^{17}O NMR Spectroscopy: Evaluation of Intra- and Intermolecular Hydrogen Bonding of Phenols to Carbonyl Groups

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^{17}O NMR spectroscopy[1] is an important method for the assessment of structural problems in organic chemistry,[2] especially hydrogen-bonding phenomena.[3] Previous studies have shown that ^{17}O NMR carbonyl data are sensitive to torsion-angle variations in aryl systems.[2,4] In rigid, planar systems, ^{17}O NMR methodology has been employed to detect lone-pair distortions (in-plane structural deformations).[2,5] ^{17}O NMR data for intramolecular hydrogen-bonded amino- and amido-substituted acetophenones have been factored into electronic, torsional, and hydrogen-bonding components.[6] ^{17}O NMR methodology has been shown[7] to be sensitive to the geometry as well as the relative pK_as of intramolecular hydrogen-bonded N–H groups in rigid carbonyl systems. We report here an ^{17}O NMR study of intra- and intermolecular hydrogen bonding of phenols to ketone carbonyl groups.

The ^{17}O NMR chemical shift data for a series of intramolecular hydrogen-bonded phenols containing carbonyl groups, **1–10**, in acetonitrile at 75 °C are listed in Table I. The signals for the intramolecular hydrogen-bonded carbonyl groups in **1–10** are shifted upfield.[3,6,8] Data for several of the compounds listed in Table I have been reported previously.[8,9] However, the ^{17}O data were obtained under varied conditions such that quantitative analysis was difficult. In addition, the influence of electronic and torsional effects were not included in the determinations of the hydrogen-bonding components of the observed shielding effects.[8,9] The contributions of intramolecular hydrogen bonding ($\Delta\delta_{HB}$) to the chemical shifts for the carbonyl groups in **1–10** ranged from 39 to 67 ppm after correction[6] for electronic and torsional factors. The average $\Delta\delta_{HB}$ for one intramolecular hydrogen bond in these systems was determined to be 51 ± 7 ppm based upon the assumptions that the pK_as of all the phenols are similar and that the basicities of the carbonyl groups are comparable.

Proton coupling to the phenol oxygen is observed directly in six of the examples listed in Table I. Representative ^{17}O NMR spectra for the OH signals (^1H-coupled and ^1H-decoupled) for 2′-hydroxyacetophenone are shown in Figure 1. This type of coupling can only occur when intramolecular proton transfer takes place without spin exchange and indicates that the solvent (acetonitrile) does not compete with the intramolecular carbonyl group on the time scale of this experiment. The absolute values of the observed coupling constants ranged from 75 to 91 Hz, which are consistent with that ($J \simeq 76$ Hz) of similar coupling deduced[10] from line-shape analysis for the enol of neat 2-acetylcyclohexanone.

The diphenolic compounds **9** and **10** yielded an interesting observation since the second OH cannot undergo effective intramolecular hydrogen bonding to the carbonyl group due to geometric constraints. Contributions from intermolecular hydrogen bonding of the free OH group to the carbonyl group of another molecule (solute–solute) would be expected to yield unusually large values of $\Delta\delta_{HB}$. However, the $\Delta\delta_{HB}$ of 50–51 ppm is consistent with formation of only one intramolecular hydrogen bond with essentially no intermolecular hydrogen bonding of the second OH to the carbonyl group in acetonitrile solution.

A series of experiments with *p*-chlorophenol (**11**) and *p*-methoxyacetophenone (**12**) were carried out in acetonitrile and in toluene at 75 °C to evaluate intermolecular hydrogen bonding in acetonitrile (Table II). Data for acetophenone (**13**) and 4′-hydroxyacetophenone (**14**) are included for comparison. In acetonitrile, the results show that intermolecular hydrogen-bonding effects on ^{17}O NMR data for the carbonyl groups are of low magnitude (~2 ppm shielding) for the standard conditions employed (0.5 M). This seems to indicate that intermolecular hydrogen

Table I. ^{17}O NMR Data (ppm) for Intramolecular Hydrogen-Bonded Phenolic Compounds in Acetonitrile at 75 °C

compd	name	δ (C=O)	δ (OH)	J(OH), Hz	δ (R)[a]	$\Delta\delta_{HB}$
1	2-acetyl-1-naphthol	468.4	92.4	80		67
2	1-acetyl-2-naphthol	513	93.3	N.O.[b]		60
3	2′-hydroxypropiophenone	481	85.2	91		45
4	2′-hydroxybenzophenone	492	85	N.O.[b]		39
5	2′-hydroxyacetophenone	491	85.5	86		43
6	2′-hydroxy-4′-methoxyacetophenone	466	91	75	67	52
7	2′-hydroxy-6′-methoxyacetophenone	484	89	87	62.5	58
8	2′-hydroxy-5′-methylacetophenone	490.4	81.6	74		43
9	2′,4′-dihydroxyacetophenone	463	90	N.O.[b]	94.5[c]	50
10	2′,6′-dihydroxyacetonphenone	481	91	N.O.[b]	91	51

[a] ^{17}O NMR chemical shift of additional substituent. [b] Not observed. [c] Tentative assignment.

