	342	6
109	2-t-Bu	361	23
110	4-t-Bu	338	
111	2,6-Di-Me	350	27

of the 2-alkyl isomers was attributed to steric interactions. Introduction of a 2-*t*-butyl group resulted in a much larger increase in deshielding (23 ppm), presumably the result of greater steric interactions and/or a consequence of disruption of solvent structure around the polar N-oxide function. A slight diminution of the deshielding effect (see Δ values in Table 13) with increasing size of the 2-alkyl group (except for the 2-*t*-butyl group) was noted.[8]

In order to determine if similar steric effects were observable for a less polar functional group, structurally similar *t*-butylanisoles were studied.[8] The ^{17}O NMR chemical shifts for *o*- and *p*-*t*-butylanisoles were obtained in acetonitrile at 75°C (δ 49 and δ 44 ppm, respectively). The chemical shift values for the anisoles were near those reported in chloroform for a series of *para*-substituted anisoles.[48] The ^{17}O NMR chemical shift of *o*-*t*-butylanisole was 5 ppm downfield from its analog, *p*-*t*-butylanisole. Steric effects in other anisole systems are consistent with these observations.[49] The shift in these hindered anisoles was in the same direction (deshielding) as observed for similarly substituted N-oxides; however, the magnitude of the shift is less by a factor of approximately 5.

3.1.3. *Quinoline N-oxides.* An additional example of steric effects on the ^{17}O NMR chemical shifts of N-oxides was found by comparing the results for quinoline N-oxide (**112**), benzo[*f*]quinoline N-oxide (**113**) and benzo[*h*]quinoline N-oxide (**114**).[8] Comparison of the shifts for pyridine N-oxide **102** and quinoline N-oxide **112** showed that a modest shielding effect (6 ppm) on benzene ring fusion was observed on the ^{17}O NMR chemical shift of the N-oxide function. When the ^{17}O NMR chemical



343 PPM 344 PPM 362 PPM

112 113 114

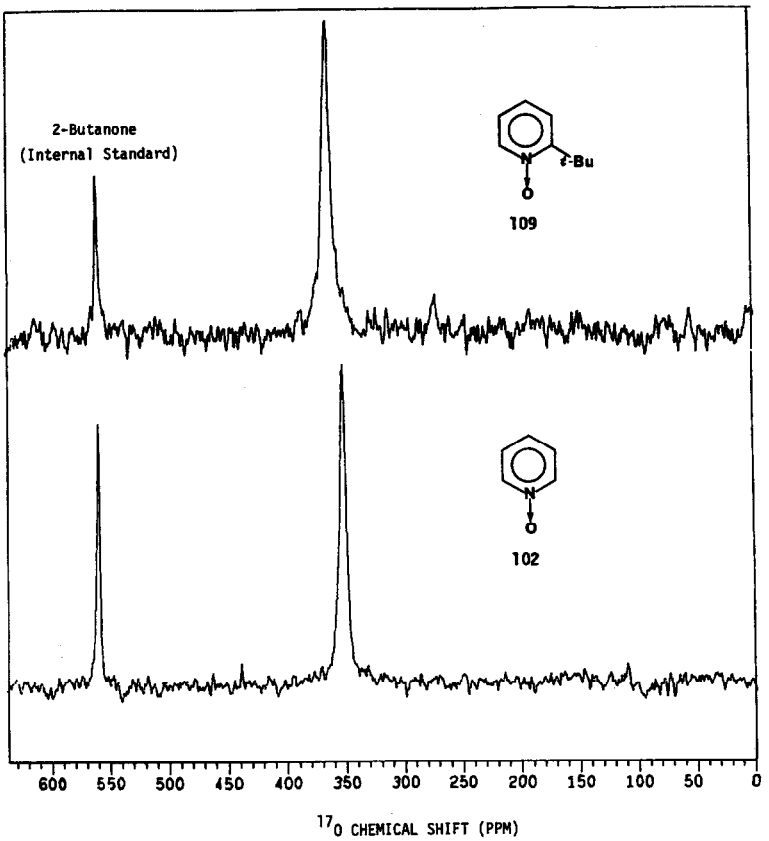
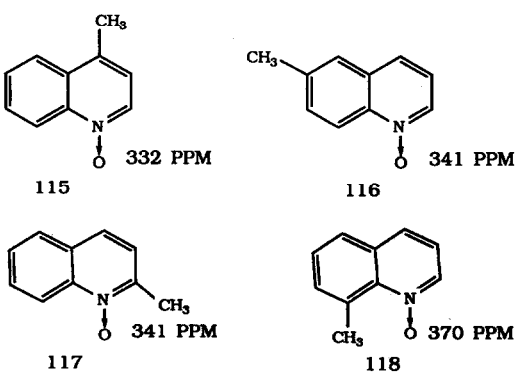


Fig. 12. Representative ^{17}O NMR spectra for pyridine N-oxides and 2-*t*-butylpyrimidine N-oxide in CH_3CN at 75°.

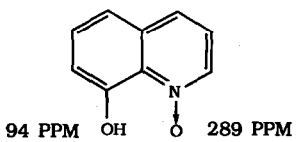
shift values for the two benzoquinoline N-oxides **113** and **114** were compared, significant deshielding (18 ppm) was noted for **114**. The location of the fused benzene ring for **114** was expected to give rise to a large steric interaction between the N-oxide function and the *peri*-like C—H and deshielding of the N-oxide function chemical shift observed was attributed to such interaction.

