

# NMR Study of Aromatic–Aromatic Interactions for Benzene and Some Other Fundamental Aromatic Systems Using Alignment of Aromatics in Strong Magnetic Field

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**Abstract:** The solvent dependence of proton–proton dipolar couplings in a strong magnetic field was used to characterize the aromatic–aromatic interactions of benzene, hexafluorobenzene (HFB), naphthalene, and some monosubstituted benzenes under various conditions. The very accurate analysis of the spectral parameters of benzene also allowed observation of isotope effects on coupling constants and solvent effects on the <sup>13</sup>C isotope shifts. The results indicate that benzene, naphthalene, and the monosubstituted benzenes favor structures in which the aromatic ring is parallel-stacked with HFB. According to the concentration-dependent experiments, the benzene–HFB complex behaves like a dimer. For benzene–dimer, benzene–naphthalene, and some benzene–monosubstituted benzene complexes there is evidence for T-shaped structures; for benzene in water no clear preference is seen. The complexes express only in very high concentrations, which means that the interaction has significance only in conditions where the entropy of the complex formation is small or is compensated by some other interactions.

## Introduction

The interactions between aromatic rings are of wide chemical interest, as recently discussed by Jorgensen et al.<sup>1</sup> Although the interaction free energies are relatively small, the interactions are believed to play important roles in many phenomena in nature, as in the stabilization of protein structures,<sup>2</sup> the recognition of mRNA by cap binding protein,<sup>3</sup> and the biological reduction by NADH.<sup>4</sup> The interaction also offers a useful device for the design of molecular recognition<sup>5</sup> and catalysis.<sup>6</sup> The aromatic stacking has been applied, for example, in the development of self-replicating molecules,<sup>7</sup> a molecular clip,<sup>8</sup> and a synthetic NADH mimic.<sup>9</sup>

The aromatic interaction can be divided into three types of contributions: (i) the Coulombic type “polar/ $\pi$ ” interactions, (b) dispersion interactions, and (c) hydrophobic interactions if water solutions are concerned.<sup>10</sup> It is obvious that the Coulombic contribution is predominant for example in interactions

of nucleotides.<sup>11</sup> On the other hand, the phenyl arrangement in proteins is supposed to be at least partly a consequence of hydrophobic interaction.<sup>2</sup> In the protein structure the aromatic  $\pi$  hydrogen bonding<sup>1,2,12</sup> may compete with the hydrophobic interaction.

The basic experimental knowledge of even the most characteristic systems in solution is still scarce or is based on indirect measurements or computational models. A dissociation energy of  $11 \pm 2$  kJ/mol for the benzene dimer has been determined in the gas phase via an ionization experiment.<sup>13</sup> There is plenty of experimental evidence for the T-shaped benzene dimer both in the gas phase<sup>14</sup> and in solids.<sup>15</sup> The T structure is predominant in proteins<sup>2</sup> and an “edge-to-face” structure has been documented in solution.<sup>16</sup> Also the <sup>2</sup>H quadrupolar couplings of mono-<sup>2</sup>H-benzene support the T structure in concentrated benzene solutions.<sup>17</sup> On the other hand, the presence of benzene trimer and tetramer in supersonic beams has been reported<sup>18</sup> and some spectroscopic results support even parallel-stacked-

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(1) Jorgensen, W. L.; Severance, D. L. *J. Am. Chem. Soc.* **1990**, *112*, 4768 and the references therein.

(2) Burley, S. K.; Petsko, G. A. *Science* **1985**, *229*, 23. Burley, S. K.; Petsko, G. A. *J. Am. Chem. Soc.* **1986**, *108*, 7995.

(3) Ueda, H.; Doi, M.; Inoue, M.; Ishida, T.; Tanaka, T.; Uesugi, S. *Biochem. Biophys. Res. Commun.* **1988**, *154*, 199.

(4) Murakami, Y.; Aoyama, Y.; Kikuchi, J.; Nishida, K. *J. Am. Chem. Soc.* **1982**, *104*, 5189.

(5) See for example: Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1304.

(6) (a) Kelly, T. R.; Bridger, G. J.; Zhao, C. *J. Am. Chem. Soc.* **1990**, *112*, 8024. (b) Amabilino, D. B.; Ashton, P. R.; Brown, C. L.; Cordova, E.; Godinez, L. A.; Goodnow, T. T.; Kaifer, A. E.; Newton, S. P.; Pietraszkiewicz, M.; Douglas, P.; Raymo, F. M.; Reder, A. S.; Rutland, M. T.; Slawin, A. M. Z.; Spencer, N.; Stoddart, J. F.; Williams, D. J. *J. Am. Chem. Soc.* **1995**, *117*, 1272.

(7) Wintner, E. A.; Conn, M. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 8877.

(8) Sijbesma, R. P.; Wijmenga, S. S.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1992**, *114*, 9807.

(9) Pierre, J.-L.; Gagnaire, G.; Chautemps, P. *Tetrahedron Lett.* **1992**, *33*, 217.

