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MULTINUCLEAR, VARIABLE-TEMPERATURE NMR STUDY OF HYDROGEN BONDING IN TWO *ORTHO*-MANNICH BASES

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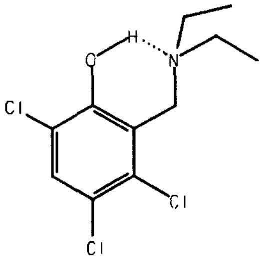
^{1}H and ^{13}C NMR data for 2-diethylaminomethyl-3,4,6-tri- and -tetrachlorophenols in CH_2Cl_2 solutions at a variety of temperatures are reported. The results are consistent with intramolecular hydrogen bonding and proton transfer as shown in the structure 3. Concentration dependence of the NMR data for the perchloro compound shows an additional hydrogen bonding process attributed to the solute self-association. The ^{1}H, ^{13}C and ^{15}N NMR data support the proposed proton transfer structure.

INTRODUCTION

It is well known that many biological processes involve proton transfers[1] which usually occur with the participation of solvent molecules. Previously we have studied[2] proton transfer in OH···N hydrogen bonded *ortho*-Mannich bases from the ΔpK_a dependence of ^{1}H NMR data at room temperature and from ^{1}H NMR spectra at temperatures between room and −60 °C for 2-diethylaminomethylphenol and its methylated analogue.[3] It was found that for the hydrogen-bonded bridge protons, the effects of pK_a on the ^{1}H NMR results are essentially the same for both inter- and intramolecular hydrogen bonding,[2] whereas for 2-diethylaminomethyl-3,4,6-trichlorophenol (**1**), the variable-temperature ^{1}H NMR data showed splitting of the signals related to the $-CH_2-$ protons of the ethyl groups below −30 °C, which is attributed to hindered nitrogen inversion corresponding to a breaking of the intramolecular hydrogen bond.[3]

In this paper, we report the ^{13}C NMR spectra of **1** taken at temperatures between 22 and −100 °C and the ^{1}H spectra over a similar temperature range in CH_2Cl_2 as a solvent. We also report results from analogous measurements on the corresponding 3,4,5,6-tetrachloro compound **2**, together with some ^{15}N NMR results.



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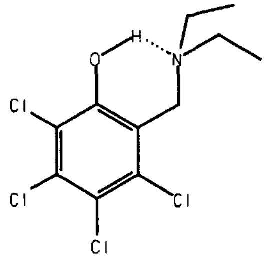

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RESULTS AND DISCUSSION

The ^{13}C NMR chemical shifts for a 0·2 M solution of **1** in CH_2Cl_2 are given in Table 1 as a function of temperature between room temperature and −102 °C. In general, a small sensitivity to temperature variation is noted. Exceptions are the results for C(1) and C(6). The shielding for C(1) decreases by 1 ppm as the temperature is lowered from 22 to −102 °C whereas the shieldings for all other carbons increase over the same range, the largest effect, of 2·28 ppm, being observed for C(6).

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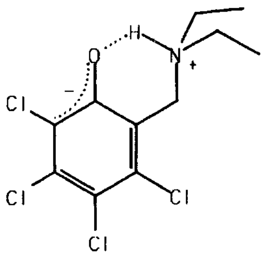
Table 1. Variable-temperature ^{13}C NMR chemical shifts (δ, ppm) for **1** taken on a solution in CH_2Cl_2 of concentration 0·2 M

Temperature (°C)	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)
22	155·21	121·31	129·20	119·64	128·83	120·95	54·69	46·49	10·52
−6	155·21	120·99	129·08	119·40	128·63	120·56	54·47	46·35	10·43
−28	155·26	120·76	129·01	119·25	128·50	120·25	54·33	46·10	10·35
−40	155·30	120·64	128·98	119·19	128·43	120·09	54·28	45·99	10·31
−51	155·37	120·51	128·95	119·13	128·37	119·91	54·22	45·86	10·27
−62	155·47	120·37	128·92	119·09	128·31	119·70	54·14	45·73	10·22
−85	155·78	120·09	128·88	119·05	128·20	119·21	54·10	45·48	10·10
−102	155·21	119·92	128·93	119·19	128·19	118·67	54·08	45·34	9·99
$\Delta\delta_{max}$	−1·00	1·39	0·32	0·59	0·64	2·28	0·61	1·35	0·53