Furthermore, a series of isomeric methyl quinoline N-oxides, **115–118**, were examined and the data are shown below.[50] Isoquinoline N-oxide **119** was included for comparison and has a chemical shift (δ 351 ppm) very close to that of pyridine N-oxide **102**. It was noted that the chemical shifts



for **115** and **117** were shielded by approximately 5 ± 1 ppm compared with those of the analogous pyridine N-oxides.[8,46] The shielding effect was consistent with those observed for the N-oxides of quinoline and two benzoquinolines and thus appears to be a general effect of benzene ring fusion. The chemical shift difference between **115** and **117** was similar to the chemical shift difference observed for the 2- and 4-methylpyridine N-oxides.[8] The electronic effect of the methyl at position-6 was greatly reduced in magnitude compared to that at position-4. Electronic effects of alkyl groups on the heterocyclic ring were comparable to those observed[8] for pyridine N-oxides; however, the effects of those substituents on the fused benzene ring appeared to be more complex. As expected, the signal for the 8-substituted compound **118** was deshielded, 29 ppm, compared to the one for its electronically equivalent isomer **116**. The chemical shift difference for the 8-methyl group was equivalent to that observed for a 2-*t*-butyl group in the pyridine system.

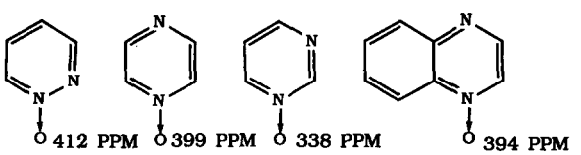
8-Hydroxyquinoline N-oxide, **120**, contains function groups located in a geometrically interesting relationship.[21] Our previous results had shown that N-oxide chemical shifts were extensively shielded by hydrogen bonding to water.[46] The ^{17}O NMR signal for **120** at 289 ppm (N-oxide) was sub-



120

stantially shielded from that of quinoline N-oxide **112**, at 343 ppm. Shielding, attributed to intramolecular hydrogen-bonding, had also been described for the carbonyl oxygens of 5,8-dihydroxynaphthoquinone.[51,52] It is difficult to assess the magnitude of the shielding for **120** attributable to hydrogen-bonding. Compressional effects of the 8-hydroxy group upon the N-oxide oxygen would be expected to be deshielding. The difference of 54 ppm for the chemical shifts of **112** and **120** should be regarded as the minimum effect due to hydrogen-bonding. The hydroxy oxygen (δ 94 ppm) participating in the hydrogen bond was deshielded relative to the signal for phenol (δ 79 ppm)[52] and other related phenolic compounds (δ 87 ppm).[51] The influence of the effects of structural variation on ^{17}O chemical shift data for a single bonded oxygen atom is not well documented.

3.1.4. *Diazene* N-*oxides*. The ^{17}O NMR chemical shift values of the isomeric diazine N-oxides, **121–123**, and of benzopyrazine N-oxide, **124**, are shown below.[50] When compared with that of pyridine N-oxide **102**, the order of ^{17}O NMR chemical shifts was **121** > **122** > **102** > **123**, with the

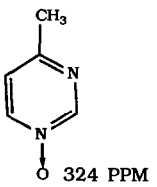


121 122 123 124

larger value corresponding to the greater double bond character for the NO bond. This order of double bond character was in reasonable agreement with that suggested by Paudler and Jovanovic[53] based upon ^{15}N NMR chemical shifts. The only difference in the bond order estimates based on ^{15}N NMR data and the ^{17}O NMR results was that the former predicted that **102** and **123** should exhibit comparable NO bond orders. The ^{17}O NMR results indicated that back donation or polarization was somewhat greater for pyridine N-oxide **102** than for pyridimidine N-oxide **123**.

The ^{17}O NMR chemical shift of **121** was found downfield from that of **21** by 13 ppm. However, this downfield shift difference may not be solely attributable to differences in back donation of the two isomers. It is possible that the interaction of the lone pair of electrons on the adjacent nitrogen are contributing to the deshielding observed for **121**. The ^{17}O NMR chemical shift of the benzodiazine **124** was shielded by 5 ppm compared to its diazine parent **122** as expected for benzene ring fusion *ortho* to the N-oxide function.

To assess the effect of steric effects (deshielding) on the ^{17}O NMR chemical shifts in the diazine series, ^{17}O NMR spectra of 4-methylpyrimidine 1-oxide, **125**, and 4-methylpyrimidine 3-oxide, **126**, were obtained.[50] Since the electronic effects of the methyl group in isomers **125** and **126** are equivalent, any difference in chemical shift of the two could be attributed to steric consequences. Based upon pyridine N-oxide data[8,46] the methyl groups' electronic effect should be shielding for the signal of **125** and **126** by 13 ppm. The 1-oxide, **125**, which should be devoid of steric effects,



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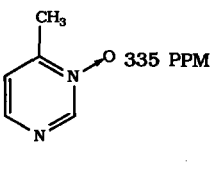
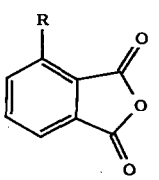


126

exhibited a chemical shift of δ 324 ppm shielded by 14 ppm compared to **123** in agreement with predictions based upon the pyridine system. The chemical shift of **126** should experience the same degree of shielding (13 ppm) arising from electronic effects as for **125**, but its signal should also be deshielded by 14 ppm arising from steric interactions (based upon pyridine results), resulting in essentially no chemical shift difference with its parent **123**. The ^{17}O NMR chemical shift observed for **126** was δ 335 ppm in good agreement with the above prediction.

