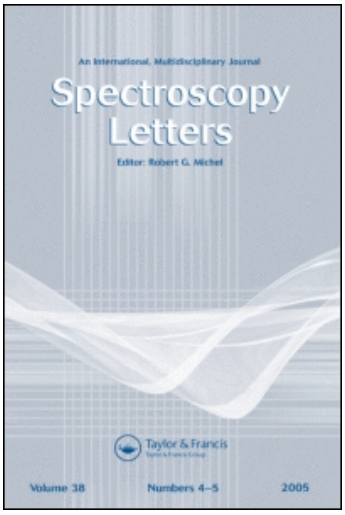

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Concentration-Dependent Variation of ^{1}H-NMR Chemical Shifts of Aromatic Protons in Sampangine Derivatives

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ABSTRACT

A concentration dependence of the ^{1}H-NMR chemical shifts of the aromatic protons in sampangine derivatives with a fused imidazole ring is observed. This variation is probably ascribable to self-association of the molecules through an intermolecular π-stacking interaction of the aromatic rings. The quantitative variation is correlated with the calculated electrostatic potential for these derivatives. The concentration variation

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appears to be independent of the nature of the substitution in the imidazole ring.

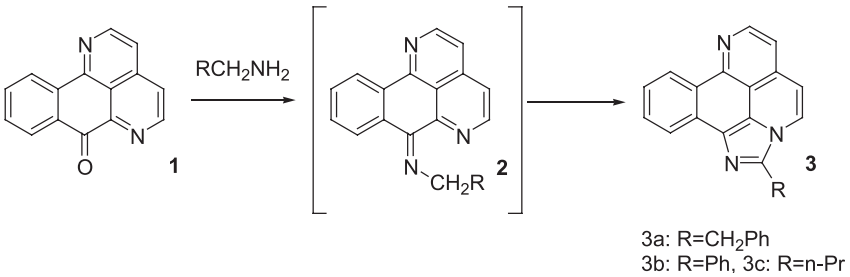
Key Words: NMR; ^{1}H; Shift variations; Concentration dependence; Molecular modeling; Intermolecular interaction; Sampangine derivatives.

INTRODUCTION

NMR spectroscopy has been demonstrated to be a very useful tool for probing the details of molecular structure. It is widely used in many research fields, especially organic chemistry, bioorganic chemistry and biochemistry. In particular, the phenomenon of concentration dependence in NMR spectra is of considerable current interest.[1–5] Concentration-dependent chemical shifts have been used to study molecular association.[6,7] Such studies have been undertaken primarily for nucleobases[8–13] and oligomers.[14–16] Fused aromatic and heteroaromatic systems are known to possess novel properties such as functional materials[17–19] and biologically active compounds.[20–22]

Sampangine (**1**), a natural alkaloid with four fused conjugated rings including a 2,7-naphthyridine moiety, is reported to be active against *Candida albicans* and *Cryptococcus neoformans*[23] and to show interesting reactivities in nucleophilic and electrophilic substitution.[24–26] In the course of studies on the structural modification of **1**, we obtained several new derivatives of sampangine (**3a–c**), possessing a fused imidazole, instead of the anticipated Shiff base (**2**)[27] (Scheme 1).

We have examined the proton NMR spectra of **3a–c** and found a concentration dependence of the NMR of the aromatic protons in **3a** and **3b**.[28]



Scheme 1. Reaction of sampangine with phenethyl, benzyl, and n-butylamine.

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EXPERIMENTAL

All spectra were recorded at ambient temperature in 3 mm sample tubes on a Bruker DRX-400 NMR spectrometer in $CDCl_3$. Deuteriated chloroform (99.8% D) was obtained from Cambridge Isotope Laboratories, Inc. (Andover , MA). Chemical shifts are reported in parts per million (ppm) relative to internal standard, tetramethylsilane (TMS) at 0.0 ppm.

