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The ^{1}H NMR Chemical Shift for the Hydroxy Proton of 4-(Dimethylamino)-2′-hydroxychalcone in Chloroform: A Theoretical Approach to Its Inverse Dependence on the Temperature

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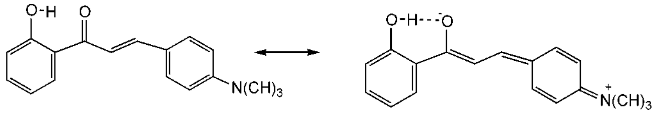
ABSTRACT



The inverse dependence of the chemical shift on the temperature experimentally found for the phenolic proton of 4-(dimethylamino)-2′-hydroxychalcone (DMAHC) is theoretically studied. As the temperature decreases, the solvent dielectric constant ϵ increases and the zwitterionic resonance form is more stabilized. Electronic calculations at the DFT level of theory were performed by immersing the solute DMAHC in chloroform cavities of different ϵ values. The values of the calculated chemical shifts for DMAHC as a function of ϵ show that the growing contribution of the zwitterionic structure justifies the experimental results.

Despite their almost universal presence and their huge importance, the understanding of many phenomena related to the hydrogen bonds still poses a challenge for both experimentalists and theoreticians. An interesting case has been reported recently by Wachter-Jurcsak and Detmer.[1] They found that 2′-hydroxychalcone (HC in Figure 1) forms an intramolecular hydrogen bond between the *o*-hydroxy group and the carbonyl oxygen in such a way that the hydroxy proton is deshielded and appears downfield at 12.5 ppm in the proton nuclear magnetic resonance spectrum in chloroform solution at room temperature. Likewise, using variable-temperature ^{1}H NMR spectroscopy, they found that the phenolic hydrogen of 4-(dimethylamino)-2′-hydroxychalcone (DMAHC, in Figure 1) in chloroform appears even more deshielded ($>$13 ppm) and moves further downfield as the temperature decreases. As a matter of fact, a linear relationship between ^{1}H NMR chemical shift and temperature has been observed.

To explain this inverse dependence on temperature, Wachter-Jurcsak and Detmer[1] hypothesized that the ground electronic state of DMAHC has a significant contribution from the zwitterionic resonance form pictured in Figure 1. This zwitterionic form is favored by the strongly electron-donating amino group in the *para* position of the styryl ring, in the sense of the resonance-enhanced H-bonding as investigated by Gilli et al.[2] At low temperatures molecular motions of chloroform would decrease in such a way that the polarization of the solvent would grow, thus amplifying the weight of that zwitterionic form. The present Letter is devoted to reproducing theoretically the experimental be-

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(1) Wachter-Jurcsak, N.; Detmer, C. A. *Org. Lett.* **1999**, *1*, 795.

(2) (a) Gilli, G.; Belluci, V.; Ferretti, V.; Bertolasi, V. *J. Am. Chem. Soc.* **1989**, *111*, 1023. (b) Gilli, P.; Ferretti, V.; Bertolasi, V.; Gilli, G. *Adv. Mol. Struct. Res.* **1995**, *2*, 67.

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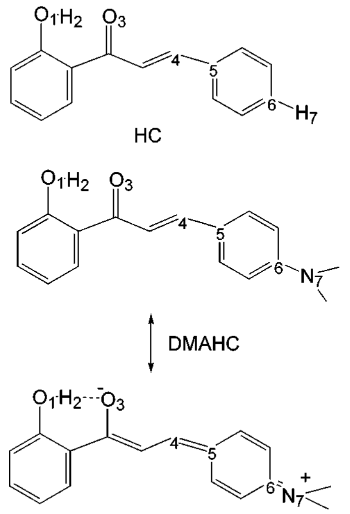

Figure 1. Structures and labels corresponding to the HC and DMAHC molecules. Two relevant resonance forms are shown for DMAHC.

havior of DMAHC and to discussing the validity of Wachter-Jurcsak and Detmer's hypothesis.