3.2. *Rigid carbonyl systems*

3.2.1. *Phthalic anhydrides and phthalides.* The large deshielding effects on the ^{17}O NMR chemical shift data observed for sterically hindered heteroaromatic N-oxides,[8,50] where torsional effects are thought to be absent, are useful for characterizing certain types of isomeric compounds. The origin of the steric factors that affect ^{17}O NMR data is unclear at present but should be studied to significantly increase the insight into molecular structure that can be gained by use of ^{17}O NMR methodology. In order to identify non-torsional steric factors, it was important to study a system which had a less polar functional group with a well-defined, planar geometry and which showed a large chemical shift range. Rigid, cyclic anhydrides seemed to satisfy these criteria,[40] and, furthermore, in certain cases the two carbonyls had been reported to exhibit differential reactivity.[54] The phthalic anhydride system was chosen for initial investigation since it seemed that large steric interactions were possible. The ^{17}O NMR data for a series of 3-substituted phthalic anhydrides (**127**) and corresponding phthalides (**128–129**) showed[43,44] that the chemical shifts were sensitive to non-torsional bond angle deformations, the net effect of which was always found to be deshielding.



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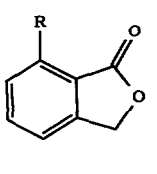

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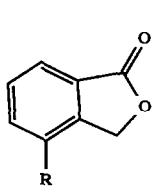


129

Table 14. ^{17}O NMR data (± 1 ppm) for 3-substituted phthalic anhydrides and phthalides in acetonitrile at 75°

Anhydrides				Lactones			
R	Compound #	δ(C=O)	δ(-O-)	R	Compound #	δ(C=O)	δ(-O-)
H	**127**	374	263	H	**128**	320	170
Me	**127a**	383 372	264	7-Me	**128a**	332	170
t-But	**127b**	396 367	262	7-t-Bu	**128b**	346	168
				4-t-But	**129a**	319	173

The natural abundance ^{17}O NMR data for phthalic anhydride **127**, 3-methylphthalic anhydride **127a**, 3-*t*-butylphthalic anhydride **127b**, phthalide **128**, 7-methylphthalide **128a**, 7-*t*-butylphthalide **128b**, and 4-*t*-butylphthalide **129a** were obtained[43] at 75°C in acetonitrile. The results are summarized in Table 14. For both **127a** and **127b**, two well-defined ^{17}O NMR signals for the sterically different carbonyl groups, separated by 11 and 29 ppm, respectively, were observed. The single bond oxygen for all the anhydrides appeared essentially unchanged at δ 263 $\pm$ 1 ppm. A representative spectrum of 3-methylphthalic anhydride is shown in Fig. 13. The ^{17}O NMR data for the two isomeric *t*-butyl phthalides (**128b**, **129a**) were employed to make the assignment of the downfield (deshielded) carbonyl signal in the substituted anhydrides to the carbonyl group adjacent to the substituent. Note that the carbonyl signal for **128b** is downfield of that of **129a** by 27 ppm.

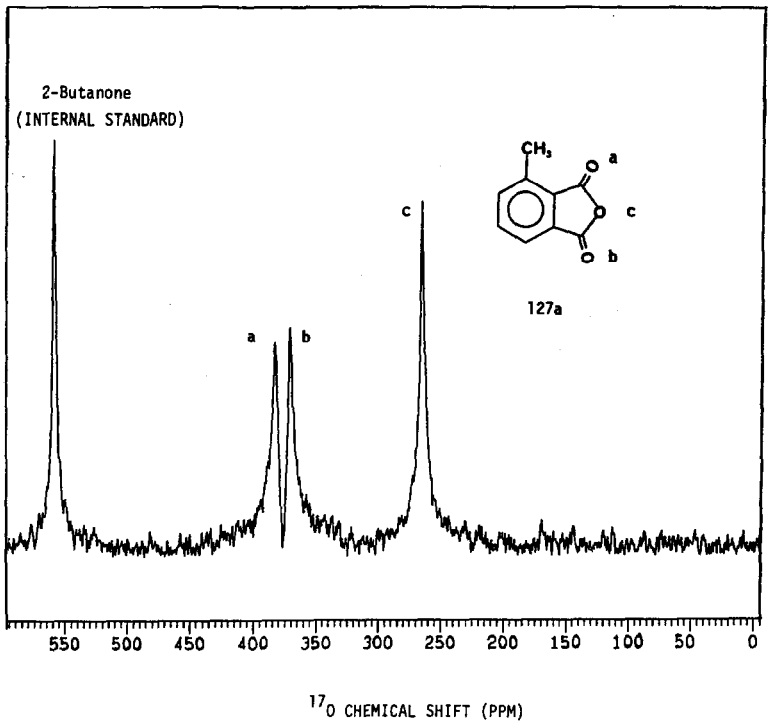


Fig. 13. ^{17}O NMR spectrum for 3-methylphthalic anhydride in CH_3CN at 75°.

Table 15. ^{17}O NMR data (±1 ppm) for 3-substituted phthalic anhydrides in acetonitrile at 75°C

Cmpd. #	R	$\delta(C=O)_1$	$\delta(C=O)_2$	$\delta(-O-)$	$\delta(R)$
127c	3-C_2H_5O	370	384	264	91
127d	3-CH_3O	371	383	264	65
127e	3-F	376	385	264	
127f	3-Cl	375	386	264	
127g	3-Br	374	385	265	
127h	3-I	373	382	263	
127i	3-NO_2	377	395	262	

The downfield shifts noted for **128–129** cannot be due to electronic effects since earlier work on the benzoate system had shown that the electronic effects of alkyl groups on the carbonyl resonance were in fact modestly shielding by 2 ppm.[22] The deshielding effect in both series (**127a, 129a**) for an *ortho*-methyl group was 9–12 ppm while a similarly located *t*-butyl group yielded a 22–27 ppm shift. It is important to note that the ^{13}C NMR chemical shifts of the two carbonyl carbons in **127a, c** were essentially identical (within 1 ppm). Consequently, the ^{17}O NMR methodology provides a dramatically more sensitive approach for exploring the effect of steric hindrance on carbonyl functional groups.

