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Self-Associative Properties of Quinoline Derivatives in Solution

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Experimental data from proton NMR studies combined with ab initio calculations (energy and GIAO chemical shifts) indicated that quinoline(s), in solution, exist in equilibrium as a series of stacks (dimers or *n*-mers) that are slightly different in mutual orientation. The self-association constant depends dramatically on the concentration of the substrate: at low concentration, recognition occurs and dimerization, with association constants that are approximately 200 times larger than for higher *n*-mers at higher concentration, was observed.

Non-covalent (hydrogen bonding, dispersion, or van der Waals, VDW) interactions play a key role in different processes in chemistry, pharmacology, and, in particular, biochemistry.[1a–f] The role of hydrogen bonding (HB) in such processes is well established and many surveys are devoted to this phenomenon.[2a,b] The importance of dispersion interactions in biological processes is also discussed in the literature, although only to a limited extent.[3a–g] These forces determine diverse phenomena because such interactions have a cooperative character. During the last decades, there has been an explosion of interest in investigations of such interactions in order to obtain insights into the interactions–activity relationship.[4a–f] But most of the studies, in particular recent ones, are theoretical.[5a–t] Progress in computational algorithms and computer hardware has opened up new horizons in modeling such systems on a higher theoretical level. Nevertheless, experimental investigation of this phenomenon for structure determination and access to thermodynamic parameters of association is of great importance and highly needed. There are only very few experimental examples dealing with intermolecular stacking association in solution based on NOE NMR data.[6a–c] But, in reality, in most of these cases the HB is also involved and, perhaps, only some contribution due to dispersion interactions can be expected. Stacking interactions in solution have been studied indirectly by monitoring chemical shift changes with variation of concentration of substrate in solution.[7a–i] Recently, unprecedented concentration ^{1}H NMR chemical shift dependences for a variety of quinolines have been reported.[8]

Quinolines and related systems are of interest because they can be considered as models for a variety of heteroaromatic compounds exhibiting biological and pharmacological activities.[9] Their activity may be either due to their ability to produce VDW complexes with different "hosts" and/or due to their ability to self-associate, leading to qualitatively different behavior compared with the monomer. The present investigation is an attempt to obtain insight concerning the association mechanism of these compounds and to propose reasonable explanations for observed ^{1}H NMR dependencies on the basis of theoretical and experimental data. The scope and limitations of the model are discussed.

Results and Discussion

Association into *n*-Mers (Dimer, Trimer, ...). The concentration dependence of ^{1}H NMR chemical shifts in heteroaromatic compounds indicates that these molecules are prone to association or self-association, and the observed data correspond to the average exchange spectra due to equilibrium between monomers and associated complex(es). To obtain a preliminary idea about the process, we tried to analyze this problem by theoretical methods. Semi-empirical methods have a drawback in the evaluation of dispersion interactions of stacked complexes. Only non-empirical calculations, with inclusion of electronic correlations, may take into account dispersion interactions.[5b] Unfortunately, computational facilities are still limited and we can not run such calculations for systems such as quinoline dimers.

To evaluate whether van der Waals interactions may lead to the stacked complexes, we first carried out ab initio calculations using pyridine as a model. These calculations revealed two stable stacked dimers in which pyridine planes are shifted (Fig. 1). These dimers are slightly more stable than a monomer. An additional stable "perpendicular" T-dimeric complex was also found to correspond to an energy minimum.

However, molecular mechanics calculations employing the MM2 force field[10] for this model also revealed stable stacked dimers, although MM calculations essentially overestimate dispersion interactions compared to MP2/6-31G results. Therefore, we concluded that, although MM calculations predict quite reasonable energy minima geometry, the energy data should be considered with great care.