(10) For recent discussions see: (a) Cozzi, F.; Cinquini, M.; Annunziata, R.; Dwyer, T.; Siegel, J. S. *J. Am. Chem. Soc.* **1992**, *114*, 5729. (b) Newcomb, L. F.; Gellman, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 4993. (c) Cozzi, F.; Cinquini, M.; Annunziata, R.; Siegel, J. S. *J. Am. Chem. Soc.* **1993**, *115*, 5330.

(11) For a leading reference, see: Pranata, J.; Wierschke, S. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991**, *113*, 2810.

(12) Atwood, J. L.; Hamada, F.; Robinson, K. D.; Orr, G. W.; Vincent, R. L. *Nature* **1991**, *349*, 683 and references given therein.

(13) Grover, J. R.; Walters, E. A.; Hui, E. T. *J. Chem. Phys.* **1987**, *91*, 3233.

(14) (a) Janda, K. C.; Hemminger, J. C.; Winn, J. S.; Novick, S. E.; Harris, S. J.; Klemperer, W. J. *J. Chem. Phys.* **1975**, *63*, 1419. (b) Steed, J. M.; Dixon, T. A.; Klemperer, J. *J. Chem. Phys.* **1979**, *70*, 4940. (c) Shi, X.; Bartell, L. S. *J. Phys. Chem.* **1988**, *92*, 5667. Henson, B. F.; Hartland, G. V.; Venturo, V. A.; Felker, P. M. *J. Chem. Phys.* **1992**, *97*, 2189.

(15) (a) Cox, E. G.; Cruickshank, D. W. J.; Smith, J. A. C. *Proc. R. Soc. London, A* **1958**, A247. (b) Williams, D. E. *Acta Crystallogr., Sect. A* **1974**, *30*, 71. (c) Hall, D.; Williams, D. E. *Acta Crystallogr., Sect. A* **1975**, *31*, 56. (d) Williams, D. E.; Starr, T. L. *Comput. Chem.* **1977**, *1*, 173.

(16) For example: (a) Ferguson, S. B.; Sanford, E. M.; Seward, E. M.; Diederich, F. *J. Am. Chem. Soc.* **1991**, *113*, 5410. (b) Paliwal, S.; Geib, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1994**, *116*, 4497.

(17) (a) Luyten, P. R.; Bulthuis, J.; MacLean, C. *Chem. Phys. Lett.* **1982**, *89*, 287. (b) Bothner-By, A. A.; Gayathri, C.; van Zijl, P. C. M.; MacLean, C. *J. Magn. Reson.* **1984**, *56*, 456.

type structures.<sup>19</sup> Theoretical calculations suggest that the T-shaped benzene-benzene dimer owns only a low preference (0.5–2 kJ/mol are given by the most recent calculations<sup>1</sup>) over other arrangements.<sup>1,20</sup> The chemically most interesting arrangement, allowing the HOMO-LUMO charge-transfer-type interaction, with parallel-stacked aromatic rings is estimated to be ca. 2 kJ/mol less stable<sup>1</sup> than the T form. The stacked arrangement is formed, for example, between benzene and hexafluorobenzene (HFB).<sup>21</sup> The solid complex is easily formed when stoichiometric amounts of benzene and HFB are mixed. However, a value of only +1.0 kJ/mol for the enthalpy of formation of the solid benzene-HFB complex has been obtained calorimetrically.<sup>22</sup> Recently Cozzi et al. showed that bringing one fluorine to the other phenyl of 1,8-diphenylnaphthalene decreases the stacked repulsion between the phenyl rings by ca. 2 kJ/mol.<sup>23</sup>

The dispersion interaction between two nonpolar aromatic ring systems is normally so weak that it is easily compensated by the entropy. Thus it can be expected to be important only in very concentrated solutions or when the interacting groups are brought together by some other interactions such as, for example, Coulombic interactions in DNA or hydrophobic interactions in proteins. Therefore also simple strategies based on, for example, the concentration dependence of chemical shifts become unambiguous. This has led to experiments in which the aromatic parts have been brought close to each other by making them substituents of the same molecule.<sup>10,23,24</sup>

Aromatic molecules align to a very small extent with a strong magnetic field.<sup>25</sup> In NMR experiments this leads to very small, typically 10 mHz at 400 MHz for monoaromatics,<sup>25–28</sup> dipolar couplings between aromatic protons. Although usually below the limit of the direct observation, the dipolar couplings can be determined indirectly for symmetric spin systems<sup>26,27</sup> if a high-quality NMR spectrum is obtained. For example, the benzene <sup>13</sup>C,<sup>1</sup>H spin system allows the extraction of the dipolar couplings. The strength of the alignment depends on the

anisotropy of the magnetic susceptibility of the molecule. The couplings, as well as corresponding <sup>2</sup>H quadrupolar couplings, can be used for determination of information about the anisotropy, or if the anisotropy depends on the structure of the assembly, about the structure of molecular assemblies. In this way we have recently shown<sup>27</sup> that for example the benzene-HFB complex is more strongly oriented in the magnetic field than are the monomers and that useful information can be derived by using the experiment. The method is similar to the method based on the <sup>2</sup>H quadrupolar splittings; however, the dipolar coupling method although very demanding does not suffer from the same limitations.<sup>29</sup>

In our preliminary report<sup>27</sup> we showed that the free energy of formation of the benzene and hexafluorobenzene (HFB) dimer is clearly negative while that of the benzene and 2,6-dichlorobenzene complex is positive. The purpose of this report is to present results for some characteristic aromatic systems. In the previous work<sup>27</sup> we used the <sup>1</sup>H-coupled <sup>13</sup>C spectrum of benzene. In this work we used mono-<sup>13</sup>C-benzene to obtain an accuracy and sensitivity that allows measurement of the dipolar couplings in dilute systems.