In order to check the ^{17}O NMR chemical shift assignments in series **127**, qualitative shift reagent studies[55a] were carried out on **127** and **127b** in $CDCl_3$. The results for the carbonyl signals for **127b** showed that the deshielded signal was relatively insensitive to the shift reagent [Eu(FOD)$_3$].[55b] The other carbonyl signal showed a sensitivity similar to that observed with the parent anhydride **127**. The shift reagent results were consistent with the chemical shift assignments described above.

In order to study the influence of substituents of varying electronic character on the properties of the two carbonyl functions of 3-substituted phthalic anhydrides, the ^{17}O NMR chemical shifts of additional series of phthalic anhydrides (**127c–h**) and related phthalides (**128c–h** and **129c–h**) were studied and may be found in Tables 15 and 16.[44] Two carbonyl signals for all the substituted

Table 16. ^{17}O NMR data (±1 ppm) for 7- and 4-substituted phthalides in acetonitrile at 75°C

7-Substituted					4-Substituted			
R	Cmpd.	$\delta(C=O)$	$\delta(-O-)$	$\delta(R)$	Cmpd.	$\delta(C=O)$	$\delta-O-)$	$\delta(R)$
CH_3O	**128c**	333	168	59	**129b**	323	170	49
F	**128d**	334	171		**129c**	325	169	
Cl	**128e**	335	170		**129d**	327	170	
Br	**128f**	334	170		**129e**	327	171	
I	**128g**	330	171		**129f**	327	171	
NO_2	**128h**	337	172	616	**129g**	325	174	582

anhydrides were observed. The assignment of the two carbonyl signals for the anhydrides **127c–i** was made by using the results from the corresponding phthalides **128** and **129** as discussed above.[43] The chemical shift data for the carbonyl group of the 7-substituted phthalides (**128**) were all deshielded by 10–26 ppm compared to that of series **129**, regardless of the electron donating or electron withdrawing effect of the substituent. The resonances for the lactone oxygen of series **128** were essentially invariant, all appearing at δ 170 $\pm$ 2 ppm. The chemical shift values for the carbonyl oxygen for series **129** were only slightly affected by substituent, appearing at δ 323 $\pm$ 4 ppm, as were those of the single bonded oxygen which appeared at δ 171 $\pm$ 3 ppm and could be explained in terms of normal electronic effects.

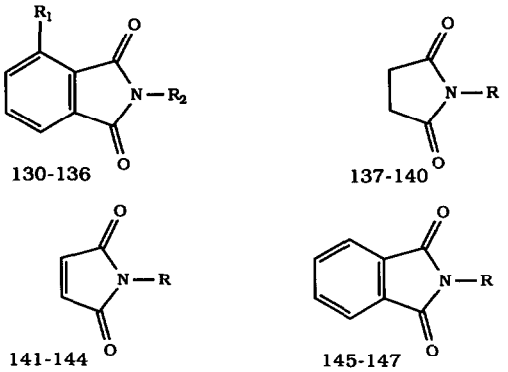
Molecular mechanics calculations[56] for **127–129** predicted[43] that all the ring systems were planar. The calculations also predicted substantial in-plane distortions of the bond angles in both rings in close proximity to the *R* group at the juncture of the two rings.[43] In order to obtain independent corroboration of the predicted geometry, the crystal structure of the most distorted anhydride, 3-*t*-butyl-phthalic anhydride, **127b** was obtained, which showed that all the atoms for **127b** were completely planar, with the exception of *t*-butyl methyl groups. Therefore, the observed deshielding effects are non-torsional in origin.

The effect of substituents on the ^{17}O NMR chemical shifts for the 3-substituted phthalic anhydrides **127** and 7-substituted phthalides **128** were similar, both exhibiting a similar magnitude of deshielding relative to their respective parent molecules.[43,44] The relative consistency in chemical shift for the substituents of varying size and electronic effects was explained in terms of competition between simple electronic effects and van der Waals interactions. One interesting conclusion to be made from these results for all the 3-substituted compounds listed in Tables 14 and 15 is that the ^{17}O NMR chemical shift values suggest that reactivity difference[54,57] for the two carbonyl groups of these compounds cannot be exclusively explained by simple electronic effects.

Differential reactivity of carbonyl functions in analogous systems has been reported and explanations for the differences have included steric blocking of the attacking reagents and the influence of electronic effects of the substituents.[54,57] The results from our study showed that steric interactions in these systems were not limited to steric blocking but also include molecular distortions, which also should affect the reactivity of the carbonyl functions. An interpretation of the ^{17}O NMR data for the anhydrides suggests greater double bond character for the hindered carbonyl which should lower its reduction potential, whereas the other carbonyl oxygen shows greater charge density and thus should be more likely to complex Lewis acids. This combination of effects must be considered in explanations of reactivity data.

