^{17}O NMR Spectroscopy: Intramolecular Hydrogen Bonding in Hydroxypyridine Carboxy Esters

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Natural abundance ^{17}O nmr chemical shift data for 8 aryl esters and 10 pyridine carboxy esters, including 6 *ortho*-hydroxy esters, recorded in acetomitrile at 75° are reported. The carbonyl group ^{17}O nmr chemical shift data for methyl 2-, 3- and 4-pyridinecarboxylate are correlated with σ^+ constants. The hydrogen bonding component ($\Delta\delta_{HB}$) to the ester carbonyl ^{17}O nmr chemical shift for the intramolecular hydrogen bonded *ortho*-hydroxy systems are 9.8 ppm, 13.6 ppm and 4.3 ppm for benzoates, 2-pyridinecarboxylates and 4-pyridinecarboxylates, respectively. The relationships of the ester $\Delta\delta_{HB}$ values to other hydrogen bond acceptor $\Delta\delta_{HB}$ values are discussed.

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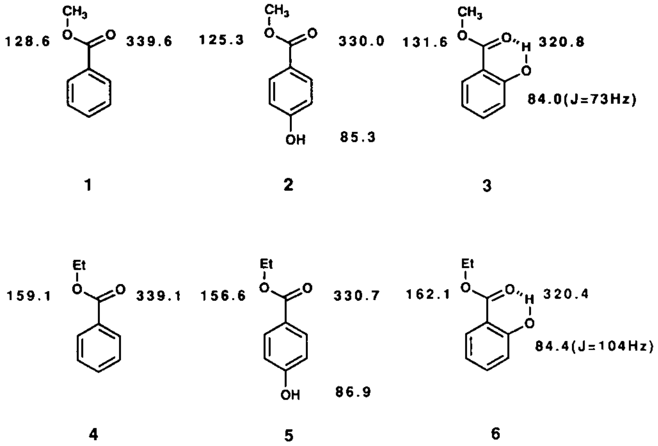
Primarily because of its importance in biological studies hydrogen bonding continues to be intensely studied [1]. ^{17}O nmr spectroscopy has been found to be an extremely valuable tool for the study of a large number of structural problems [2-4]. Recent studies have demonstrated that carbonyl ^{17}O nmr chemical shifts for diverse functional groups, including esters, are quantitatively correlated with torsion angle changes [4-6]. In rigid planar systems carbonyl ^{17}O nmr chemical shifts have been shown to be related to in-plane bond angle deformations and "local" repulsive van der Waals energies [4,7-10]. Intramolecular hydrogen-bonding in amino- and amido-substituted acetophenones has been analyzed by ^{17}O nmr methodology [11]. The chemical shift data for these systems have been factored into electronic, torsional and hydrogen bonding components ($\Delta\delta_{HB}$) [11-13]. Analysis of rigid planar intramolecular hydrogen bonding systems for which torsion angle change of the carbonyl hydrogen-bond acceptor does not occur has demonstrated the validity of the factoring methodology [12]. The hydrogen bonding component to the carbonyl ^{17}O nmr chemical shift for intramolecular hydrogen bonded phenolic ketones is considerably larger than for analogous N-H systems, and $\Delta\delta_{HB}$ values have been found to be related to the acidity of the donor [3,12,-14]. To date our studies have focused on ketone carbonyl groups as hydrogen bond acceptors. We report here an ^{17}O nmr study of intramolecular hydrogen bonding to the ester carbonyl in hydroxybenzoates and hydroxypyridine carboxy esters.

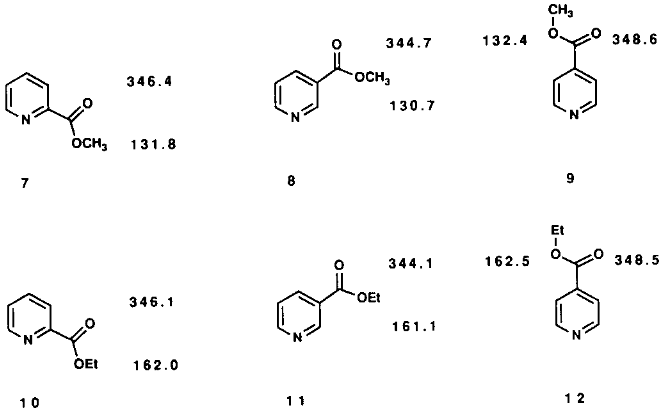
Results.