## Experimental Section

The NMR samples were filtered using 0.2- $\mu$ m microfilters, degassed, and sealed before running on a Bruker AM 400WB spectrometer equipped with 16 bit ADC, after a careful shimming was performed on the FID of TMS. The acquisition times were set to 40–60 s, and the FID was zero-filled so that the data-point resolution after the Fourier transform was 2–3 mHz. The FID was windowed as described before.<sup>30</sup> Temperatures were determined by using the methanol method<sup>31</sup> and are supposed to be correct within 1 deg.

The spectra were analyzed with the PERCH software<sup>32</sup> as previously described.<sup>27</sup> In all cases we had to use linear constraints<sup>27</sup> based on the geometry (benzene CC bond of 1.400 Å and CH bond of 1.090 Å). Figure 1 shows a portion of the benzene <sup>13</sup>C-coupled <sup>1</sup>H spectrum (a) and the computed spectrum as analyzed without (b) and with (c) the dipolar coupling constants.

## Discussion

The dipolar couplings of benzene are given in Table 1. The average values of  $D_{ortho}$ , –10.7 mHz at 320 K, for benzene in acetone, cyclohexane, and CS<sub>2</sub> can be considered as the value of the monomeric aromatic ring. The average temperature dependence (0.7 mHz/10 K) is exactly what is expected on the basis of the Boltzmann factor (1/T dependence), although the

(18) Hopkins, J. B.; Powers, D. E.; Smalley, R. E. *J. Phys. Chem.* **1981**, *85*, 3739.

(19) (a) Law, K. S.; Schauer, M.; Bernstein, E. R. *J. Chem. Phys.* **1984**, *81*, 4871. (b) Bornsen, K. O.; Selzle, H. L.; Schlag, E. W. *J. J. Chem. Phys.* **1986**, *85*, 1726.

(20) (a) MacRury, T. B.; Steele, W. A.; Berne, B. J. *J. Chem. Phys.* **1976**, *64*, 1289. (b) Fraga, S. *J. Comput. Chem.* **1982**, *3*, 329. (c) Karlstrom, G.; Linse, P.; Wallqvist, A.; Jonsson, B. *J. Am. Chem. Soc.* **1983**, *105*, 3777. (d) Pawliszyn, J.; Szczesniak, M. M.; Scheiner, S. *J. Phys. Chem.* **1984**, *88*, 1726. (e) Schauer, M.; Bernstein, E. R. *J. Chem. Phys.* **1985**, *8*, 3722. (f) Petterson, I.; Liljefors, T. *J. Comput. Chem.* **1987**, *8*, 1139. (g) Allinger, N. L.; Lii, J.-H. *J. Comput. Chem.* **1987**, *8*, 1146. (h) Shi, X.; Bartell, L. S. *J. Phys. Chem.* **1988**, *92*, 5667.

(21) (a) Patrick, C. R.; Prosser, G. S. *Nature (London)* **1961**, *187*, 1021. (b) Boyens, J. C. A.; Herstein, F. H. *J. Chem. Phys.* **1965**, *69*, 2152. (c) Steed, J. M.; Dixon, T. A.; Klemperer, W. *J. Chem. Phys.* **1979**, *70*, 4940. (d) Bartsch, E.; Bertagnolli, H.; Schulz, G.; Chieux, P. *Ber. Bunsenges. Phys. Chem.* **1985**, *89*, 147. (e) Bartsch, E.; Bertagnolli, H.; Schulz, G.; Chieux, P. *Ber. Bunsenges. Phys. Chem.* **1986**, *90*, 34. (f) Dahl, T. *Acta Chem. Scand.* **1988**, *A42*, 1. (g) Dahl, T. *Acta Chem. Scand.* **1990**, *A44*, 56.

(22) Brennan, J. S.; Brown, N. M. D.; Swinton, F. L. *J. Chem. Soc., Faraday Trans. 1* **1974**, *70*, 1065.

(23) Cozzi, F.; Ponzini, F.; Annunziata, R.; Cinquini, M.; Siegel, J. S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1019.

(24) Leonard, N. J.; Ito, K. *J. Am. Chem. Soc.* **1973**, *95*, 4010.