All our electronic structure calculations were carried out with the GAUSSIAN 94 package.[3] The split-valence 6-31G basis set was employed, which implies 214 functions for DMAHC. To introduce the electron correlation, we used the density functional theory (DFT).[4] Concretely, the three-parameter hybrid functional of Becke and the Lee, Yang, and Parr correlation functional, widely known as Becke3LYP, was chosen.[5] Full geometry optimizations at that electronic level of calculation were performed in order to locate the minimum energy structures for HC and DMAHC. The minima were characterized by diagonalizing their Hessian matrices and looking for zero negative eigenvalues in gas phase. To take into account the effect of the polarization of the solvent, the optimizations were repeated by immersing the solute DMAHC in a solvent cavity. In particular, a self-consistent isodensity surface polarized continuum model (SCI-PCM)[6] was adopted to represent chloroform solvent, using an isodensity value of 0.0004 au and several dielectric constant (ϵ) values.

To begin with, the minimum energy structures of HC (for the sake of comparison) and DMAHC were located in a vacuum ($\epsilon = 1$). Only a minimum for each molecule was found. The more relevant geometric parameters corresponding to both minima are given in the last two rows of Table 1. It can be seen that in the minimum of HC the proton forming the intramolecular hydrogen bond (H_2) is much closer to the phenolic oxygen (O_1) than to the carbonyl oxygen (O_3). The same fact occurs in the minimum of DMAHC, in which the $O_1{-}H_2$ and the $H_2{-}O_3$ distances are slightly longer and shorter, respectively, than in HC case. Likewise, the $C_4{-}C_5$ distance in DMAHC is shorter than the same distance in HC. All these geometric differences between both molecules are due to the fact that the zwitterionic resonance form pictured in Figure 1 has some significant weight in the ground electronic state of DMAHC, while its analogue in the HC molecule has a negligible contribution. The weight of that zwitterionic form provokes the shortening of the $C_4{-}C_5$ bond and increases the charge density of O_3, which, in turn, slightly moves H_2 from O_1 to O_3.

Table 1. More Relevant Geometric Parameters of the Minimum Energy Structures Corresponding to DMAHC for Different Values of ϵ. Values in Parentheses Correspond to HC for $\epsilon = 1$ (the last one indicates the value of the $C_6{-}H_7$ distance). Numbering of Atoms Is Indicated in Figure 1. Distances Are Given in Å

ϵ	$d(O_1{-}H_2)$	$d(H_2{-}O_3)$	$d(C_4{-}C_5)$	$d(C_6{-}N_7)$
6.76	1.0140	1.5945	1.4437	1.3770
6.12	1.0139	1.5953	1.4439	1.3772
5.61	1.0137	1.5962	1.4440	1.3774
4.806	1.0132	1.6001	1.4447	1.3782
4.00	1.0132	1.6003	1.4448	1.3783
3.71	1.0131	1.6002	1.4450	1.3784
3.00	1.0125	1.6035	1.4456	1.3791
2.00	1.0115	1.6105	1.4469	1.3806
1.00	1.0096	1.6230	1.4498	1.3840
	(1.0068)	(1.6389)	(1.4614)	(1.0852)

At this point we note that a similar inverse dependence of the chemical shift as a function of the temperature was previously found experimentally by Kato et al.[7] for the proton forming the hydrogen bond in the hexabenzyloxymethyl-XDK [*m*-xylidenediamine-bis(Kemp's triacid)-imide] monoanion in apolar organic media, a symmetric hydrogen bond (in the sense that the proton−donor and the proton−acceptor groups are identical) that turns out to be a low-barrier hydrogen bond. On the other hand, we have shown theoretically that this behavior in gas-phase symmetric potentials is the fingerprint of a low-barrier hydrogen bond.[8] However, this conclusion is not necessarily true for DMAHC, which contains an asymmetric intramolecular hydrogen bond, in

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[3] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T. A.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J.P.; Head-Gordon, M.; Gonzalez, C.; Pople, J.A. *Gaussian 94*; Gaussian, Inc.: Pittsburgh, PA, 1995.

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[6] Foresman, J. B.; Keith, T. A.; Wiberg, K. B.; Snoonian, J.; Frisch, M. J. *J. Phys. Chem.* **1996**, *100*, 16098.