3.2.2. *Imides and phthalamides.* The non-torsional ^{17}O NMR chemical shift effects observed for the phthalic anhydrides could be used to rationalize the regiospecificity of their reduction reactions. Sterically hindered imide systems also show regiospecificity[58] on reduction and were thus especially attractive for a ^{17}O NMR investigation. ^{17}O NMR data for a series of N-substituted phthalimides **130–136**; N-substituted succinimides **137–140**; maleimides **141–144** and phthalamides **145–147** presented below show[35] that the ^{17}O NMR chemical shift data can provide insights into structure and reactivity in systems in which steric phenomena are important.

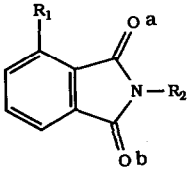
^{17}O NMR data obtained[35](natural abundance) for a series of N-substituted phthalimides (**130–136**), in acetonitrile at 75°C are summarized in Table 17. The signal for the carbonyl oxygens was deshielded as the size of the N-substituent increased, despite similar shielding electronic effects of the alkyl groups. The substitution of a N-isopropyl group for a N-methyl group yielded a 9 ppm downfield shift while the similar effect of the N-*t*-butyl group was 20 ppm. In the unsymmetrical compound **135** separate signals for both carbonyl oxygens were detected. Since electronic effects are negligible, the large difference (deshielding) observed was indicative of significant molecular distortion. The magnitude of this shift (28 ppm) was similar to that observed for the analogous phthalic anhydride and suggested in-plane molecular distortions, caused by the partial relief of the steric interactions of the substituent on the aromatic ring with the carbonyl oxygen. The results for



the doubly hindered compound **136** showed that the ring substituent deshielding effect and that due to the N-substituent were additive (*vide infra*).

Since the large deshielding effects noted in **131–136** were surprising, the N-substituted succinimides (**137–140**) and maleimides (**141–144**) were examined[35] to test the generality of these results. The ^{17}O NMR chemical shift data for the N-substituted succinimides and maleimides showed deshielding effects similar in magnitude to those for the phthalimides. In addition ^{17}O NMR data for the analogous N-substituted phthalamides (**145–147**) showed deshielding shifts for large N-substituents in agreement with the above imide systems. The data are summarized in Table 18. The signals for compounds with N-*t*-butyl groups were deshielded 20 ± 1 ppm relative to those for the N-methyl compounds for all four cases. The signals for the N-phenyl compounds were deshielded by 5 ± 1 ppm relative to those for the N-methyl compounds. The chemical shift data for the parent compounds (R=H) of each group (**130, 137, 141, 145**) are complicated as a consequence of a hydrogen-bonding component. Hydrogen bonding to a carbonyl group should clearly result in an upfield shift of the ^{17}O NMR signal.[12,51,59,60] The effect of N—H donation to another system on

Table 17. ^{17}O chemical shift data (± 1 ppm) for substituted phthalimides in acetonitrile at 75°C



Cmpd.	R_1	R_2	$\delta(C=O)_A$	$\delta(C=O)_B$
130	H	H	379.0	379.0
131	H	Me	374.0	374.0
132	H	i-Pr	383.0	383.0
133	H	t-Bu	394.0	394.0
134	H	Ph	378.3	378.3
135	t-Bu	H	407.3	370.6
136	t-Bu	t-Bu	423.3	385.3

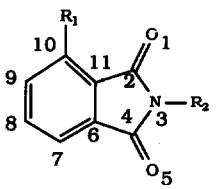
Table 18. ^{17}O NMR data (±1 ppm) for N-substituted maleimides, succinimides and phthalamides in acetonitrile at 75°C

Succinimides			Maleimides			Phthalamides		
Cmpd.	N-R	δ(C=O)	Cmpd.	N-R	δ(C=O)	Cmpd.	N-R	δ(C=O)
137	H	373.5	**141**	H	411	**145**	H	282
138	Me	371	**142**	Me	407	**146**	Me	281
139	t-Bu	392	**143**	t-Bu	426	**147**	t-Bu	300
140	Ph	376	**144**	Ph	412			

the carbonyl of the donor imide is not as clear.[60,61] The overall effect of differential hydrogen bonding is complex.[60] Consequently, the chemical shift differences between these compounds and those for the N-substituted compounds were difficult to interpret.

Molecular mechanics (MM2) calculations[56] were carried out[35] on **130, 133, 136**; see Table 19 for selected bond angles (Entries 1–9). The calculations predicted in-plane angle distortions of the planar molecules with the larger N-substituents. The bond angle of the carbonyl group opened

Table 19. Molecular mechanics calculated bond angles (±1°) and X-ray data for phthalimides **130, 133, 136**



130 R1 = R2 = H
133 R1 = t-Bu ; R2 = H
136 R1 = R2 = t-Bu

		130		133		136	
Entry	Angle	MM2	(X-ray)[a]	MM2	(X-ray)[b]	MM2	(X-ray)[c]
1	$O_1C_2N_3$	124°	(124.8°)	126°	(126.3°)	124°	(125.5°)
2	$C_{11}C_2N_3$	105°	(105.2°)	107°	(108.6°)	108°	(106.8°)
3	$C_{10}C_{11}C_2$	131°	(130.0°	131°	(131.9°)	133°	(132.8°)
4	$C_2N_3C_4$	114°	(112.2°)	111°	(110.6°)	111°	(110.5°)
5	$N_3C_4O_5$	124°	(125.4°)	126°	(129.6°)	126°	(126.6°)
6	$N_3C_4C_6$	105°	(106.2°)	107°	(104.6°)	107°	(107.4°)
7	$C_4C_6C_7$	131°	(120.3°)	131°	(125.9°)	128°	(127.2°)
8	$C_2N_3R_2$	122°	--	122°	(122.1°)	122°	(122.6°)
9	$C_{11}C_{10}R_1$	--	--	--	--	126°	(125.2°)

a) Literature values taken from Ref. 62.