(25) The alignment of aromatic molecules in strong magnetic field and the applications of the phenomenon is well-documented, see for example: (a) van Zijl, P. C. M.; Ruessink, B. H.; Bulthuis, J.; MacLean, C. *Acc. Chem. Res.* **1984**, *17*, 173. (b) Bastiaan, E. W.; MacLean, C. *NMR Basic Princ. Prog.* **1991**, *25*, 17 and the references therein.

(26) (a) Anet, F. A. L. *J. Am. Chem. Soc.* **1986**, *108*, 1354. (b) Laatikainen, R. *J. Magn. Reson.* **1988**, *78*, 127.

(27) Laatikainen, R.; Santa, H.; Hiltunen, Y.; Lounila, J. *J. Magn. Reson.* **1993**, *A104*, 238.

(28) We use the same definition of dipolar coupling as used by MacLean and co-workers.<sup>33</sup>

(29) The interaction between the <sup>2</sup>H nuclear quadrupole moment and the C–D bond electric field gradient leads to a splitting of the <sup>2</sup>H NMR signal of a molecule oriented by a magnetic field.<sup>25</sup> The splitting is proportional to both the electric field gradient and the anisotropy of the molecular magnetic susceptibility. For example, the ca. 30% increase of the quadrupolar splitting of mono-<sup>2</sup>H-benzene from the gas to the liquid phase can be accounted for by the solvent reaction field (van Zijl, P. C. M.; MacLean, C.; Skoglund, C.; Bothner-By, A. A. *J. Magn. Reson.* **1985**, *65*, 316. Huis, L.; Bulthuis, J.; van der Zwan, G.; MacLean, C. *J. Phys. Chem.* **1987**, *91*, 3430). Also the 30% variation of the <sup>2</sup>H splittings of nitrobenzene in non-aromatic solvents (Plantenga, T. M.; Bultink, H.; Maclean, C.; Lohman, J. A. B. *Chem. Phys.* **1981**, *61*, 271) could be explained in the same way. Because the dipolar couplings do not depend on the molecular electric fields, they are more credible than the quadrupolar splittings in complex formation studies, especially if the complex formation affects the electric field at <sup>2</sup>H. Another aspect, the limitations arising from the line widths, has been discussed before.<sup>25,26a</sup>

(30) Laatikainen, R.; Tuppurainen, K.; Hiltunen, Y.; Lötjönen, S. *Magn. Reson. Chem.* **1990**, *28*, 939.

(31) Van Geet, A. L. *Anal. Chem.* **1968**, *40*, 2227.

(32) Laatikainen, R.; Niemitz, M.; Sundelin, J.; Hassinen, T. *PERCH (PEak reseARCh) software*; PERCH Project, Department of Chemistry, University of Kuopio, Finland. The software is meant for manipulation and handling interface prior to spectral analysis in personal computers.

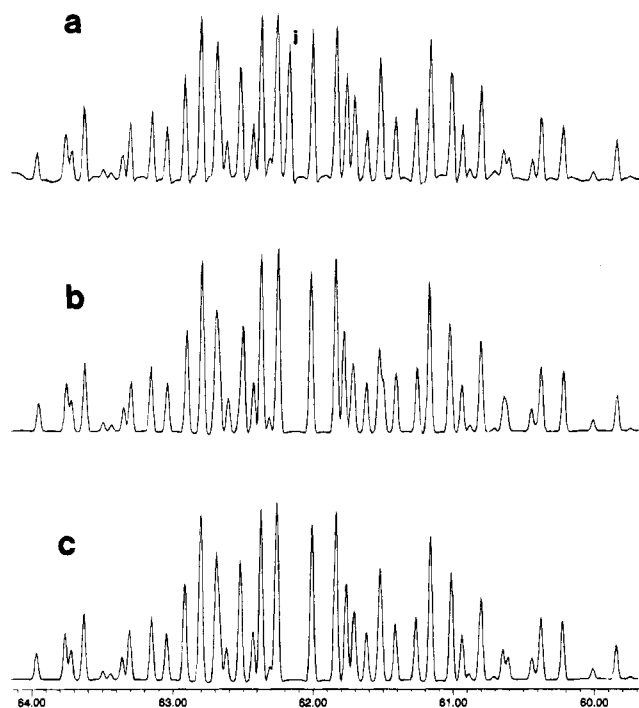
**Table 1.** Ortho Proton  $^1\text{H}$ - $^1\text{H}$  Dipolar Coupling Constants of Benzene, Fluorobenzene, Chlorobenzene, Bromobenzene, and 1,2-Difluorobenzene under Various Conditions<sup>a</sup>