[7] Kato, Y.; Toledo, L. M.; Rebek, Jr., J. *J. Am. Chem. Soc.* **1996**, *118*, 8575.

[8] Garcia-Viloca, M.; Gelabert, R.; González-Lafont, A.; Moreno, M.; Lluch, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 10203.

chloroform. As a matter of fact, as we have already mentioned, DMAHC has an unique minimum energy structure in which the proton of the intramolecular hydrogen bond is attached to the O_1 atom. When the rest of the geometric parameters are optimized to build up a monodimensional potential energy profile in the gas phase for the intramolecular proton transfer along the hydrogen bond at different H_2-O_3 distances, we obtain a single well centered at the O_1-H_2 value corresponding to the unique minimum (1.0096 Å). To move the proton up to a H_2-O_3 distance of 1.01 Å, which would roughly correspond to the second minimum if it existed (as shown, it is not the case), would require 7.70 kcal/mol. Thus it is clear that the hydrogen bond in DMAHC is not a low-barrier hydrogen bond as in the case described by Kato et al.[7] As a consequence, the inverse dependence of the chemical shift on the temperature in DMAHC cannot be attributed to the presence of a low-barrier hydrogen bond.

It is interesting to note that another magnitude that exhibits an inverse dependence on the temperature is the dielectric constant of the solvent, chloroform in this case. As temperature is lowered, the solvent becomes more polarizable and its ϵ increases in such a way that the solvent is more and more able to stabilize a charged solute or a structure involving charge separation (as a zwitterionic structure). In effect, as the dielectric constant of the cavity solvent in which DMAHC is immersed varies, the geometry of the corresponding minimum energy structures slightly changes. It can be observed (Table 1) that the greater the dielectric constant, the longer the O_1-H_2 distance, but the shorter the H_2-O_3, C_4-C_5, and C_6-N_7 distances. This evolution of the geometry is a clear indication of the increasing weight of the zwitterionic resonance form shown in Figure 1. To confirm this fact we performed a natural resonance theory (NRT) analysis of the molecular electron density of DMAHC in terms of resonance structures and their weights ($W^{(r)}$), according to the general formalism given by Weinhold and co-workers.[9] A number of reference structures have been progressively included in order to approach to a converged NRT analysis. With 25 resonant structures a consistent reference set was reached. The major results as a function of the dielectric constant are shown in Table 2. The sum of the weights of the four reference structures associated with the nonzwitterionic resonance form of DMAHC pictured in Figure 1 are given in the second column. In turn, the sum of the weights of the two reference structures similar to the zwitterionic resonance form exhibited in Figure 1 are presented in the third column. Finally, the ratios between both sets of weights are indicated in the last column. From these results it becomes evident that a decrease in temperature, which provokes an augment of the dielectric constant of chloroform, tends to reinforce the contribution of the zwitterionic resonance forms in DMAHC, as predicted by Wachter-Jurcsak and Detmer.[1] The growing contribution of the zwitterionic structure gives a stronger and more ionic intramolecular hydrogen bond, which leads to a more deshielded proton, justifying the inverse dependence of the chemical shift on the temperature.

Table 2. Weights of Reference Resonant Structures ($W^{(r)}$) Arising from an NRT Analysis of DMAHC (see text) for Different Values of ϵ

ϵ	nonzwitterionic structures	zwitterionic structures	relative weights
6.76	0.5276	0.2879	1.833
6.12	0.5281	0.2871	1.840
5.61	0.5286	0.2863	1.846
4.806	0.5301	0.2840	1.867
3.71	0.5310	0.2819	1.884
2.00	0.5354	0.2727	1.963
1.00	0.5390	0.2592	2.080

It should be pointed out that five of the values of the dielectric constant in Tables 1 and 2 were chosen because they correspond to the known experimental values[10] of ϵ of chloroform at particular temperatures within the range 213−373 K (see Table 3).