Table II. Effect of Solvent on ^{17}O NMR Data (ppm) for Intermolecular Hydrogen Bonding between *p*-Chlorophenol (11) and *p*-Methoxyacetophenone (12)

compd(s)	solvent	δ (C=O)	δ (OH)	δ (OMe)	δ (ref)	Δδ (ref)
p-ClC_6H_4OH (11)	CH_3CN		76.5		557.1	2
p-$MeOC_6H_4Ac$ (12)	CH_3CN	536		60.3	559	0
11/12	CH_3CN	534.3	76.8	60.1	557.6	~1
acetophenone (13)	CH_3CN	552			559	0
4′-hydroxyacetophenone (14)	CH_3CN	531	88		557	2
11	toluene	553.7	75.0		553.7	17
12	toluene	547.0		60	571.0	0
11/12	toluene	529.5	76.1	59.5	558.7	12[a]
13	toluene	562			571	0
14	toluene	521	88		557	14

[a] Δδ for carbonyl of **12** is 17 ppm.

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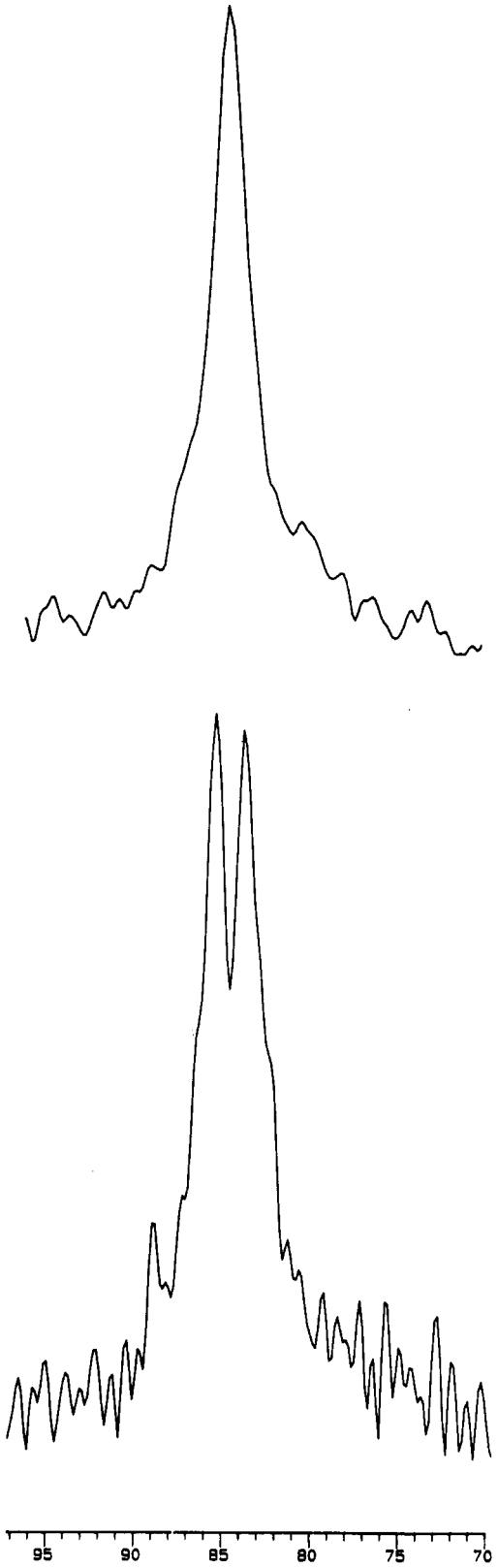

Figure 1. ^{17}O NMR spectra for the phenolic oxygen of 2′-hydroxyacetophenone (0.5 M) in acetonitrile at 75 °C: ^{1}H-decoupled (top) and coupled (bottom).

bonding of free phenolic groups may be taking place preferentially to acetonitrile rather than to the carbonyl oxygens. The situation in toluene is more complex; large (~12–17 ppm) upfield shifts are observed for the internal standard (2-butanone) and/or the added carbonyl compounds indicative of significant hydrogen bonding. However, the data show that intermolecular hydrogen bonding of 11 to 12 is only partial. The reference signal is shielded by 12 ppm in the presence of both 11 and 12 rather than 17 ppm with only 11 present indicative of the competition between 2-butanone and 12 for intermolecular hydrogen bonding with the phenol. The sensitivity of the internal reference signal in toluene can be used to detect "free" OH groups.