system (mol ratio)	T (K)	rms <sup>b</sup>	signals <sup>c</sup>	line width <sup>d</sup>	$D_{\text{ortho}}$ <sup>e,f</sup>
benzene-acetone (1:19)	320	0.7	225	40	-10.6(2)
	300	0.5	244	33	-11.0(2)
benzene-cyclohexane (1:19)	320	0.6	268	28	-10.6(2)
	300	0.8	261	30	-11.4(2)
benzene-CS <sub>2</sub> (1:19)	320	0.7	206	32	-10.8(2)
	300	0.6	258	27	-11.8(2)
benzene (neat)	325	1.4	222	43	-9.0(4)
	320	1.5	222	53	-9.6(6)
	310	1.5	217	55	-8.6(4)
	300	1.3	237	48	-9.6(4)
benzene-HFB (1:1)	320	1.6	232	44	-16.2(6)
	310	1.0	249	33	-16.8(2)
	300	1.1	237	37	-18.0(4)
benzene-HFB (1:4)	320	1.7	246	37	-18.4(6)
	310	1.3	224	34	-19.4(4)
	300	1.6	234	38	-20.6(4)
benzene-pyridine (1:4)	320	0.9	225	38	-9.0(2)
	310	0.8	225	38	-9.2(2)
	300	0.7	239	35	-8.8(2)
benzene-naphthalene-Ac-d <sub>6</sub> (1:1:3)	300	2.1	165	65	-6.4(6)
benzene (2 vol %) - H <sub>2</sub> O <sup>g</sup>	300	1.9	222	54	-11.2(6)
benzene (1 vol %) - H <sub>2</sub> O <sup>h</sup>	300	2.6	140	64	-11.4(10)
fluorobenzene-HFB (1:5)	320	0.3	104	38	-16.6(4)
	303	0.3	101	38	-18.2(4)
fluorobenzene-benzene (1:4)	300	0.3	117	32	-9.0(4)
chlorobenzene-HFB (1:5)	300	0.6	64	37	-18.0(4)
chlorobenzene-benzene (1:4)	300	0.6	65	38	-8.8(4)
bromobenzene-HFB (1:5)	300	2.6	52	59	-13.4(32)
1,2-difluorobenzene-HFB (1:5)	300	2.0	58	45	-16.6(8)

<sup>a</sup> All the parameters are given in mHz (1 mHz = 0.001 Hz). <sup>b</sup> rms = residual root mean square. <sup>c</sup> The number of peak tops used in the analysis.

<sup>d</sup> The line-width used in computing the theoretical peak-top frequencies. <sup>e</sup> The 90% confidence limits are given in parentheses. <sup>f</sup> Only one dipolar coupling parameter can be determined from the spectra; the other H,H dipolar couplings were bound together by using the geometry of the ring.<sup>27</sup>

<sup>g</sup> 50% methanol was added to improve the solubility of the benzene. <sup>h</sup> 25% methanol was added to improve the solubility of the benzene.



**Figure 1.** (a) A portion of the spectrum containing the para proton signals of mono- $^{13}\text{C}$ -benzene neat at 300 K as fitted (b) without dipolar couplings (rms was 6.1 mHz) and (c) with D couplings (rms 1.3 mHz). The line width of 27 mHz and the line shape containing 120% of Gaussian and -20% Lorentzian contributions were used in the computed spectra.

significance of the temperature dependencies is rather low. The anomaly found for the 2,6-dichlorobenzaldehyde-benzene system<sup>27</sup> is not shown now.

The total orienting torque due to the magnetic moment arising from the parallelly stacked rings is at most the sum of the individual torques, and  $D_{\text{ortho}}$ , being proportional to the total anisotropy,<sup>25,17,33</sup> grows in the same ratio. Thus the  $D_{\text{ortho}}$  of the rigid benzene-HFB stacked complex should be the sum of the dipolar couplings between ortho protons of the monomers. Because our attempts to estimate the F,F dipolar couplings in hexafluorobenzene<sup>34</sup> gave relatively poor estimates, a fair estimate of the dimer values is ca. -21 mHz. In 1:1 molar solution the coupling is -16.2 mHz, and in 1:4 it is -18.4 Hz: assuming a simple  $\text{B} + \text{HFB} = \text{B}^*\text{HFB}$  equilibrium gives a  $\Delta G$  of -5 kJ/mol. Rather surprising is that the same order of  $\Delta G$  is obtained for the fluorobenzene-HFB, chlorobenzene-HFB, and even difluorobenzene-HFB complexes. Also naphthalene forms a relatively strong complex with HFB; the value of -32.2 mHz even indicates a presence of some trimer.

In the T-shaped benzene-benzene complex  $D_{\text{ortho}}$  should be only 50% of the value of the monomer, ca. -5.4 mHz at 320 K.<sup>33</sup> The values of -9.6, -8.8, -9.0, and -6.4 mHz (at 300 K) for benzene-benzene, benzene-pyridine, fluorobenzene-benzene, and benzene-naphthalene indicate clearly the presence of the T-shaped form. It is notable that the dipolar coupling

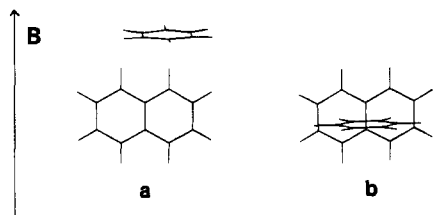
(33) Bastiaan, E. W.; Bulthuis, J.; MacLean, C. *Magn. Reson. Chem.* **1986**, *24*, 723.

