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VT ^{1}H NMR Investigations of Resonance-Assisted Intramolecular Hydrogen Bonding in 4-(Dimethylamino)-2′-hydroxychalcone

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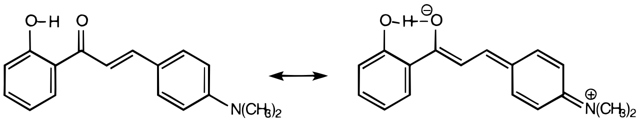
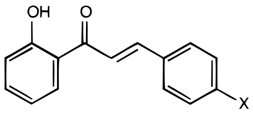
ABSTRACT



Resonance-assisted intramolecular hydrogen bonding in both polar aprotic and nonpolar solutions of 4-(dimethylamino)-2′-hydroxychalcone (DMAHC) has been investigated by variable-temperature proton NMR spectroscopy. In both nonpolar and polar solvents, the signal for the phenolic hydrogen moves downfield as the temperature is lowered. In each solvent system studied, a linear relationship between chemical shift and temperature was observed.

Because intramolecular hydrogen bonds play an important role in the conformations of biomolecules and are essential to many biochemical reactions, their properties are of special interest. Nuclear magnetic resonance spectroscopy is useful for investigating hydrogen bonds in solution.[1] When hydrogen bonding occurs, the chemical shift of the proton involved in bonding appears further downfield. 2′-Hydroxychalcone (**1a**) is capable of intramolecular hydrogen bonding between the *o*-hydroxy group and the carbonyl oxygen. Infrared and proton NMR spectroscopic data support the existence of an intramolecular hydrogen bond; the O−H stretch is very broad and appears at lower frequencies (2500−3100 cm^{-1}) than in simple phenolic systems, and the hydroxy proton is deshielded and appears downfield at 12.5 ppm in chloroform solution at ambient temperature.[2] While the energies of hydrogen bonds in the gas phase have been correlated with the crystallographic data for many substances capable of either intermolecular or intramolecular hydrogen bonding, few solution studies have been conducted involving multiple solvents of different polarities.[3]



1 a, X = H
1 b, X = N(CH$_3$)$_2$

We have measured the ^{1}H NMR spectra of 4-(dimethylamino)-2′-hydroxychalcone (DMAHC; **1b**) in a variety of

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deuterated polar aprotic, weakly polar, and nonpolar sovents at varying temperatures and herein report that, in both nonpolar and polar environments, the signal for the phenolic hydrogen appears far downfield (> 13 ppm) and shifts further downfield as the temperature is lowered (Tables 1 and 2).

Table 1. ^{1}H NMR Chemical Shifts in ppm for Hydroxy Protons of DMAHC at Various Temperatures in *d*-Chloroform, d_2-Methylene Chloride, d_3-Acetonitrile, and d_6-Acetone

temp (K)	$CDCl_3$	CD_2Cl_2	CD_3CN	$(CD_3)_2CO$
213	13.530	13.474		13.704
223	13.483	13.444		13.661
233	13.469	13.413	13.442	13.62
243	13.409	13.380	13.410	13.579
253	13.367	13.347	13.380	13.536
263	13.325	13.314	13.348	13.494
273	13.282	13.280	13.314	13.449
288	13.220	13.231	13.263	13.384
298	13.178	13.198	13.231	13.341
$\Delta\delta$ (ppb)/ΔK	−4.18	−3.27	−3.26	−4.27

The measured proton NMR chemical shift values (ppm from the signal for TMS) for the phenolic proton of DMAHC in deuterated solvents were plotted against the temperature (in K) and appear in Figures 1 and 2. The data presented in Tables 1 and 2 and graphically illustrated in Figures 1 and 2, respectively, clearly demonstrate that the hydroxy proton chemical shift is inversely proportional to the temperature, and a linear relationship between the chemical shift and temperature is observed in each case.