Natural abundance ^{17}O nmr data for methyl benzoates **1-3** and ethyl benzoates **4-6** obtained for acetonitrile solutions are given in Scheme 1. The carbonyl chemical shifts for **1-6** range from 320 to 340 ppm. The methoxy signal in **1-3** ranges from 125 to 131 ppm, whereas the ethoxy signal for **4-6** varies between 156 and 162 ppm. The chemical shifts of the OH signals for **2, 3, 5** and **6** are 85 ±2 ppm. Proton-oxygen coupling is directly observed for **3** (J = 73 Hz) and **6** (J = 104 Hz). The torsion angles for **1-6** predicted by molecular mechanics (MM2) calculations are 1 ±1 degrees. Hence, the carboxy ester functional group and the aryl ring are essentially coplanar and torsion angle contribution to the ^{17}O nmr chemical shift is negligible.

Scheme 1



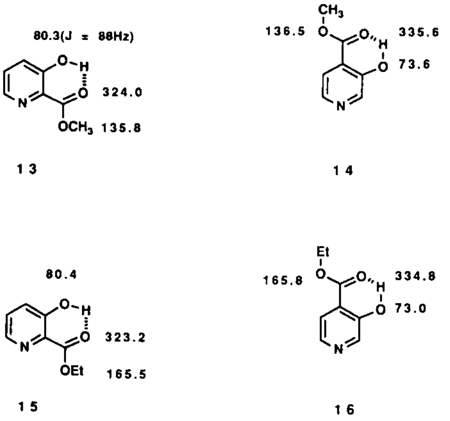
Scheme 2



The ^{17}O nmr data for the three isomers of methyl and ethyl pyridinecarboxylates **7-12** are shown in Scheme 2. The carbonyl signals range from 344 to 348 ppm, downfield from the 339 ppm value of the benzoate esters. The methoxy signals for **7-9** appear at 131 ±1 ppm whereas the value for the ethoxy signals for **10-12** are 161.5 ±1 ppm. The MM2 predicted torsion angles for **7-12** are 1 ±1 degrees, essentially the same as the benzoate values.

^{17}O nmr data for the methyl and ethyl 3-hydroxypyridinecarboxylates **13-16** are shown in Scheme 3. The carbonyl signals for the 3-hydroxy-2-pyridinecarboxylates **13** and **15** appears at 323.6 ±0.4 ppm and the values for the 3-hydroxy-4-pyridinecarboxylates **14** and **16** are 335.2 ±0.4 ppm. The chemical shifts of the methoxy signal in **13** and **14** fall at 136 ppm whereas the ethoxy signals for **15** and **16** appear at 165 ppm. The OH ^{17}O nmr signal for **13** and **15** appears at 80 ppm whereas the OH signal for **14** and **16** falls at 73 ppm. Proton-oxygen coupling was directly observed only for **13**, and the coupling constant noted was 88 Hz. The MM2 predicted values for the carbonyl group-aryl ring torsion angle is essentially zero for the series **13-16** as noted for all the esters in this study.

Scheme 3



Discussion.

A limited number of studies on ^{17}O nmr properties of functional groups attached to heterocyclic systems have appeared [15-16]. In order to fully analyze hydrogen bonding in the pyridinecarboxy ester series it is important to understand the influence of the heterocyclic nitrogen atom on the ^{17}O nmr chemical shift for simple pyridine esters. The values for the carbonyl group ^{17}O nmr chemical shifts for 2-, 3-, and 4-pyridinecarboxylic esters are all downfield of that of the corresponding benzoate esters. Compare the carbonyl ^{17}O nmr values of 339 ppm for **1** and **4** with those for **7-12** which are all greater than 344 ppm. Further examination of the ^{17}O nmr carbonyl values for the pyridine esters reveals that the 4-carboxy ester system shifts are greater than the 2- and 3-carboxy ester values. In fact, the values parallel the σ^+ values for the 2-, 3-, and 4-substituted pyridines [17]. We have previously demonstrated that the ^{17}O nmr chemical shifts of substituted methyl benzoates are correlated with σ^+ constants [18]; however the data were obtained in acetone at 40°. To test the relationship of the carbonyl ^{17}O nmr chemical shift of pyridine methyl esters **7-9** we obtained ^{17}O nmr data for the electronic extremes methyl *p*-nitrobenzoate (**17**) and methyl *p*-methoxybenzoate (**18**) in acetonitrile at 75°. Figure 1 contains a plot of the carbonyl ^{17}O nmr chemical shift data for three methyl benzoates **1**, **17**, and **18** and three methyl pyridinecarboxylates **7-9** *versus* σ^+ values. This result [$\delta = 8.7\ \sigma^+ + 339.8$; $\delta = 0.989$] indicates that ^{17}O nmr data for both benzoates and pyridinecarboxalates are reasonably well described by σ^+ constants; and that the heterocyclic nitrogen causes deshielding for the ^{17}O nmr carbonyl chemical shift in a predictable manner.