Table 3. ^{1}H NMR Chemical Shifts (δ) in ppm for Hydroxy Protons of DMAHC as a Function of the Dielectric Constant of Chloroform. The Second Column Indicates the Temperature to Which the Experimental Dielectric Constant of Chloroform Is the Value Exhibited in the First Column

ϵ	temperature (K)	DMAHC δ(calc)	DMAHC δ(exp)
6.76	213	14.928	13.530
6.12	233	14.862	13.469
5.61	253	14.800	13.367
4.806	293	14.677	
4.00		14.520	
3.71	373	14.467	
3.00		14.249	
2.00		13.790	
1.00		12.926	

A more definitive proof of the last statement would be the calculation of the ^{1}H NMR chemical shift (δ). Unfortunately, GAUSSIAN 94 does not allow for the calculation of δ inside a solvent cavity. However, to obtain a reasonable estimation of the δ values we performed the following strategy. When the solute is surrounded by a solvent cavity, the reaction field created by the solvent polarizes the solute. That is, the electronic wave function of the solute changes from the corresponding wave function in a vacuum. We will assume here that this solute polarization is the main component of the variation of δ under the influence of the solvent cavity. In other words, the NMR shielding constant (σ) is the second derivative of the total electronic energy with respect to the external magnetic field and the nuclear

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(9) (a) Glendening, E. D.; Weinhold, F. *J. Comput. Chem.* **1998**, *19*, 593. (b) Glendening, E. D.; Badenhoop, J. K.; Weinhold, F. *J. Comput. Chem.* **1998**, *19*, 628. (c) Glendening, E. D.; Badenhoop, J. K.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. NBO 4.M; Theoretical Chemistry Institute, University of Wisconsin, Madison, 1999.

(10) *Handbook of Chemistry and Physics*, 62nd ed.; CRC Press: Cleveland, OH, 1981−82.

magnetic moment of the nucleus.[11] We will assume that the more relevant contribution to σ (or, at least, to its variation) comes from the second derivative of the electronic energy of the solute in a vacuum once polarized, the second derivative of the energy corresponding to the interaction with the reaction field not being considered. In this way we evaluated the δ values of the minimum energy structures located inside the solvent cavity by calculating the corresponding δ in a vacuum but keeping the geometries and electronic wave functions (that is, the ones already polarized) found with the solute immersed in the solvent cavity frozen. The chemical shifts were obtained relative to hydrogen atoms in $Si(CH_3)_4$ from NMR shielding tensors calculated through the gauge invariant atomic orbital (GIAO) method[12] at the electronic level described above.

The values of the calculated chemical shifts of the hydroxy proton of DMAHC along with the experimental values in chloroform (really in *d*-chloroform) as a function of the dielectric constant (and, as a consequence, of the temperature) are given in Table 3. The corresponding plot vs the temperature is presented in Figure 2. It can be seen that, although somewhat larger than the experimental values, the calculated δ values are quite good, which validates the reliability of our strategy. An inverse dependence of the calculated chemical shifts on the temperature is effectively found for DMAHC in chloroform, leading to a nearly linear plot with a slope of -0.00313 ppm/°C within the range of temperatures 200−300 K, in quite good agreement with the experimental value (-0.00418 ppm/°C). It is expected that the corresponding slopes associated with different compounds derived from HC can be modulated by choosing conveniently the substituent group in the *para* position of the styryl ring.

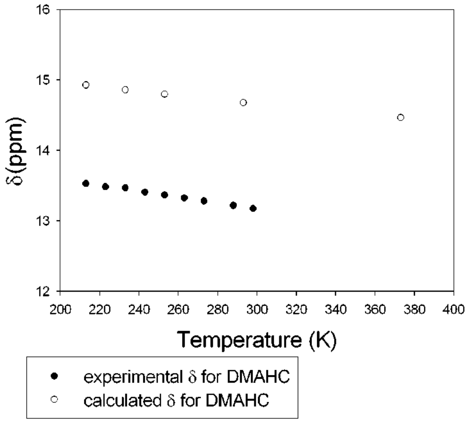

Figure 2. ^{1}H NMR chemical shifts for hydroxy protons of DMAHC vs the temperature.

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