Geometry optimization for quinoline **1** dimers was performed in the frame of the MM method. According to MM calculations, the most stable structures are stacked dimers, which are close in energy and differ only in mutual orientation of the

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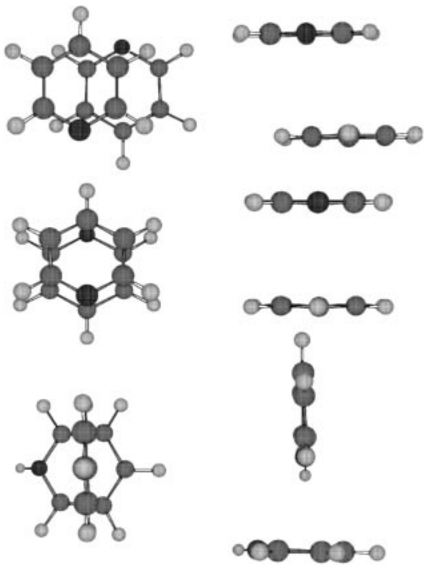


Fig. 1. MP2//6-31G optimized pyrimidine dimers.

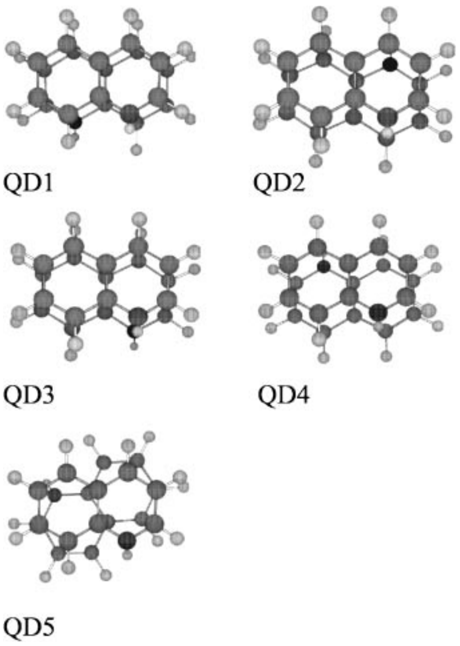


Fig. 2. Most stable dimers of quinoline **1** according to MM calculations.

planes and by the rotation angle around the axis perpendicular to the plane of the molecule (Fig. 2). Trimers of quinoline **1** also correspond to stable complexes (Fig. 3). Such a structure should lead to shielding effects for most of the protons; this is qualitatively in accordance with experimentally observed high field shifts for most of the protons when the concentration of the compound is increased.

We then decided to qualitatively estimate if the structure of the associated complex depends on the particular structure of the quinoline (Q, **1**) (Scheme 1) derivative, that is, if it is only self-association or if the same association process occurs with any compound of this type. MM calculations for the complex of Q **1** with 6-Me quinoline (6-Me-Q, **2**) suggest that stabilization of the stacked complex should be essentially the same. We monitored the chemical shifts of quinoline **1** itself when the concentration of 6-Me quinoline **2** was varied: the dependences of quinoline **1** chemical shifts with variations of concentration of Q **1** itself and of 6-Me-Q **2** in both experiments are the same (Table 1). Thus, substitution on the quinoline ring and the position of the substituent on the ring exert only slight influences on the structure of the complex. The reverse should be observed in the case of flat complexes.

Another complementary proof of the above conclusion was obtained from NOE experiments.[11] We referred to the fact that if there is some preferred type of complex, then NOE's should be observed due to intermolecular dipole–dipole proton inter-

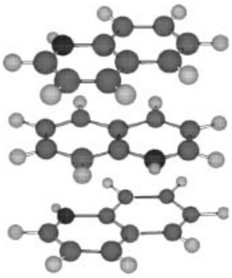
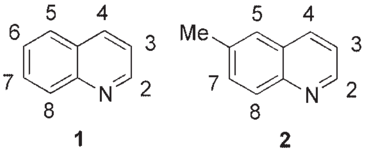


Fig. 3. One of the stable trimers of quinoline **1**.



Scheme 1.