(34) The spectral analysis of the  $^{13}\text{C}$ -satellite spectrum of hexafluorobenzene (neat) yielded the following chemical shift differences (at 300 K, 400 MHz):  $\nu_1 - \nu_2 = -20.488(2)$ ;  $\nu_1 - \nu_3 = -29.480(2)$ ;  $\nu_1 - \nu_4 = -27.871(2)$  and couplings.  $^{13}\text{C}$ ,F couplings (hertz):  $^1J = -251.610(6)$ ;  $^2J = 13.710(1)$ ;  $^3J = 3.138(1)$ ;  $^4J = 5.216(1)$ . F,F couplings (hertz):  $^3J_{12} = -20.090(3)$ ;  $^3J_{23} = -20.125(1)$ ;  $^3J_{34} = -20.124(1)$ ;  $^4J_{13} = -3.017(2)$ ;  $^4J_{24} = -3.042(1)$ ;  $^4J_{26} = -3.039(2)$ ;  $^4J_{35} = -3.037(2)$ ;  $^5J_{14} = 3.973(3)$ ;  $^5J_{25} = 3.939(1)$  Hz;  $D_{\text{ortho}} = -6.2(2.0)$  mHz. The numbers in parentheses give the standard deviations of the estimate. The root mean square was 3.8 mHz for 75 observed signals. The analysis yielded small isotope effects on the couplings, otherwise the values are in agreement with those given by: Wray, V.; Ernst, L.; Lustig, E. *J. Magn. Reson.* **1977**, *27*, 1.

**Table 2.**  $^1\text{H}$ - $^1\text{H}$  Dipolar Coupling Constants for Naphthalene under Various Conditions<sup>a</sup>

system (mol ratio)	T (K)	rms <sup>b</sup>	signals <sup>c</sup>	line width <sup>d</sup>	$D_{\alpha\beta}$ <sup>e,f</sup>	$D_{\alpha\alpha}$
naphthalene-acetone (1:9)	320	1.9	252	30	-18.0(4)	-19.8(6)
	310	1.9	253	35	-18.4(4)	-19.8(6)
naphthalene-benzene (1:4)	320	1.6	259	29	-17.0(4)	-25.2(4)
	310	1.5	250	29	-17.2(4)	-25.2(4)
naphthalene-HFB (1:17)	320	2.0	205	38	-32.2(4)	-32.0(6)

<sup>a-c</sup> See Table 1. <sup>f</sup> Only two dipolar coupling parameters were optimizable and thus  $D_{\beta\beta}$  was set equal to  $D_{\alpha\beta}$ .



**Figure 2.** Two benzene-naphthalene assemblies in which the interaction between the benzene ring and the magnetic field ( $B$ ) leads to an increased  $D_{\alpha\alpha}/D_{\alpha\beta}$  ratio.

ratio  $9.6/11.4 = 0.84$  for benzene (neat) vs benzene monomer is the same as that of the  $^2\text{H}$  quadrupolar splittings (0.42/0.50) for 80 mol % vs 1 mol % mono- $^2\text{H}$ -benzene in acetone.<sup>17</sup> In the cases of pyridine and fluorobenzene the T-shaped form is expected to be favored also by the polar/ $\pi$  interactions. The question remains whether the equilibrium is simply between the T dimer and monomer or if the stacked dimer should be included. If the equilibrium was between the T dimer and monomer, a dipolar coupling of ca. 9 mHz would mean only a less than 33% contribution of the T complex and thus the lower temperature should in fact favor the monomer. This would also lead to as strong a temperature dependence as that observed for monomer. On the basis of our measurements it is fairly sure that the temperature dependence is smaller for the benzene-benzene and pyridine solutions. This indicates that the equilibrium is between the two dimers. Assuming  $D(\text{monomer}) = -10.7$ ,  $D(\text{T dimer}) = -5.4$ , and  $D(\text{stacked}) = -21.5$  or  $-30$  for benzene-naphthalene, we can estimate that the T-shaped benzene-benzene is favored by up to  $-3$  kJ/mol over the stacked form, depending on the proportion of the monomer, and for benzene-naphthalene even by  $-5$  kJ/mol.

If some non-rigidity of the complex is allowed (as suggested by the diffraction analysis<sup>21</sup>), the total torque is smaller than the sum of the monomers. Correspondingly the free energies of complex formation are then more negative. The complex may contain also more than two rings, but if the free energy of the second complex is the same as that of the first one (in fact, the complex formation entropy favors for example the trimer by ca. 2.3 kJ/mol, as computed by the formula proposed by Finkelstein and Janin<sup>35</sup>), the proportion of the trimers and tetramers is expected to be low.

**Naphthalene.** For naphthalene we can determine two independent  $D$ -dipolar couplings, see Table 2. If the ring is oriented perpendicular to the magnetic field and if the experimental H-H distances<sup>36</sup> are used, the ratio  $D_{\alpha\alpha}/D_{\alpha\beta}$  should be 1.05, which equals within experimental error our observed ratio of 1.10. In the benzene solution the ratio is increased significantly, up to 1.45. Qualitatively this means that assemblies like those shown by Figure 2 are formed and that there is again evidence for the T-type structures. The solvent isotope shifts for benzene in the benzene-naphthalene-acetone solution, see below, give some support also for the a-type structure.