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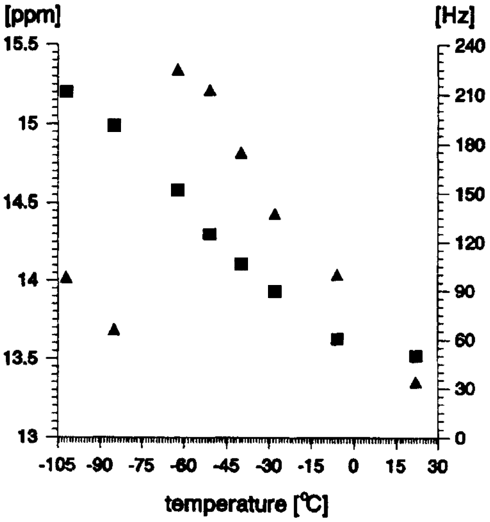
These data are consistent with an increase in the contribution of structure **3** at low temperatures. This indicates the enhanced probability of intramolecular proton transfer at lower temperatures, which is consistent with the results from the limited temperature range of ^1H NMR data observed previously.[3]

Figure 1 shows the half-width of the NMR signal for the bridging proton as a function of temperature. As the temperature decreases, the line width increases at temperatures between room temperature and about −60 °C. Following this, the line width decreases until the temperature reaches −85 °C and then it increases again. Hence it appears that a significant change occurs in the environment of this proton at about −60 °C. Such a change could be the proton transfer from the oxygen to the nitrogen atom. In agreement with this interpretation, the shielding of this proton continues to decrease monotonically at temperatures between 0 and −100 °C (Figure 1).

The temperature dependence of the $-CH_2-$ proton NMR signals of the *N*-ethyl groups are shown in Figure 2. The signal shape changes from a sharp singlet at 30 °C to an approximate AB quartet at −60 °C and to a stronger coupled AB quartet at −105 °C. These changes are observed with a 500 MHz NMR spectrometer and they differ at a given temperature from those observed on a 200 MHz instrument.[3] Therefore, we suggest the involvement of a dynamic process as the temperature is



t[°C]	δ_4[ppm]	$\Delta\nu_{½}$ [Hz]
22	13.52	34
-6	13.63	100
-28	13.93	137.5
-40	14.11	175
-51	14.30	212.5
-62	14.58	225
-85	14.99	66
-102	15.20	98

Figure 1. Plot of the chemical shift (■), δ_H, and one half-width (▲), $\Delta\nu_{1/2}$, of the bridging proton of the **1** in CH_2Cl_2 solution

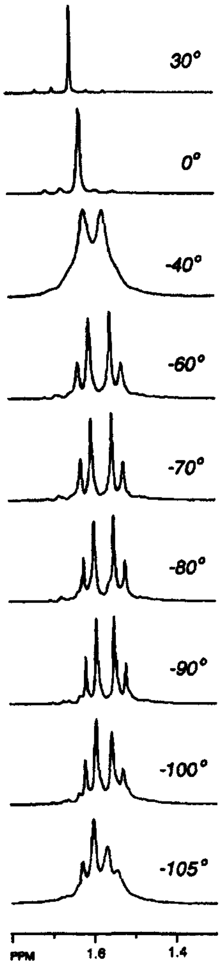
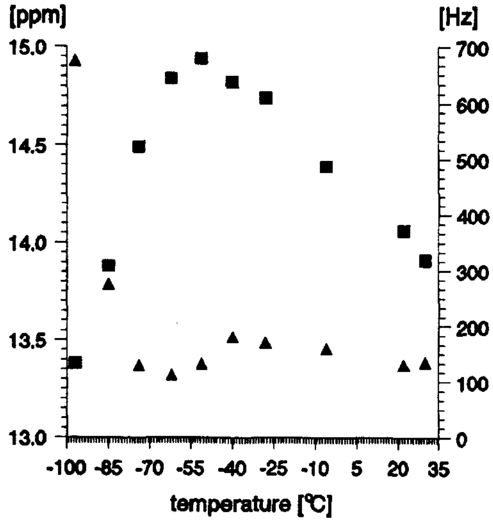