Table 1. Dependence of ^{1}H NMR Chemical Shifts of **1** on Concentration of **2** in Solution of $CDCl_3$ at Room Temperature

[**1**]/[**2**] (mM)	H2	H3	H4	H5	H6	H7	H8
0.1/0	8.856	7.341	8.106	7.759	7.487	7.660	8.063
0.1/0.015	8.852	7.336	8.100	7.754	7.482	7.649	8.059
0.1/0.06	8.848	7.322	8.084	7.744	7.473	7.647	8.042
0.088/0.78	8.771	7.200	7.996	7.631	7.372	7.559	7.954
0.062/2.78	8.620	br	br	br	br	br	br
0.81/0.71	8.726	7.126	7.969	7.565	7.321	7.505	7.878

In ppm; all spectra referred to TMS = 0; br: broad signals.

actions. Therefore we tried to observe such effects between the protons of quinoline **1** and those of 6-Me quinoline **2**, because in the latter most of the resonances differ from quinoline **1** and, in addition, at least the 6-Me resonance is separate from the rest of the resonances and therefore can be irradiated selectively.

These experiments (1D DPFGNOE[12]) have not shown any selective NOE that could be expected if a flat ribbon-like structure was well populated. There are only intramolecular effects between 6-Me and H5/H7 in **2** and intermolecular effects between the 6-Me group of **2** and a variety of aromatic protons of **1** and **2** (Fig. 4) which are two orders of magnitude less strong than intramolecular ones.[13]

Such NOE signals due to irradiation of the 6-Me group can be explained if quinolines exist in equilibrium with a series of stacks (dimers or *n*-mers) which are slightly different in mutual orientation (Fig. 2).

Thus, flat ribbon-like structures can be excluded from consideration as having any notable population and we focused our attention instead on the analyses of stacked complexes.

We next tried to establish which is the most stable dimer and what kind of equilibrium occurs in this case. To this end, we evaluated the chemical shifts of the protons of quinoline **1** in the structures considered above (Fig. 2). Calculations were carried out using a GIAO DFT approach[14a–h] with geometries optimized by the MM method. The calculated data for stacked structures are given in Table 2.

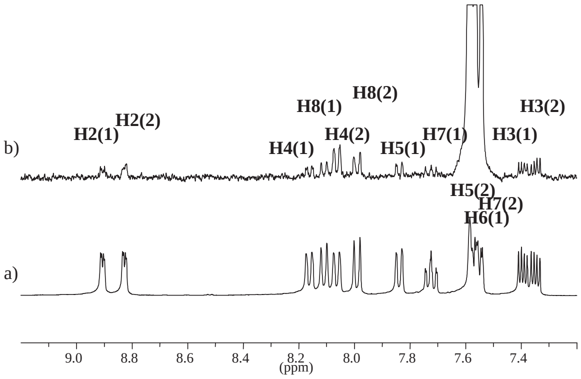


Fig. 4. Low field region of ^{1}H NMR spectra of the mixture **1** and **2** (0.1 mM/0.1 mM) in CD_2Cl_2 at room temperature (a) normal spectrum and (b) 1D NOE with irradiation of 6-Me of **2** (mixing time 0.8 sec).

High field shifts for most of the protons except H8 in stacked forms are predicted by theory. Minimal changes are expected for H2 (0.2 ppm) and the most spectacular changes should be for H4 (2 ppm). For H8, dependence may even be reversed if the role of the QD1 dimer is important. These results are in qualitative agreement with experimental data,[8] i.e. maximal changes are observed for H4, a minimal change for H2 and some reverse effect was seen for H8 in the range of concentrations used.

In order to verify if there is a dimer or *n*-mer formation process, to discover which complex is predominant and to evaluate the association constant of the process, we decided to repeat the experiments described in Ref. 8. When we ran the experiments with the mixture of Q **1** and 6-Me quinoline **2**, we started from a minimal concentration at ca. 0.01 M, because according to Ref. 8 at concentrations around 0.02–0.04 M no changes of chemical shifts were seen. In fact in our case also, up to 0.005 M concentrations the dependences were very similar to the ones described in Ref. 8. In order to calculate thermodynamic parameters according to the approach given in Ref. 15, we needed the chemical shifts of a monomer. We decided to obtain parameters at lower concentration to ensure that those observed at 0.005 M correspond to the monomer. But unexpectedly, at 0.001 M most of the lines started to move dramatically to low field again (see Fig. 5).

