Effect of Phenol Acidity on the Structure of Phenol-Piperazine 2:1 Complexes Using NMR

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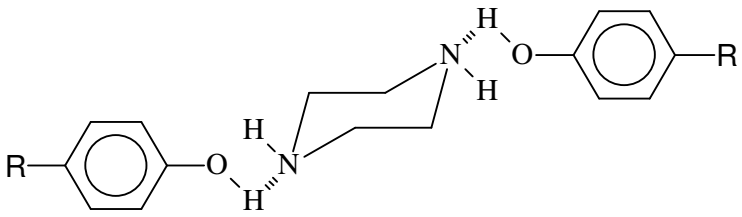
Abstract: *NMR relaxation (R_1, R_1^S and R_1^{DS} and NULL) and inter-proton distance determination, using selective excitation with DANTE, and ab initio molecular modeling (HF-STO3G) studies on the 2: 1 phenols complexes of 4-methyphenol and 4-chlorophenol with piperazine showed that both phenols form complexes stable in solution. It was found that the greater acidity of 4-chlorophenol leads to shorter OH—CH_2 distances and a tighter association between phenols and piperazine. NOE and diffusion experiments were carried out to confirm the existence of the complexes in solution. The calculated OH—CH_2 distances agree with the experimental data, being the greatest discrepancies found for the NULL method.*

It is beyond any doubt that hydrogen bonding is one of the most important interactions, from both the viewpoint of fundamental chemical physics, and also of practical importance in biochemical processes, molecular recognition,[1] and organic synthesis.[2] In fact hydrogen-bonding has received significant attention in recent years, from both experimental and theoretical viewpoints. However, there are still several experimental observations that have not been understood, and fundamental questions that have not been answered, particularly for systems with relatively strong hydrogen bonds. Recently, we have demonstrated that 2:1 phenol-piperazine complexes, studied by X-ray[3] diffraction techniques, do exist as such in solution. In this work, we use non-selective, selective, double selective and NULL[4] longitudinal relaxation rates (R_1, R_1^S and R_1^{DS}) to determine inter-proton distances, correlation times(τ_c)[5], and molecular self-diffusion coefficients (D) using DOSY[5] to study the effect of the acidity of phenol in the structure of some complexes in solution. Thus, we have made a comparison between the piperazine complexes of 4-methylphenol (**1**) and 4-chlorophenol (**2**) with piperazine (Figure 1).

The ^1H relaxation measurements (R_1, R_1^S and R_1^{DS}) and NULL experiments were carried out in a Varian UNITY-300 NMR spectrometer using 0.2M solutions in $CDCl_3$ at room temperature. The maximum pulses for the DANTE trains in each experiment did not exceed 300, and each pulse potency was attenuated to 45 Db. The DOSY experiments were carried out using STE-PFG pulse sequence in a Bruker DRX-400 NMR spectrometer; the duration of field gradient pulse (10 ms) and of diffusion time (20 ms) were constant.

The theoretical structures of the complexes were optimized using the Gaussian98/ Gaussian View 2.1 package with the HF-STO3G method. The OH—CH_2 distances obtained by this calculation were compared

with the distances determined by NMR in solution.



1 R=CH_3
2 R=Cl

Figure 1

Molecular diffusion NMR and NOE experiments were conducted to confirm the existence of complexes in solution. The results for OH—CH_2 distances for both compounds are shown in Table 1.

The results from Table 1 indicate that the increase in phenol acidity leads to a decrease in OH—CH_2 distance. Clearly, as phenol acidity increases the tendency to transfer phenol OH to the basic nitrogen of piperazine increases, thus decreasing OH—CH_2 distance.

Table 1. Results for OH—CH_2 distance for complexes **1** and **2,** determined using double selective T_1 relaxation, NULL, molecular modeling, and phenol pKa.

	OH—CH_2 distance (Å)	
Method	**1**	**2**
pKa	10,23	9,38
T_1^{DS}	3,31	2,87
Null	3,29	2,47
M. M.	3,16	2,79

For a salt, H transfer must be complete, and OH—CH_2 distance should be similar to that between NH-CH_2 in pure piperazine (2.39 Å).

Our results also show that the easiest and most reliable method for distance determination is using T_1^{DS}, as NULL using DANTE needs a careful pulse calibration and determination of the number of pulses for the DANTE train. Besides, small deviations may lead to discrepancies.

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