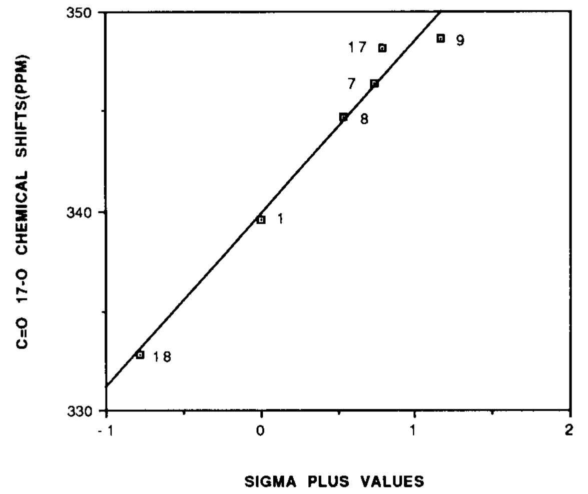
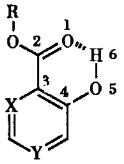


Figure 1. Plot of ^{17}O nmr chemical shifts of carboxymethyl carbonyl *vs* sigma plus constants.

It is well known that ester carbonyl groups are less basic than ketone carbonyls [19] and, consequently, ester carbonyl groups are expected to be poorer hydrogen bond acceptors than ketone carbonyl groups. ^{17}O nmr spectroscopy appears to be a sensitive method which should allow the study of intramolecular hydrogen bonding for ester carbonyls. Prior to evaluation of hydrogen bonding to pyridine carboxy esters, it is necessary to determine the effect of hydrogen bonding in aromatic hydrocarbon carboxy esters. The results listed in Table 1 show that the $\Delta\delta_{HB}$ for the ester carbonyl group in methyl and ethyl benzoate **3** and **6** is approximately 10 ppm. This value is significantly smaller than the corresponding value of 51 ±7 ppm noted for the ketone carbonyls [12], but is consistent with the lower basicity of ester carbonyl groups.

Table 1

MM2 Calculated Hydrogen Bond Distances, Bond Angles and $\Delta\delta_{HB}$ for **3**, **6**, **13-16** [a]



Compound No.	X	Z	R	H_6---O_1 (Å)	$O_1H_6O_5$	$\Delta\delta_{HB}$
3	CH	CH	CH_3	1.83	135.7	9.2
6	CH	CH	CH_2CH_3	1.83	135.7	10.3
13	N	CH	CH_3	1.85	137.0	13.4
14	CH	N	CH_3	1.83	135.0	4.0
15	N	CH	CH_2CH_3	1.85	136.0	13.9
16	CH	N	CH_2CH_3	1.84	136.0	4.7

[a] The MM2 calculated torsion angles $O_1C_2C_3C_4$ for all compounds was 1° ± 1°. [b] Hydrogen bonding component (shielding) calculated as previously described [11,12]; the electronic contribution of the OH group in **13-16** is assumed to be the same as the values for **3** and **6**.

The hydrogen bonding component ($\Delta\delta_{HB}$) for the pyridine ester carbonyl groups listed in Table 1 show interesting trends. Based upon σ^+ constant considerations (electron attraction by the heterocyclic nitrogen should lower the basicity of the ester carbonyl group) $\Delta\delta_{HB}$ values for both 2- and 4-pyridine carboxy esters should be smaller than the benzoate values. The $\Delta\delta_{HB}$ values for the 4-pyridine carboxy esters **14** and **16** are consistent with expectation; the values are 4.3 ±0.3 ppm. In contrast the values for the 2-isomers **13** and **15** are approximately 13.5 ppm, higher than the values for benzoates (*ca.* 10 ppm). This result suggest that in the intramolecular hydrogen bond complex for 2-pyridine carboxy esters that the carbonyl group is more basic than both the isomeric pyridines **14** and **16** as well as somewhat more basic than the corresponding benzoates. One rationalization of the larger $\Delta\delta_{HB}$ values is that in **13** and **15** repulsions between the nitrogen non-bonded and the alkoxy non-bonded electron pairs causes an increase in the carbonyl electron density and hence the basicity of the carbonyl group.

The data indicate that the shielding effect of intramolecular hydrogen bonding of a phenolic OH to an ester carbonyl ranges from 4 to 13 ppm; considerably smaller than the value of 51 ±7 ppm for analogous ketone carbonyl groups. As judged from $\Delta\delta_{HB}$ values the ester carbonyl group of 2-pyridinecarboxylate is more basic than that of benzoates or 4-pyridinecarboxylate. It is clear that ^{17}O nmr spectroscopy can be used to detect intramolecular hydrogen bonding even in systems for which the hydrogen bonds are only of moderate strength.