At a concentration of ca. 0.0002 M we were able to observe the collapse of several signals and then at lower concentration (0.000045 M) the signals became sharper again. The line shape

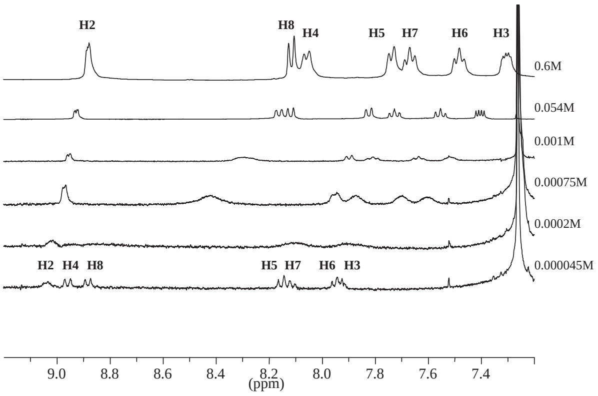


Fig. 5. ^{1}H NMR spectra of quinoline **1** in $CDCl_3$ at different concentrations (M).

Table 2. Calculated Chemical Shifts (GIAO B3LYP 6-31G(2d)//MM2, in ppm) of Quinoline **1** in Monomer and Different *n*-Mers[a)]

Proton	Q	QD1	QD2	QD3	QD4	QD5	QT (inner cycle)	QT (side cycle)
H2	8.349	8.123	8.085	8.163	8.104	8.122	7.921	7.808
H3	7.733	6.270	6.417	6.354	6.286	6.422	5.771	6.362
H4	9.053	7.017	7.241	7.053	7.125	7.055	6.301	6.963
H5	7.722	6.814	6.900	6.813	7.012	6.875	6.633	6.451
H6	7.693	6.711	6.680	6.690	6.768	6.796	6.779	6.343
H7	7.406	7.004	6.931	6.924	6.934	6.941	6.281	6.799
H8	7.332	7.395	7.156	7.273	7.176	7.084	6.187	6.978

a) Notation corresponds to Figs. 2 and 3.

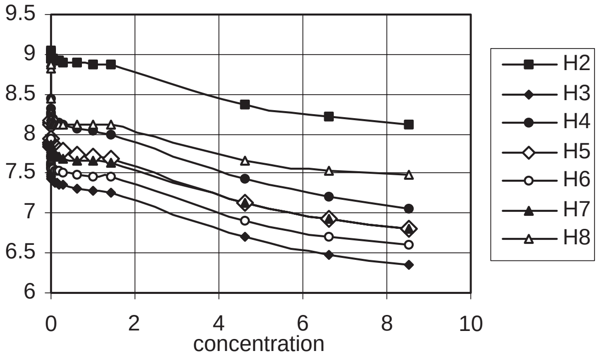


Fig. 6. Chemical shift (δ, ppm) vs concentration (M) for the protons of quinoline **1**.

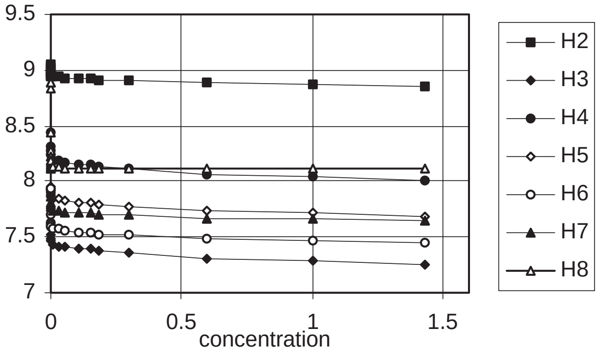


Fig. 7. Chemical shift (δ, ppm) vs concentration (M) for the protons of quinoline **1** at intermediate concentrations.

evolution was very similar to that when the exchange rate is passing through a slow exchange regime on the NMR time scale, during a variable temperature experiment. This seems likely due to the low concentration of the substrate, so low that the probability of two molecules of quinoline meeting to produce a dimer is small. Then the half-life of the resulting dimer would be so short that these molecules could only be observed in monomeric form.