Table 2. ^{1}H NMR Chemical Shifts in ppm for Hydroxy Protons of DMAHC at Various Temperatures in d_{12}-Cyclohexane and d_6-Benzene

temp (K)	C_6D_{12}	C_6D_6
293	13.028	14.072
303	12.997	13.990
313	12.959	13.906
323	12.914	13.820
333	12.870	13.734
343	12.825	13.647
$\Delta\delta$ (ppb)/ΔK	−4.12	−8.47

While there is little difference in the calculated slopes of the lines for the cyclohexane and chloroform solutions of DMAHC (m[*d*-chloroform] = −0.004 18 ppm/°C and $m[d_{12}$-cyclohexane] = −0.004 12 ppm/°C), a greater difference is observed in the slope calculated for the methylene chloride solution of DMAHC ($m[d_2$-methylene chloride] = −0.003 27 ppm/°C). The inverse linear relationship between the hydroxy proton's downfield chemical shift with decreasing temperature is indicative of the strength of hydrogen bonding in DMAHC. As the temperature decreases, the NMR chemical shift of the proton involved in hydrogen bonding increases, implying that the hydrogen is further from the phenolic oxygen. An inverse temperature dependence of amide proton chemical shifts for di- and tripeptide protons involved in intramolecular hydrogen bonding has been attributed to conformational changes which occur as the temperature is varied.[4] Temperature-dependent proton chemical shifts reflect an NH group initially sheltered from its environment, buried

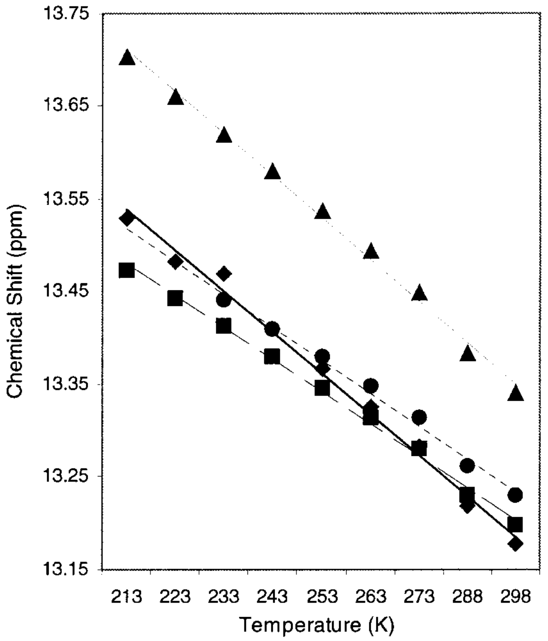

Figure 1. VT ^{1}H NMR data for the phenolic protons of methylene chloride (■), chloroform (◆), acetonitrile (●), and acetone (▲) solutions of DMAHC.

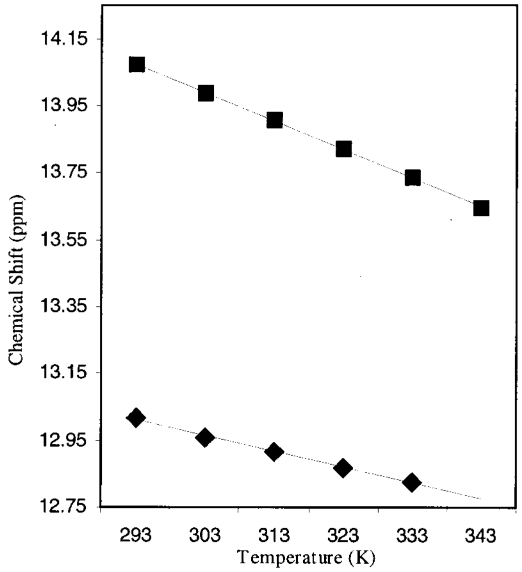

Figure 2. VT ^{1}H NMR data for the phenolic protons of benzene (■) and cyclohexane (◆) solutions of DMAHC.

either within the molecule or through hydrogen bonding, which becomes exposed to the solvent at higher temperatures. A small temperature dependence reflects a proton that is exposed to the solvent or one that is permanently shielded from its environment. Gellman has used variable-temperature infrared spectroscopy with polyamide to quantify intramolecular hydrogen bonding in polyamides dissolved in nonpolar solvents.[4b] While these investigations provide information about hydrogen bonding in nonpolar solutions of small peptides, it is controversial whether a realistic model for protein folding can be achieved in nonpolar environments.