Computational calculations were performed with the SPARTAN V 5.0 program (Wavefunction Inc., CA) mounted on the Indigo^2 Workstation (Silicon Graphics, Inc. CA). The geometries of **3** were optimized at the AM1, and electrostatic potential maps were calculated using these geometries at the HF/6-31G*.

RESULTS AND DISCUSSION

We have found that the proton chemical shifts of **3a–c** are dependent on their concentration in solution. Table 1 shows the ^{1}H-NMR spectra of **3a–c** in $CDCl_3$ at various concentrations (mM).

The magnitude of the shift variation for **3a–c** decreases in the order H-4 > H-5 > H-3 > H-2 > H-8, 11 $\gg$ H-9, 10.

It is worth noting that the best-dispersed spectra are obtained at 60 and 90 mM; this implies that the a suitable concentration exists to obtain the best spectrum, which is important for smooth assignment of signals. The magnitude of the variation increased in CD_3OD, while it decreased in DMSO-d_6, CD_3CN, and benzene-d_6 compared with in $CDCl_3$. These effects suggest that the magnitude of the variation in ^{1}H shifts is not necessarily dependent on hydrophilicity, polarity, or aromaticity of the solvents. As has already been described for aromatic systems,[7] the chemical shift variations observed in this study do not appear to be due to the change in conformational population (with concentration) of the pendant groups in **3a–c**.[29] In order to consider the origin of this phenomenon, we examined the electronic configuration of **3a–c** by use of molecular modeling. The electrostatic potential map for **3a** clearly indicates that the aromatic protons are positively charged and that nitrogen atoms (N-1 and N-7) are negatively charged (Figure 1).

The most remarkable observation is that the magnitude of the electrostatic potential of these protons is proportional to the observed chemical shift variations. The NMR signals for H-3, -4, and -5, which exhibited greater positive charge, were observed to have a greater concentration variation than those of H-9 and-10, which are less positively

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Table 1. Relative changes in chemical shifts ($\Delta\delta$) of **3a**, **3b**, and **3c** with the change of sample concentration [mM] in their ^{1}HNMR spectra in $CDCl_3$. The positive changes are downfield, shown in ppm, relative to signals measured for 120 mM.

Compound	**3a**						**3b**						**3c**					
Concentration [mM]	7	15	30	60	90	120	7	15	30	60	90	120	7	15	30	60	90	120
H-2	0.13	0.11	0.08	0.06	0.02	**8.95**	0.17	0.16	0.11	0.06	0.04	**8.95**	0.12	0.10	0.08	0.07	0.01	**8.99**
H-3	0.22	0.19	0.14	0.10	0.05	**7.33**	0.23	0.23	0.18	0.12	0.05	**7.37**	0.22	0.19	0.13	0.10	0.02	**7.41**
H-4	0.30	0.25	0.19	0.11	0.06	**6.65**	0.30	0.27	0.20	0.11	0.05	**6.85**	0.30	0.22	0.19	0.12	0.02	**6.80**
H-5	0.25	0.21	0.16	0.11	0.06	**7.50**	0.24	0.23	0.15	0.09	0.04	**8.17**	0.29	0.26	0.18	0.12	0.03	**7.78**
H-8	0.06	0.06	0.04	0.03	0.01	**8.69**	0.10	0.10	0.08	0.04	0.02	**8.70**	0.06	0.05	0.04	0.04	0.00	**8.66**
H-9	0.00	0.01	0.00	0.01	0.00	**7.86**	0.08	0.08	0.06	0.03	0.01	**7.82**	0.04	0.02	0.02	0.02	0.00	**7.84**
H-10	0.00	0.00	0.00	0.00	0.00	**7.73**	0.06	0.06	0.04	0.02	0.01	**7.70**	0.04	0.02	0.02	0.02	0.00	**7.71**
H-11	0.06	0.06	0.05	0.04	0.02	**9.29**	0.13	0.13	0.09	0.04	0.03	**9.24**	0.04	0.03	0.02	0.02	0.00	**9.29**