b) Sigma values ≈1.5.

c) Sigma values ≈0.5.

toward the ring (Entries 1 and 2), and the internal bond angle of the imide (Entry 4) decreased as the N-substituent increased in size. Unlike the 3-substituted anhydride system, the distortion for the N-substituted imides resulted in a symmetrical opening of the carbonyl angles (Entries 1 and 2, Table 19). The X-ray structures of phthalimide,[62] **130** and N-*t*-butylphthalimide[35] **133** have been reported. Both structures were found to be planar which is in agreement with the molecular mechanics calculations. Unfortunately, the X-ray results showed that the crystal structures for **130** and **133** were not symmetrical around an axis through the nitrogen bisecting the molecule, making quantitative comparisons with the molecular mechanics calculations difficult. Despite this complication the bond angle distortions noted were in qualitative agreement with those predicted by the calculations (Table 19).

The ^{17}O NMR signal for the doubly hindered carbonyl of **136** was deshielded by 50 ppm, which was much larger than any for the other systems. The magnitudes of the deshielding effects on the carbonyl signals were consistent with expectations based upon the ^{17}O NMR data for **130**, **129b** and **134**. The X-ray structure of **133** was obtained[35] for comparison with molecular mechanics calculations (Table 19) and again confirmed the molecule to be planar. The calculations predicted essentially identical values for the angles for $(C{=}O)_B$ in both structures (**133** and **136**) and the X-ray results were qualitatively in agreement; compare entries 1 and 5 for compounds **133** and **136**. For **136** the doubly hindered carbonyl, $(C{=}O)_A$, was influenced in opposing directions by the two *t*-butyl groups; consequently, no unusual distortion was apparent in the structure. Nevertheless, the ^{17}O results clearly showed that this carbonyl, $(C{=}O)_A$, was subject to severe van der Waals interactions and illustrates the sensitivity and importance of the ^{17}O NMR method for detection of subtle steric effects.

Interestingly, the ^{13}C NMR signals of sterically hindered imides were found[35] to be remarkably insensitive to compression effects. For example, the two carbonyl signals for **136** were within 0.5 ppm of one another whereas in marked contrast the ^{17}O NMR data for the double bonded oxygens attached to these carbons differed by 50 ppm. These results demonstrate once again the sensitivity of ^{17}O NMR chemical shifts of carbonyl groups to steric interactions and the value of the methodology for studying steric effects.

The ^{17}O NMR results for imide systems gave interesting new insights into ground state structure. In certain systems (*cf* **136**) the ^{17}O NMR method provided detailed information not accessible by other methods. The results for planar amides (**145–147**) showed that the N-substituent deshielding effects are not limited to imides. However, it is not clear that these effects will be predominant in conformationally mobile (acyclic) systems. Insights into the regiospecificity of imide reductions[58] may be obtained from the ^{17}O NMR results. In systems in which reduction by electron transfer is rate determining, one would expect the carbonyl which shows the most deshielded ^{17}O NMR chemical shift value to undergo reaction preferentially. The regiospecific zinc reduction of a hindered imide[63] is consistent with the above expectation.

3.2.3. *Quinones and flavones.* To further examine the influence of steric effects on the ^{17}O NMR data of planar compounds, a series of quinones **148–154** and flavones **155–157** were investigated.[64] This system allows the study of larger *peri*-like interactions. In anthraquinone, **148**, the carbonyl and the α-hydrogen are essentially parallel. This is in contrast to the phthalic anhydride and imide series in which the carbonyl is slightly tilted away from the 3 hydrogen atom. Thus, for the anthraquinone system greater steric interactions between the α-substituents and the carbonyl function are predicted.

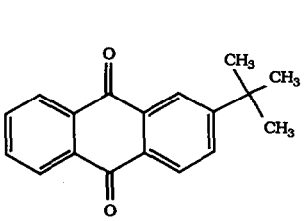
The ^{17}O NMR data of a series of anthraquinones **148–152**, naphthoquinone **153**, 1,4-chrysenequinone **154**, and several flavones **155–157** in acetonitrile at 75°C are shown in Table 20. In compounds which contained hindered and unhindered carbonyl groups two well-separated signals were observed. Spectra for the 2- and 1-methylanthraquinones (**149**, **150**) are shown in Fig. 14. The data for **149** showed the small shielding effects expected based upon electronic interactions of the methyl group.[22] Of the two signals observed for **150**, one was found to be slightly shielded as

Table 20. ^{17}O chemical shift data (±1 ppm) for (^{17}O-enriched) substituted quinones and flavones (±1 ppm) in CH_3CN at 75°C

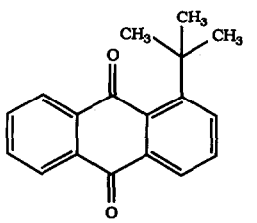
No.	Compound	$\delta(C=O)_1$[a]	$\delta(C=O)_2$
148	anthraquinone	524	524
149	2-methylanthraquinone	524	519
150	1-methylanthraquinone	552	521
151	2-t-butylanthraquinone	523[b]	523[b]
152	1-t-butylthraquinone	572	522
153	naphthoquinone	572	572
154	1,4-chrysenequinone	602	575
155	flavone	--	438
156	7,8-benzoflavone	--	433
157	5,6-benzoflavone	451	--

a) The hindered carbonyl group. b) At natural abundance, a broad (500-650 Hz) unresolved singal was observed.