**Benzene in Water.** The question of the structure of the benzene-benzene solution in a hydrophilic environment and

the hydrogen-bond-type interactions between aromatic ring  $\pi$ -electrons and a hydroxyl bond are of wide chemical interest.<sup>1,2,12,37</sup> In our previous study<sup>27</sup> the similarity of the solvent effects of methanol and cyclohexane led to the conclusion that the specific hydroxyl  $\pi$ -interaction is not stronger than the benzene-cyclohexane dispersion interaction. The use of  $^{13}\text{C}$ -labeled benzene allowed the study of benzene in the water-methanol system. The results clearly show that benzene in these conditions is neither stacked nor T-type dimer or that the equilibrium between the two dimers is such that it gives the value of the monomer.

**Temperature and Solvent Effects on Scalar Couplings and  $^1\text{H}$  Isotope Shifts.** A set of parameters has been collected into Table 3, and the rest of the spectral parameters are available on request. Especially the  $^1\text{H}$ ,  $^1\text{H}$  spin-spin couplings are usually assumed to be solvent and temperature independent and high-quality spectra are needed for the estimation of the dependencies. The results of the present analyses are in agreement with the previous ones,<sup>38</sup> however our ca. 10 times better rms allows some new conclusions. First, the isotope effects on H,H couplings are very small: in the three- and five-bond H,H couplings no isotope effects are seen within confidence limits, for the four-bond couplings in comparison with  $^4J_{13}$ ,  $^4J_{24}$  is  $0.7 \pm 0.5$  mHz larger,  $^4J_{35}$  equal, and  $^4J_{26}$   $0.9 \pm 0.5$  mHz larger.<sup>39</sup> Second, also the solvent and temperature effects on the couplings of benzene are of considerable fundamental interest. Our analysis shows that the vicinal and five-bond couplings decrease ca. 0.01%/K, with the four-bond couplings increasing by 0.02%/K, and that the solvent effects are an order of 0.1 to 0.5%, with the magnitudes of the couplings increasing with the polarity of the solvent. The changes are of the same order as we have recently reported for fluorobenzene<sup>40</sup> and naphthalene.<sup>26b</sup> Third, the solvent effects on the isotope chemical shifts vary as much as 60 mHz (0.00015 ppm) and even their temperature dependencies vary with solvent (Table 3). Notable is that the smallest values are always for the acetone and HFB solutions and the largest for the benzene solution. If the variations are assumed to arise from variations of the vibrational freedom of the benzene C-H bond, the observation suggests for the benzene solution a structure, like the T complex, where the C-H force field is specially affected. In the same way the shifts in the pyridine solution support an equilibrium with emphasis on the structure in which the positively charged pyridine  $\gamma$ -proton interacts with the benzene  $\pi$ -system. The isotope shifts in the benzene-naphthalene-acetone solutions are similar to those in pyridine, suggesting that the naphthalene C-H bonds are at least partly located as in the benzene-benzene T complex.

## Conclusion

The solvent dependence of dipolar couplings allows the determination of the association thermodynamics of an aromatic

(35) Finkelstein, A. V.; Janin, J. *Protein Eng.* **1989**, 3, 1.

(36) Brock, C. P.; Dunitz, J. D. *Acta Crystallogr., Sect. B* **1982**, 32, 2218.

(37) Suzuki, S.; Green, P. G.; Bumgarner, R. E.; Dasgupta, S.; Goddard, W. A., III; Blake, G. A. *Science* **1992**, 257, 942 and the references cited therein.

(38) Chertkov V. A.; Sergeev, N. M. *J. Magn. Reson.* **1983**, 52, 400.

(39) The numbers are averages of 20 spectra.

(40) Suntioinen, S.; Laatikainen, R. *Magn. Reson. Chem.* **1992**, 30, 415.

**Table 3.**  $^{13}\text{C}$ - $^1\text{H}$  and  $^1\text{H}$ - $^1\text{H}$  Spectral Parameters ( $P$ , in Hz) and Temperature-Induced Changes of the Parameters ( $\Delta P$ ) of Benzene in Different Pyridine, Acetone- $d_6$ , Cyclohexane,  $\text{CS}_2$ , Benzene, Hexafluorobenzene (HFB),  $\text{H}_2\text{O}$ /Methanol, and Naphthalene-Acetone at 400 MHz Magnetic Field<sup>a</sup>