Figure 2. NMR signals of the methylene protons of the *N*-Et groups of **1** in a 0·2 M CH_2Cl_2 solution as a function of temperature

varied related to a change in equilibrium between three non-equivalent pairs of structures arising from intramolecular hydrogen bonding.[3]

In the case of the tetrachloro compound **2** more extensive NMR data, including ^{1}H and ^{13}C measurements taken on solutions in CH_2Cl_2 both as function of temperature and concentration, can be obtained. As shown in Table 2, the temperature dependences of the ^{13}C NMR signals for C(1) and C(6) are similar to those found for **1** and differ from those shown by the other carbon atoms. The larger changes shown by C(1) and C(6) for **2** compared with those found for the analogous carbon nuclei of **1** indicate that the proton transfer structure **3** is more important for **2** than for **1** in the same temperature range. This is consistent with the acidity of **2** being greater than that of **1**, the pK_a values being 3·04 and 2·72, respectively.[2]

Figure 3 shows the variation of the chemical shift and linewidth for the bridging proton of **2** as a function of temperature. A critical change occurs in these plots at about −50 °C. This critical temperature is close to that of −60 °C for **1**. A 100 MHz NMR study of **2** has shown that about −60 °C is the significant temperature for such changes to occur.[2] This perhaps suggests that the observed process is frequency dependent, which is consistent with results from vibrational



t[°C]	δ_H[ppm]	$\Delta\nu_{1/2}$ [Hz]
30	13.91	135
22	14.06	130
-6	14.39	160
-28	14.74	170
-40	14.82	180
-51	14.94	132.5
-62	14.84	112.5
-74	14.49	130
-85	13.88	275
-97	13.38	675

Figure 3. Plot of the chemical shift (■) δ_H, and one half-width (▲), $\Delta\nu_{1/2}$ of the bridging proton of **2** in CH_2Cl_2 solution

Table 2. Variable-temperature ^{13}C NMR chemical shifts (δ, ppm) for **2** taken on a solution in CH_2Cl_2 of concentration 0·2 M

Temperature (°C)	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)
30	156·32	118·98	130·03	119·90	131·38	120·27	54·71	46·68	10·37
−6	156·51	118·57	129·89	119·68	131·09	119·66	54·47	46·31	10·21
−28	156·78	118·29	129·84	119·61	130·95	119·19	54·35	46·09	10·11
−40	156·88	118·21	129·83	119·60	130·91	119·04	54·31	46·03	10·08
−51	157·33	117·95	129·81	119·62	130·80	118·37	54·18	45·81	9·90
−62	157·78	117·83	129·83	119·72	130·76	117·76	54·15	45·68	9·73
−74	158·40	117·79	129·91	119·92	130·77	116·95	53·97	45·58	9·48
−85	159·37	117·86	130·08	120·26	130·81	115·66	53·80	45·49	9·08
−97	160·25	118·05	130·28	120·61	130·86	114·43	53·64	45·47	8·72
$\Delta\delta_{max}$	−3·93					5·84	1·07	1·21	1·65