It is interesting to analyze the dependence of ^{1}H NMR chemical shifts with concentration. If we start from a high concentration (Fig. 6) we see one slope that corresponds to one specific process. Such dependence is probably due to equilibrium between different *n*-mers where *n* is high. From a concentration of ca. 1.5 up to 0.01 M (Fig. 7) there is another process, which could correspond to the equilibrium between *n*-mers of lower *n*.

At concentrations lower than 0.01 M, we see the evolution of the signals corresponding to equilibrium between monomer and dimers (Fig. 8). Moreover, there is almost no modification of the chemical shift of the H2 proton. When one takes into account the results of shielding effect calculations for different dimers, this suggests that the main process is the equilibrium between the monomer and one of the dimers.

At intermediate concentrations, H8 changes only slightly; this can be interpreted as being due to QD**1** dimer contributions becoming more notable.

Self-Association Constants. To derive self-association constants, we employed the isodesmic model.[15] This model of solute self-association is based on the assumption that solute molecules associate to form stacks (dimers, trimers, etc.) where the equilibrium constant K_a for each step is the same. Thus:

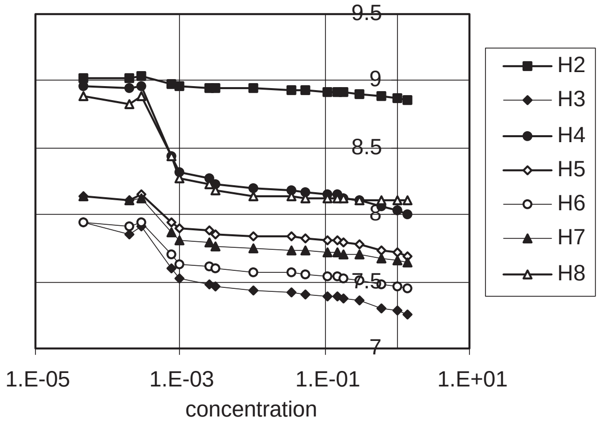


Fig. 8. Chemical shift (δ, ppm) vs concentration (M) for the protons of quinoline **1** at low concentrations.

$$\begin{aligned} &\mathrm{A} + \mathrm{A} \rightleftharpoons \mathrm{A}_2 \\ &\mathrm{A} + \mathrm{A}_2 \rightleftharpoons \mathrm{A}_3 \\ &\mathrm{A} + \mathrm{A}_{n-1} \rightleftharpoons \mathrm{A}_n. \end{aligned} \tag{1}$$

In the framework of the model, the following simplifying assumptions are made:

i. Successive association constants are identical.
ii. The effects of magnetic anisotropy of neighboring molecules are additive.
iii. Only the magnetic anisotropy of nearest neighbors is taken into account.

The observed chemical shift (δ) will be given by the following relationship.

$$\delta - \delta_a = (\delta_{max} - \delta_a)K_a[\mathrm{A}]_0\{2/[1 + (4K_a[\mathrm{A}]_0 + 1)^{1/2}]\}^2, \tag{2}$$

where δ_a is the proton chemical shift of the monomer, δ_{max} is the maximal proton chemical shift of a solute A present in a stack, and $[\mathrm{A}]_0$ is the total concentration of solute A.

Straightforward calculations with the above simplifications lead to

$$\sqrt{(\delta - \delta_a)/[\mathrm{A}]_0} = \sqrt{K_a/2\delta_{max}}(2\delta_{max} - (\delta - \delta_a)). \tag{3}$$

Note that a dimerization model which assumes only the possible shift values δ_a and δ_{dimer}, with an association constant K_{dimer}, leads to the equation that has an almost identical form, the only differences being that K_a is replaced by $2K_{dimer}$, and $(\delta_{max} - \delta_a)$ is replaced by $(\delta_{dimer} - \delta_a)$.