Table III. ^{17}O NMR Data (ppm) for Intramolecular Hydrogen-Bonded Phenolic Compounds in Toluene at 75 °C

compd	δ(C=O)	δ(OH)	J(OH), Hz	δ(ref)	$\Delta\delta_{HB}$
4	494	86	N.O.[a]	571	45
5	496	88	92	571	48
6	472	94	85	571	56
7	488	91	N.O.[a]	571	64
9	468	92	N.O.[a]	558	55
10	485	89.5	N.O.[a]	560	57

[a] Not observed.

The data for selected intramolecular hydrogen-bonded phenolic carbonyl compounds were obtained in toluene (Table III). Coupling of the proton to the phenolic oxygen was observed in two of the cases. The average $\Delta\delta_{HB}$ value obtained was 55 ± 5 ppm (shielding), within experimental error of that obtained in acetonitrile (perhaps a little larger). The $\Delta\delta_{HB}$ values for the diphenolic compounds 9 and 10 again indicate the presence of only one intramolecular hydrogen bond and little or no intermolecular hydrogen-bonding effects. However, the large upfield shift (~12 ppm) for the internal reference is due to the presence of a strong intermolecular hydrogen bond from the second OH group in each compound. Thus, within the sensitivity of the method, the data show that the intramolecular hydrogen-bonded carbonyl groups of 9 and 10 do not readily form intermolecular hydrogen bonds.

In conclusion, the results show that the hydrogen-bonding contribution of a phenol to an intramolecular carbonyl group is an ^{17}O NMR shielding value of 50–55 ppm. This value is of substantially greater magnitude than that (~30 ppm)[6,7] found for the most acidic NH studied (trifluoromethylamido) in an analogous system. The results show that intermolecular hydrogen-bonding effects are masked in acetonitrile but are readily detected in toluene. Intramolecular hydrogen-bonded carbonyl groups show little or greatly lowered sensitivity to intermolecular hydrogen-bonding effects in the ^{17}O NMR data. In toluene, the chemical shift of the internal standard 2-butanone is sensitive to "free" acidic protons and can be used as a measure of the availability of donor groups for intermolecular hydrogen bonding.

Experimental Section

The compounds used in this study were commercially available from Aldrich. The ^{17}O NMR spectra were recorded on a Varian VXR-400 spectrometer equipped with a 10-mm broad-band probe. All spectra were acquired at natural abundance, at 75 °C in acetonitrile or toluene (Aldrich, anhydrous gold label under nitrogen) containing 1% 2-butanone as an internal standard. The concentration of the compounds employed in these experiments was 0.5 M. The signals were referenced to external deionized water at 75 °C. The 2-butanone resonance (558 ± 1 ppm) was used as an internal check on the chemical shift measurements for these compounds. The instrumental settings were spectral width 35 kHz, 2K data points, 90° pulse angle (40 μs pulse width), 200 μs acquisition delay, 29 ms acquisition time. Typically 40000–100000 scans were required. The spectra were recorded with sample spinning and without lock. The signal-to-noise ratio was improved by applying a 25-Hz exponential broadening factor to the FID prior to Fourier transformation [except when analyzing for J(OH)]. The data point resolution was improved to ±0.1 ppm by zero filling to 8K data points. The reproducibility of the chemical shift data is estimated to be better than ±1.0 ppm.

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Amination of Olefinic Compounds with Bis(2,2,2-trichloroethyl) Azodicarboxylate†

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Although allylic amines are important functional groups,[1] few options are offered to synthetic chemists for their preparation from olefins. Existing methods employ sulfur or selenium diimido compounds[2-4] and, more recently, *N*-sulfinylbenzenesulfonamide[1] as an aminating species for olefins. Presumably with the diimido compounds, the amination occurs via an ene reaction followed by a [2,3]-sigmatropic rearrangement.[3] With *N*-sulfinylbenzenesulfonamide[1] the ene adduct is isolated and silylation induces the rearrangement. Therefore, in all cases the aminated product is obtained with the double bond at its initial position. However, transformation of the N-SO_2R[1,3,4] and N-CO_2Me[2] (after cleavage of the RN-S-NR (R = Ts, CO_2Me), TsN-Se-NTs, or $PhSO_2$-N-S-$OSiMe_3$) to the corresponding free amines requires harsh conditions.