expected. However, the other signal for **150** was deshielded by 28 ppm and assigned to the hindered carbonyl *ortho* to the methyl group. As expected, this downfield shift for **150** was larger than that noted for analogous phthalide and phthalimide systems.[36,43] The signal for the hindered carbonyl of 1-*t*-butylanthraquinone **152** was even further downfield (50 ppm) despite the fact that the electronic effects were essentially constant. In the chrysene compound **154** the carbonyl adjacent to a *peri* type hydrogen was deshielded whereas the signal for the unhindered carbonyl group was essentially the same as in the parent naphthoquinone. Consistent with these observations, the hindered carbonyl of the flavone **157** showed substantial deshielding effects in contrast to that of the unhindered isomer **156** which showed a modest shielding effect compared to the results for the parent **155**. It was clear that the deshielded signals arise from the hindered carbonyls and the 50 ppm downfield shift for **152** is the largest steric induced shift observed to date for a single substituent.



151



152

Molecular mechanics[14,56] calculations predicted that all compounds in this series were planar. In-plane bond angle distortions were noted for the hindered carbonyl group in each case. For example, in the system which showed the largest deshielded signal, **152**, the hindered carbonyl was predicted to show a bond angle of 125°. To confirm the molecular mechanics calculations, an X-ray structure for the most hindered compound **152** was obtained. The results from the X-ray analysis

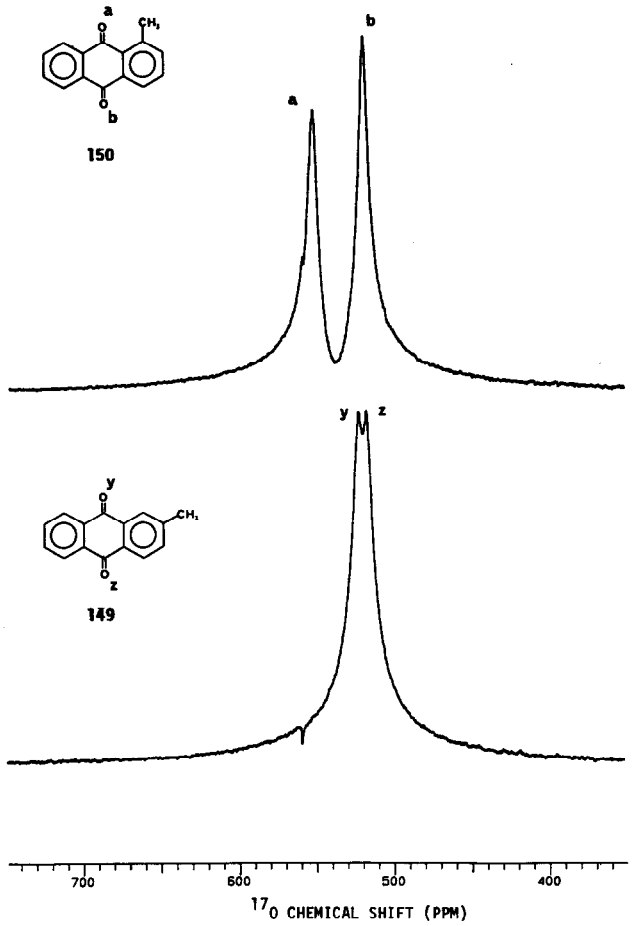


Fig. 14. ^{17}O NMR spectra for 1- and 2-methylanthraquinones.

were in excellent agreement with the MM2 predictions; the hindered carbonyl bond angle was 125° and the anthraquinone ring system was shown to be planar.

3.3. *Summary*

Significant compressional effects[8,50] have been shown for 2-substituted pyridine N-oxides, for benzo[*h*]quinoline N-oxides and for various substituted quinoline N-oxides. Deshielding effects are large enough in many cases to use the ^{17}O NMR chemical shifts to distinguish between isomers, and this approach should be applicable to many other systems. The ^{17}O NMR studies on the N-oxides were carried out at natural abundance on 0.5 *M* solutions in acetonitrile at 75° and usually required 6–8 h of instrument time (2 to 3 times greater than those for many other functional groups). Although less than optimal, this time requirement should not deter one from using this methodology.

The origin of these deshielding effects for the N-oxides is speculative. The greater sensitivity to compressional effects of the N-oxide oxygen compared with that of the anisoles can be attributed to the double bond character of the N-oxide and/or difference in solvation between the polar and neutral molecules. Deshielding effects comparable to those of the N-oxide system are also seen in carbonyl systems. These results suggest that ^{17}O NMR methodology is better able to detect steric interactions when substantial π-interactions are involved. The sensitivity of N-oxides may involve

some contribution from alteration of the solvent structure around the polar functional groups on introduction of large hydrocarbon groups in close proximity. Paudler and Jovanovic[53] had rationalized the ^{15}N NMR data and IR data for other sterically hindered N-oxides as a result of steric inhibition of back-donation through alteration of coplanarity of the NO group and the ring. It is not clear that this type of ring–NO group deformation is the only explanation for these results. As we have shown for planar carbonyl systems, in-plane bond deformation and the residual repulsive van der Waals effects[65] could explain the ^{17}O NMR deshielding effects.