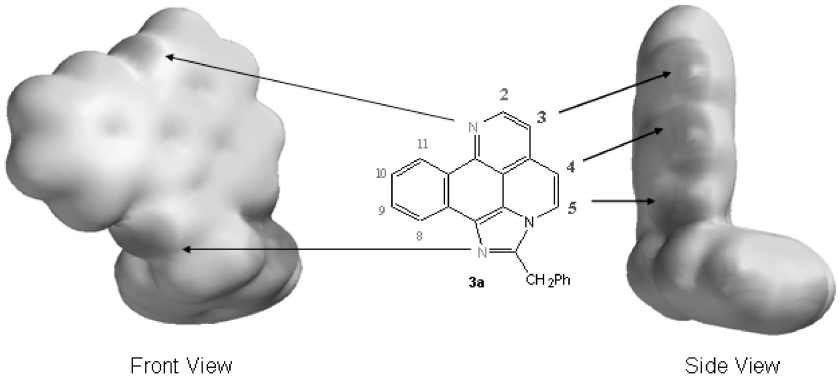

Figure 1. Electrostatic potential map for **3a**. *(Go to www.dekker.com to view this figure in color.)*

charged.[a] These finding were also observed for **3b**[b] and hence led to the assumption that the protons in one molecule interacted with the nitrogen atoms in the other one (or more). Nitrogen-15 NMR experiments at various concentrations, however, indicated an absence of such interactions because the magnitudes of the variation in ^{15}N shifts are very small in contrast to those in ^{1}H shifts. These observations suggest the possibility of an aromatic interaction between A, B, E and phenyl rings in the R group, whose π-systems are neutral over a wide range. Interactions between aromatic rings have been theoretically proposed on the basis of studies of free energy profiles for the association of the benzene dimer in solution such as liquid benzene, chloroform, and water,[30] in all cases the dimer is energetically preferred and stacked structures become increasingly favorable with increasing arene size. This seems to provide a rational explanation of our experimental results.

To further explore the possibility that substitution on the imidazole ring of sampangine was not responsible for the chemical shift variation, the *n*-propyl derivative **3c** (R = *n*-Pr)[c] was prepared and studied. Investigation of the ^{1}H-NMR spectra was conducted on **3c** and sampangine (**1**) in $CDCl_3$ at various concentrations. As with **3a** and **3b**, **3c** showed similar proton chemical shifts that were extremely dependent on the concentration.

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[a]Electrostatic potentials (kcal/mol) for **3a** on H-3, -4, and -5 are 31.6, 35.2, and 37.7, while that on H-9 and -10 are 20.3 and 19.4, respectively.

[b]Electrostatic potentials (kcal/mol) for **3b** on H-3, -4, and -5 are 31.5, 38.0, and 43.3, while that on H-9 and -10 are 20.2 and 21.0, respectively.

[c]The derivative **3c** was prepared by using the same method described in Ref. [27].

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The fact that substitution on sampangine with phenyl groups (R = Ph, R = CH_2Ph) or n-propyl (R = n-Pr) gave similar concentration-dependent chemical shifts indicated that the phenyl group substituted on the imidazole ring was not involved in the aromatic interaction. On the other hand, the shift variation of **1** is much smaller than that of **3**. These results suggest, therefore, that the fused imidazole (E ring) plays a very important role in the sampangine derivatives in the interactions between aromatic rings, and that these interactions do not appear to be affected by substitution.

CONCLUSION

In conclusion, we have found concentration-dependent variation in chemical shifts of aromatic ring protons in the sampangine derivatives **3a–c**. This concentration-dependent variation of proton chemical shift is probably ascribable to the self-association of these molecules in solution. Such phenomenon may be observed in various fused aromatic and heteroaromatic compounds.

SUPPORTING INFORMATION AVAILABLE

Graphical presentation of chemical shift *vs.* concentration for the protons of **3a** in CD_3OD, DMSO-d_6, CD_3CN, benzene-d_6, chemical shift *vs.* concentration for the protons of **1** in $CDCl_3$, and chemical shift *vs.* concentration for the nitrogen atoms of **3a** in $CDCl_3$. This material is available from the authors on request.

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