An interesting alternative for the synthesis of 2-alkenylamines from alkenes which would also be complementary to the other methods is where the aminating agent is an azo compound. Thus the amination of an olefin could take place via an ene reaction with the azo compound to afford the aminated product with transposition of the double bond. For this reaction, a sufficiently reactive azo reagent is required to give the ene products under mild conditions. In addition, the enophile should contain functions that could be removed under such conditions that will allow the cleavage of the N-N bond and provide the free amine without alteration of the double bond.

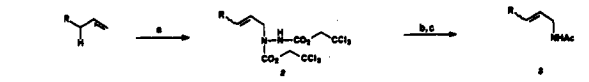
The ene reaction of diethyl azodicarboxylate (DEAD) and dienes has already been reported.[5a] Also in 1976, Stephenson and Mattern had studied the stereochemistry of an ene reaction between 1-phenyl-4-methyl-2-pentene and dimethyl azodicarboxylate (DMAD).[5b] However, since only a poor yield of the ene adduct was obtained, it became apparent that DEAD and similar azo compounds would not be suitable. Furthermore the resulting ene adducts could be converted to the corresponding allylic amines only with difficulties.

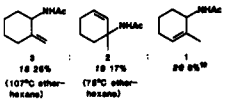
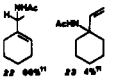
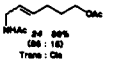
Herein is reported our results for the ene reaction of bis(2,2,2-trichloroethyl)azodicarboxylate (BTCEAD) and olefinic compounds. As shown in Table I, BTCEAD undergoes an ene reaction with olefins, under mild conditions, to provide the protected 3-hydrazinoalkenes **2**. With cyclopentene (**4**) and cyclohexenes (**5**) as substrates, the reaction was complete after 12 h[6] (24 h for **5**) at 80 °C in benzene, to give the ene adducts **10** and **11** in 77% and 70% yields, respectively. In order to explore the regioselectivity of the reaction, alkenes with more than one allylic site were used as substrate. For 1-methylcyclohexane (**6**) a mixture of regioisomers of the ene products **12** was obtained (based on the deprotected products) whereas with both 3-methylcyclopentene (**7**) and ethylidenecyclohexane (**8**) as substrates, a high selectivity was observed to provide predominantly the more substituted olefinic compounds **13** and **14** in high yields. In these last two cases the reaction took place at 40 °C[7] as for the acyclic olefin **9** where the trans and cis ene adducts (85:15) were obtained in 85% yield.

The cleavage of the N-N bond of the protected 3-hydrazinoalkenes (**10-15**) and the removal of the protecting groups were achieved in a single operation under conditions developed in our laboratories[8] (Zn, HOAc, acetone). The free amines were then protected as the acetamido derivatives (**16-24**).

In summary, BTCEAD is an efficient enophile in the ene reaction with olefins. The amination of olefins via an ene reaction make it possible to prepare, from a given

Table I



olefin	ene adduct site 1	site 2	acetamide
	10 73%[d] (132 °C, ether–hexane)		
	11 70%[e] (155 °C, ethyl acetate–hexane)		
	12 60%[f,g]		
	13 75%[a] (114–115 °C, ethyl acetate–hexane)	5%[a]	
	14 88%[a]	6%[a]	
	15 85%[a] (85:15) trans:cis		

[a] $Cl_3CCH_2O_2CN{=}NCO_2CH_2CCl_3$ 1.2 equiv, 40 °C, 18 h. [b] Zn dust, 3 equiv by weight, HOAC then acetone, room temperature, 2 h. [c] Ac_2O, py, CH_2Cl_2, room temperature, 18 h. [d] As *a* except 80 °C, 12 h. [e] As *a* except 80 °C for 6 h then 80 °C for 18 h with additional reagent (0.5 equiv). [f] As *a* except 18 h at 54 °C.

† Dedicated to Brian J. Fitzsimmons.

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(6) The progress of the reactions were initially followed by ^1H NMR in benzene-d_6.
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(9) The isomeric mixture was not separated at this stage. The formation of diene adducts was observed (≈10%).
(10) This isomer has not been isolated in a pure form.
(11) The two isomers **22** and **23** were separated by flash chromatography.

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