^{17}O NMR compressional effects on the carbonyl systems provide a direct method to assess steric hindrance in rigid, planar systems. The ^{17}O NMR deshielding effects paralleled[36,43,44,64] the relative degree of in-plane distortions in all the planar systems investigated to date. The in-plane distortions are reflective of repulsive van der Waals interactions (that have been only partially relieved). Plots

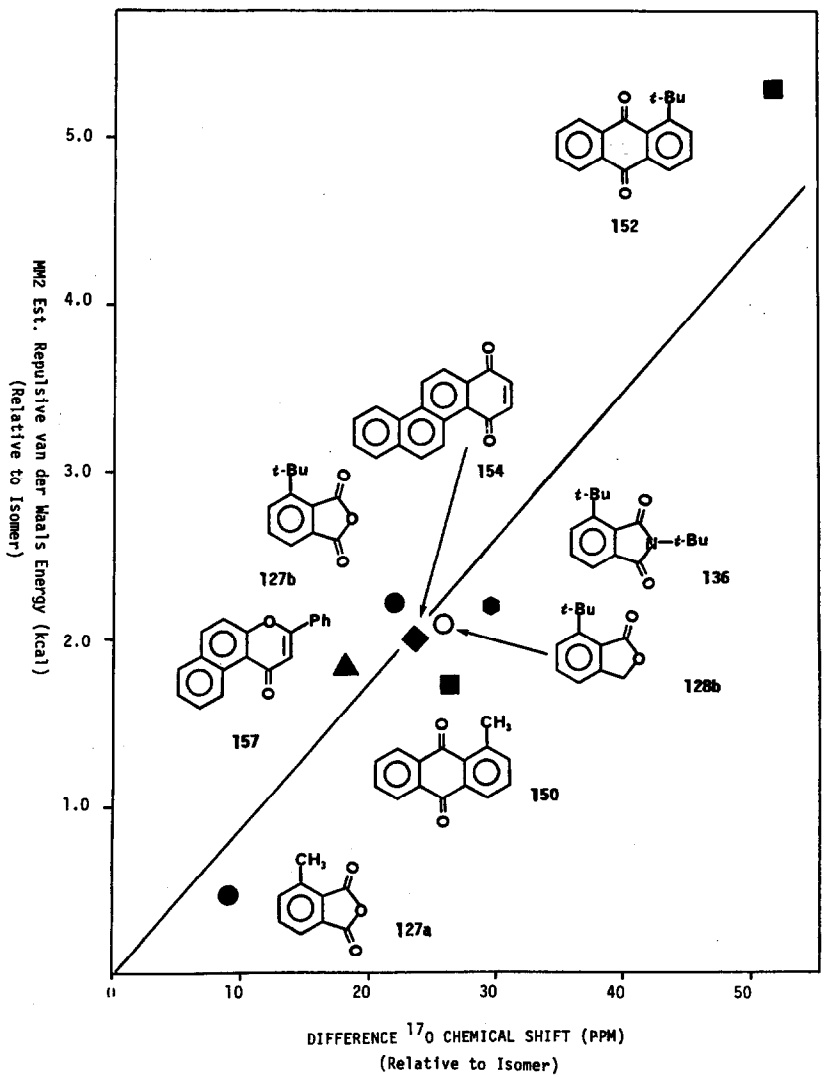


Fig. 15. Plot of estimated repulsive van der Waals energy vs difference ^{17}O chemical shift for rigid planar systems.

of total van der Waals energy (MM2 calculation) vs ^{17}O NMR chemical shift showed[3] a fair correlation with increasing van der Waals interactions whereas total steric energy did not correlate. This relationship must be corrected to reflect the repulsive van der Waals contributions which as Chesnut has shown[65] should be responsible for deshielding effects in other systems. For example, Chesnut showed[65] that repulsive van der Waals interactions could explain deshielding trends for ^{13}C and ^{31}P NMR data and suggested this explanation is general for other resonant nuclei. Also, a correlation between local steric energies and ^{13}C NMR data was demonstrated. He suggested that orbital size contraction influenced the paramagnetic term to yield a net deshielding shift.[65] The difference in van der Waals energy could be estimated by comparison of total van der Waals energies of the sterically-hindered (deshielded) compared with that for an unhindered isomer. Compounds for which no conformational problems were present were chosen. Thus, 4-substituted phthalic anhydrides and 6-substituted phthalides were taken as models for series **127** and **128**. No reasonable model was apparent for the N-substituted imides; however, the di-*t*-butyl compound **136** could be modeled as above. The *β*-*t*-butyl compound was used as the model for **152**. The estimated repulsive van der Waals energies for several series of planar compounds gave a reasonable correlation[64] (see Fig. 15) with the difference in ^{17}O NMR chemical shift (relative to the parent compound in each series). Thus, it appears that residual repulsive van der Waals energies and the degree of molecular distortion parallel the deshielding effects observed on the ^{17}O NMR chemical shift data. Thus, the above correlation of repulsive van der Waals interactions with the change in ^{17}O NMR chemical shifts agrees with Chesnut's postulation[65] of the influence on the r^{-3} term of the Karplus–Pople equation. Since the carbonyls are clearly distorted in these cases, the ΔE^{-1} and the charge density terms should also be affected.[65]

4. EXPERIMENTAL CONSIDERATIONS

A number of the problems earlier associated with acquiring ^{17}O NMR data have been minimized. High field instruments (greater than 50 MHz for ^{17}O) reduced base line-roll difficulties associated with transmitter break-through. Selection of low viscosity solvents, especially the avoidance of solvents such as chloroform which are capable of hydrogen bonding,[10] help narrow linewidths. Acquisition of data at elevated temperature also contributes to reduction of linewidth which reduces accumulation time. The use of moderately enriched samples dramatically reduces the acquisition time required to obtain reasonable S/N values (see reference 4 for enrichment methods). Our standard conditions for data collection on a 270 MHz and a 400 MHz instrument may be found in reference 35.

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