The magnitude of the slope of the plot of proton chemical shift with temperature is indicative of the sensitivity of the hydrogen bond strength to its environment. The inverse relationship of the dependence of the proton chemical shift with temperature observed for the hydroxy proton of solutions of DMAHC is consistent with the hypothesis that there is significant contribution from the zwitterionic resonance form of 2′-hydroxy-4-(dimethylamino)chalcone in its ground-state electronic structure. 4-(Dimethylamino)chalcones exhibit relatively large ground-state dipole moments, suggestive of significant intramolecular charge transfer (ICT) in these systems.[5] Delocalization of the π electrons produces a zwitterionic resonance form. Resonance-assisted hydrogen bonding (RAHB) has been investigated by Gilli et al.[6] In DMAHC charge redistribution enhances the contribution of an enolate which is stabilized by intramolecular hydrogen bonding (Figure 3). The strongly electron-donating amino group in the *para* position of the styryl ring, therefore, strengthens hydrogen-bonding interactions *and* facilitates proton transfer. As the pK_b of the carbonyl oxygen approaches that of the phenolate ion, intramolecular hydrogen bonding is enhanced.

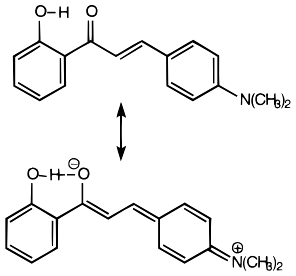

Figure 3. Resonance-assisted intramolecular hydrogen bonding in DMAHC.

The similarity in slopes for the cyclohexane and chloroform solutions of DMAHC suggests that intramolecular hydrogen bonding in these two solvent systems is similar. DMAHC solutions in methylene chloride, a slightly more polar solvent, are less susceptible to temperature fluctuations.

More curious, however, are the values calculated for the slopes for the temperature dependence of the phenolic proton of DMAHC in acetone and in acetonitrile solutions. Although both are polar aprotic solvents, their slopes are significantly different from one another. While the slope for the solution of DMAHC in acetone is similar to that calculated for the chloroform and cyclohexane solutions of DMAHC ($m[d_6\text{-acetone}] = -0.004\,27$ ppm/°C), the phenolic proton's chemical shift in the acetonitrile solution exhibits less sensitivity to temperature variations. Indeed, the slope of the plot is identical with that calculated for the methylene chloride solution of DMAHC ($m[d_3\text{-acetonitrile}] = -0.003\,27$ ppm/°C). The similarity of the plots of the acetone and chloroform solutions and of the acetonitrile and methylene chloride solutions reflects similar temperature-dependent proton delocalization. Proton deshielding, however, results from different types of hydrogen-bonding interactions in the different solvent systems.[7] In less polar solvents (cyclohexane and chloroform, for example) weaker electrostatic interactions occur between the solute and solvent. At low temperatures molecular motions decrease, solvent contraction occurs, and the viscosity of the solution increases.[8,9] As a result, the polar solute induces dipoles in the solvent molecules immediately surrounding it. The induced polarization of the solvent in turn amplifies intramolecular charge transfer in the solute. Consequently, resonance-assisted intramolecular hydrogen bonding, which increases with increasing intramolecular charge transfer in DMAHC, is enhanced at lower temperatures. Acetone, on the other hand, has a permanent dipole moment and is capable of strong solute−solvent interactions. However, acetone is also capable of hydrogen bonding with the solute, thus disrupting intramolecular hydrogen bonding. At reduced temperatures solvation by the polar solvent stabilizes charge transfer in the solute, promoting both *intra*molecular and *inter*molecular hydrogen-bonding interactions. The increase in molecular motions at higher temperatures disturbs both intramolecular and solute−solvent interactions. The significant slope observed for the plot of temperature versus the phenolic proton chemical shift for the acetone solution of DMAHC suggests that hydrogen bonding in the polar aprotic solvent is just as temperature dependent as it is in nonpolar DMAHC solutions.