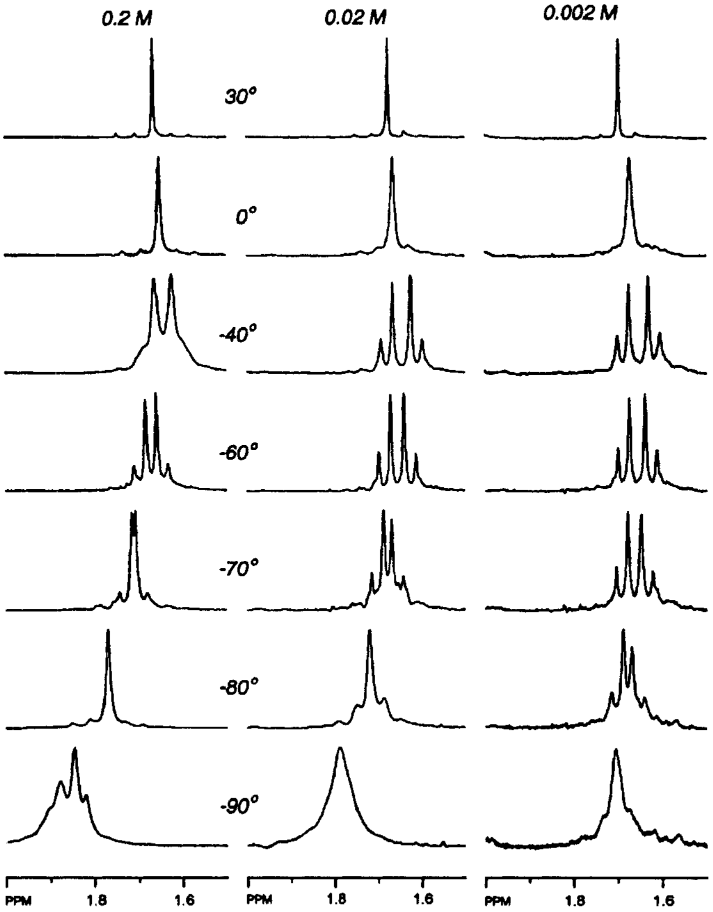


Figure 4. NMR signals of the methylene protons of the *N*-Et groups of **2** in a CH_2Cl_2 solution as a function of temperature and concentration

spectroscopy.[4] Further support is provided by the shape of the chemical shift plot given in Figure 3. The increase in the ^{1}H linewidth below about −60 °C corresponds to the transfer of the bridging proton to the nitrogen atom, where it is subject to line broadening produced by scalar relaxation of the second kind due to the ^{14}N nucleus.

Figure 4 shows the dependence of the NMR signals of methylene protons of the *N*-Et groups as a function both of temperature and concentration in CH_2Cl_2. The changes in lineshape of these signals as the temperature decreases are comparable to those observed for the analogous protons of **1** and may be attributed to a similar source, namely a change in equilibrium between three non-equivalent pairs of structures due to intramolecular hydrogen bonding.[3] The effect of the change in concentration suggests that a different process may be taking place, and we suggest that this is due to a self-association followed by the reopening of the intramolecular hydrogen bonds and possible intermolecular proton transfer.[5,6]. For each solution studied the shielding of the methylene protons decreases as the temperature decreases. In comparison with this, at temperatures below −70 °C, the ^{1}H shielding decreases as the concentration decreases, by about 0·05 ppm on going from 0·2 M to 0·002 M. Hence both decreasing temperature at a given concentration and decreasing concentration at a given temperature have comparable effects on the NMR signals of the methylene protons. This suggests that the observations are probably due to intra- and intermolecular hydrogen bonding and a self-association process, respectively.

Finally, we mention that ^{15}N NMR measurements on 0·2 M solutions of **2** in CH_2Cl_2 as a function of temperature reveal a sharp line at temperatures above −40 °C; below this temperature line broadening is observed. We have taken a spectrum at −88 °C, and did not observe ^{15}N signals. This suggests that on the NMR time-scale one or more dynamic averaging processes occur in this temperature range.

EXPERIMENTAL

All NMR measurements were made on a Bruker AM 500 spectrometer. A standard variable-temperature unit was employed. An external TMS standard in acetone-d_6 was used together with CH_2Cl_2 as solvent. The ^{1}H measurements on the *N*-Et group were performed with irradiation of the CH_3 protons and saturation of the solvent signal. For the INEPT ^{15}N measurements using long-range spin–spin couplings the delays used were taken from studies an a closely related model compound,: *N,N*-diethylbenzylamide.

Compounds **1** and **2** were prepared by previously published procedures.[7]

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