A plot of $\sqrt{(\delta - \delta_a)/[\mathrm{A}]_0}$ against $(\delta - \delta_a)$ will thus give a straight line whose slope and *x*-axis intercept are $\sqrt{K_a/2\delta_{max}}$ and $2(\delta_{max} - \delta_a)$, respectively.

According to the model leading to Eq. 3, a plot of $\sqrt{(\delta - \delta_a)/[\mathrm{A}]_0}$ vs $(\delta - \delta_a)$ gives curved lines for all the protons of quinoline in the concentration range investigated (0.00005–8.4 M) and not a straight line as should be expected (Fig. 9. Only the graph for H-3 is given. For other protons, very similar dependences were seen). Taking into account assumptions (ii) and (iii) in the model based on a reasonable

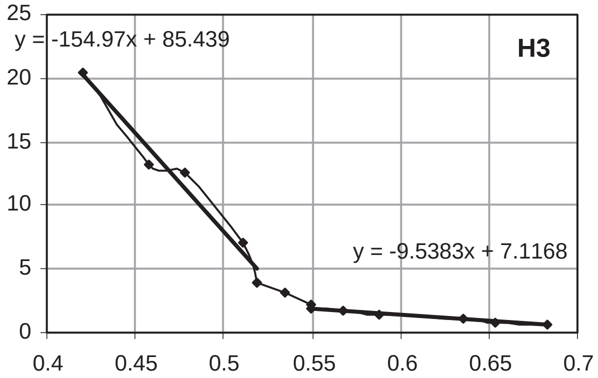


Fig. 9. Plot of $\sqrt{(\delta - \delta_a)/[\mathrm{A}]_0}$ vs $(\delta - \delta_a)$ for H3 proton of quinoline **1**.

Table 3. The Self-Association Constants (K_a) and Maximum Changes in Chemical Shifts ($\Delta\delta_{max}$) for Quinoline **1** in $CDCl_3$ at 298 K

	Low concentration		High concentration	
	K_a/L mol^{-1}	$\Delta\delta_{max}$/ppm	K_a/L mol^{-1}	$\Delta\delta_{max}$/ppm
H2	17.5×10^3	0.094	15.7	0.1
H3	6.5×10^3	0.55	67.5	0.38
H4	8.5×10^3	0.83	117	0.51
H5	5.5×10^3	0.33	32.8	0.26
H6	8×10^3	0.39	73	0.27
H7	7.5×10^3	0.43	114	0.27
H8	8.4×10^3	0.79	0.57	1.63
Average	**8.8×10^3**		**45**	

physical background, we can conclude that the first assumption concerning successive association constants being identical is not correct. The slope in each point reflects an actual association constant at that concentration and we can easily distinguish at least three different areas of concentration with different microscopic association constants: large K_a at low, intermediate K_a at intermediate and very small K_a at high concentrations, respectively. We can roughly estimate K_a by approximations of the curves by straight lines, for example, at low concentrations and others at high concentrations. From these approximations, the association constants were calculated and are given in Table 3.

Thus, we can conclude that the association constant depends dramatically on the concentration of substrate. Particularly, at low concentration we observe dimerization with an association constant that is approximately 200 times larger than for higher *n*-mers at higher concentration. These results are of significant importance in NMR studies of recognition of substrates by heteroaromatic compounds. It is thus important to take into account such effects in studies which rely on the variations of chemical shifts observed.

Experimental

^{1}H NMR spectra were recorded on an Avance 400 and MSL 400 NMR spectrometer, in $CDCl_3$ (Aldrich) solutions. $CDCl_3$ was used without particular precautions, since no changes were observed using a solvent passed though a short pad of Alumina. Chemical shifts (ppm) are internally referenced to TMS in all cases. One- and two-dimensional NMR spectra were measured with standard pulse sequences. 1D and 2D NOESY: mixing time 0.8 s. The temperature was controlled to 0.1 °C. Molecular mechanics (employing the MM2 force field) calculations were performed by the CS Chem3D Ultra 6.0 (CambridgeSoft Corporation) on an AuthenticAMD Athlon(Im) computer. Ab initio electronic structure calculations were performed using GAUSSIAN 98.[16]

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