The smaller slope observed for the methylene chloride solution of DMAHC, which has a slightly larger dielectric constant than chloroform, suggests that less solvent reorganization is occurring about the polar solute on solvent contraction. Although methylene chloride can weakly hydrogen bond with the solute, it cannot compete effectively

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(7) While the O−H stretch in the IR spectra of nonpolar solutions of DMAHC appears as a broad band between 2500 and 3100 cm^{-1}, indicative of a strong intramolecular hydrogen bond, two bands are observed between 3300 and 3550 cm^{-1} for polar aprotic solutions of DMAHC.

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with the carbonyl oxygen of DMAHC. As a result, the intramolecular hydrogen bond is less susceptible to temperature variations. Similarly, acetonitrile, which has a larger dielectric constant than acetone, is expected to be highly organized in the region immediately surrounding the polar solute and little reorganization would occur as the temperature is reduced.[9] While acetonitrile is expected to hydrogen bond with the solute, the smaller slope observed for the plot of temperature versus the phenolic proton chemical shift for the acetonitrile solution of DMAHC suggests that there is little change in the types of solute−solvent hydrogen-bonding interactions occurring as the temperature is varied.

The chemical shift of the phenolic proton in the benzene solution of DMAHC, on the other hand, exhibits a strong temperature dependence ($m[d_6\text{-benzene}] = -0.008\,47$ ppm/°C). While the phenolic proton appears far downfield in each of the solvents employed (+13 ppm at room temperature), benzene solutions of DMAHC have the largest δ_H values. Aromatic-solvent-induced shifts (ASIS) have been previously observed and are considered to arise from quadrupole−dipole interactions between the planar solvent molecules and a dipolar solute.[10] The flat surface of the planar aromatic solvent molecules are oriented so that the electron-rich π bonds face the positive end of the solute, thereby shielding protons near the positive pole of the dipolar solute. The negative pole of the solute is solvated by the electron-deficient edge of the aromatic ring. This orientation reduces solvent shielding of the protons near the negative end of the dipole.

The steep slope observed for the benzene solution of DMAHC is a result of solvent−solute quadrupole−dipole interactions. These weak electrostatic forces are most pronounced at reduced temperatures when the solvent becomes more viscous and its thermal motions are slowed. As the vibrational energies of the molecules increase with increasing temperature, these weak interactions are easily disrupted. Consequently, the proton chemical shift for the benzene solution of DMAHC is very susceptible to changes in temperature.

In summary, moderately polar and polar aprotic solvents stabilize intramolecular charge transfer and thus enhance RAHB in DMAHC. However, intermolecular hydrogen bonding in polar solvents disrupts intramolecular interactions and the magnitude of the temperature-dependent proton chemical shift for the hydrogen involved in these interactions most likely reflects conformational changes resulting from different types of solute−solvent interactions. Stabilization of the dipolar solute by weakly polar or quadrupolar solvents is also inversely dependent on the temperature. Solvent contraction and the degree of solvent molecule reorganization stabilizes charge polarization in the polar solute and supports resonance-assisted intramolecular hydrogen bonding. Additional investigations of DMAHC and related systems by variable-temperature ^{13}C NMR, infrared, and ultraviolet spectroscopy are underway.

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