EXPERIMENTAL

The esters used in this study were prepared by literature methods (**7** [20], **13** [21], **14** [22], **15** [21], **16** [23]) and gave physical constants consistent with literature values or were available from Aldrich. The ^{17}O nmr spectra were recorded on a Varian VXR-400 spectrometer equipped with a 10 mm broadband probe. All spectra were acquired at natural abundance, at 75° in acetonitrile (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°. 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, 2 K data points, 90° pulse angle (40 μs pulse width), 200 μs acquisition delay, 29 ms acquisition time. Typically 40,000 scans were required. The spectra were recorded with sample spinning and without lock. The signal-to-noise ratio was improved by applying a 10 Hz exponential broadening factor to the FID prior to Fourier transformation. The data point resolution was improved to ±0.1 ppm by zero filling to 8 K data points. The reproducibility of the chemical shift data is estimated to be better than ±0.1 ppm.

Acknowledgements.

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REFERENCES AND NOTES

[1] G. A. Jeffrey and W. Saenger, Hydrogen Bonding in Biological Structures, Springer-Verlag, Berlin, 1991.

[2] D. W. Boykin, ed, ^{17}O NMR Spectroscopy in Organic Chemistry, CRC Press, Boca Raton, FL, 1991.

[3] A. L. Baumstark and D. W. Boykin, ^{17}O NMR Spectroscopy: Applications to Structural Problems in Organic Chemistry, in Advances in Oxygenated Processes, Vol. **III**, A. L. Baumstark, ed, JAI Press, 1991, pp 141-176.

[4] D. W. Boykin and A. L. Baumstark, *Tetrahedron*, **45**, 3613 (1989).

[5] A. L. Baumstark, P. Balakrishnan, M. Dotrong, C. J. McCloskey,

M. G. Oakley and D. W. Boykin, *J. Am. Chem. Soc.*, **109**, 1059 (1987).

[6] D. W. Boykin and A. Kumar, *Spectros. Letters*, **24**, 723 (1991).

[7] D. W. Boykin, R. L. Hertzler, J. K. Delphon and E. J. Eisenbraun, *J. Org. Chem.*, **54**, 1418 (1989).

[8] A. L. Baumstark, M. Dotrong, R. R. Stark and D. W. Boykin, *Tetrahedron Letters*, 2143 (1988).

[9] D. W. Boykin, A. L. Baumstark, M. M. Kayser and C. M. Soucy, *Can. J. Chem.*, **65**, 1214 (1987).

[10] A. L. Baumstark, M. Dotrong, M. G. Oakley, R. R. Stark and D. W. Boykin, *J. Org. Chem.*, **52**, 3640 (1987).

[11] A. L. Baumstark, S. S. Graham and D. W. Boykin, *J. Chem. Soc., Chem. Commun.*, 767 (1989).

[12] D. W. Boykin, A. L. Baumstark and M. Beeson, *J. Org. Chem.*, **56**, 1969 (1991).

[13] A. L. Baumstark, S. S. Graham and D. W. Boykin, *Tetrahedron Letters*, 957 (1990).

[14] A. L. Baumstark and D. W. Boykin, *New J. Chem.*, in press.

[15] D. W. Boykin and R. A. Rhodes, *J. Heterocyclic Chem.*, **25**, 643 (1988).

[16] R. Benassi, U. Folli, D. Iarossi, A. Mucci, L. Schenetti and F. Taddei, *J. Mol. Struct.*, **246**, 81 (1991).

[17] D. S. Noyce, J. A. Virgilio and B. Bartman, *J. Org. Chem.*, **38**, 2657 (1973).

[18] P. Balakrishman, A. L. Baumstark and D. W. Boykin, *Org. Magn. Reson.*, **22**, 757 (1984).

[19] J. March, Advanced Organic Chemistry, 3rd Ed, John Wiley and Sons, New York, 1985, p 220.

[20] E. M. Mena and E. J. Nunez, *Ciencia*, **14**, 156 (1954); *Chem. Abstr.*, **49**, 14762h (1955).

[21] H. Bojarska-Dahling and T. Uzbanski, *Rocz. Chem.*, **26**, 158 (1952).

[22] J. D. Crum and C. H. Fuchsman, *J. Heterocyclic Chem.*, **3**, 252 (1966).

[23] L. Novacek, K. Palat, M. Celadnik and E. Matuskova, *Cesk. Farm.*, **11**, 76 (1962); *Chem. Abstr.*, **57**, 15067f (1962).