coupling	acetone $P/\Delta P$ 300/320 K	cyclohexane $P/\Delta P$ 300/320 K	$\text{CS}_2$ $P/\Delta P$ 300/320 K	$\text{C}_6\text{D}_6$ $P/\Delta P$ 300/320 K	pyridine $P/\Delta P$ 300/320 K	HFB (1:4) $P/\Delta P$ 300/320 K	$\text{H}_2\text{O}^b$ $P$ 300 K	$\text{C}_{10}\text{H}_8^c$ $P$ 300 K
$^1J_{\text{CH}}$	158.735/-0.0266	157.917/0.0153	158.132/0.0035	158.380/-0.0206	158.642/-0.0250	158.646/-0.0502	159.187	158.607
$^2J_{\text{CH}}$	1.1820/-0.0040	1.0870/0.0009	1.0882/0.0001	1.1310/-0.0028	1.1637/-0.0036	1.1798/-0.0072	1.2150	1.1595
$^3J_{\text{CH}}$	7.5988/0.0036	7.6296/0.0021	7.6138/0.0020	7.6062/0.0035	7.590.9/0.0043	7.6130/0.0067	7.5824	7.5974
$^4J_{\text{CH}}$	-1.2879/-0.0021	-1.2947/-0.0041	-1.2833/-0.0040	-1.2845/-0.0063	-1.2801/-0.0035	-1.2964/-0.0027	-1.2814	-1.2882
$^3J_{12}$	7.5483/0.0005	7.5581/-0.0001	7.5364/0.0002	7.5450/-0.0004	7.5367/0.0005	7.5619/0.0007	7.5544	7.5401
$^3J_{23}$	7.5482/0.0005	7.5575/0.0001	7.5355/0.0005	7.5440/0.0014	7.5365/0.0004	7.5628/0.0003	7.5541	7.5400
$^3J_{34}$	7.5485/0.0008	7.5574/0.0002	7.5350/0.0004	7.5415/0.0031	7.5362/0.0006	7.5631/-0.0008	7.5544	7.5418
$^4J_{13}$	1.3801/-0.0025	1.3743/-0.0024	1.3781/-0.0024	1.3828/-0.0027	1.3874/-0.0028	1.3811/-0.0028	1.3893	1.3811
$^4J_{24}$	1.3804/-0.0027	1.3749/-0.0026	1.3788/-0.0023	1.3843/-0.0035	1.3882/-0.0029	1.3829/-0.0036	1.3908	1.3838
$^4J_{26}$	1.3802/-0.0027	1.3744/-0.0026	1.3787/-0.0028	1.3830/-0.0033	1.3874/-0.0023	1.3807/-0.0032	1.3891	1.3803
$^4J_{35}$	1.3810/-0.0022	1.3752/-0.0029	1.3786/-0.0019	1.3853/-0.0047	1.3881/-0.0030	1.3828/-0.0024	1.3898	1.3848
$^5J_{14}$	0.6654/0.0004	0.6597/0.0014	0.6505/0.0020	0.6570/0.0024	0.6572/0.0008	0.6678/0.0015	0.6661	0.6553
$^5J_{25}$	0.6649/0.0005	0.6597/0.0012	0.6504/0.0016	0.6569/0.0020	0.6570/0.0012	0.6669/0.0018	0.6660	0.6594
$\nu_1-\nu_2$	-0.4829/0.0002	-0.4951/0.0012	-0.4940/0.0017	-0.5159/0.0028	-0.4968/0.0005	-0.4825/0.0004	-0.4847	-0.4939
$\nu_1-\nu_3$	-0.8128/0.0044	-0.8277/0.0051	-0.8250/0.0052	-0.8622/0.0080	-0.8357/0.0054	-0.8040/0.0040	-0.8148	-0.8326
$\nu_1-\nu_4$	-0.8874/0.0056	-0.9063/0.0058	-0.9025/0.0061	-0.9449/0.0087	-0.9134/0.0055	-0.8804/0.0043	-0.8877	-0.9110
signals	244/225	261/268	258/206	237/222	239/225	234/246	222	165
rms	0.0005/0.0007	0.0008/0.0006	0.0006/0.0007	0.0013/0.0015	0.0007/0.0009	0.0016/0.0017	0.0019	0.0021

<sup>a</sup> The predicted standard deviations of the parameters are from 0.3 to 0.7 times the rms, except for  $^1J$  for which it may be considerably larger because the value of the coupling is sensitive to phasing. <sup>b</sup> The sample contained 2% (v/v) of mono- $^{13}\text{C}$ -benzene and 50% perdeuteromethanol. <sup>c</sup> The sample contained benzene, naphthalene, and acetone- $d_6$  in the molar ratio 1:1:3.

compound with fair accuracy, if a suitable symmetric spin system is available. The results show that benzene, naphthalene, and some monosubstituted benzenes tend to stack parallelly with HFB; for the benzene-naphthalene complexes evidence for the T-type structure was found. The behavior of the dipolar couplings of benzene in pyridine and neat benzene, with support from the proton isotope shifts, suggests an equilibrium between the two structures. For benzene in water no preference was found.

The  $D_{\text{ortho}}$  of benzene suggests that the T-shaped arrangement is up to 3 kJ/mol more stable than the parallel-stacked form. In the case of benzene-hexafluorobenzene the free energy of complex formation of the parallel-stacked arrangement is slightly negative. These numbers indicate that the aromatic-aromatic

interaction is a weak interaction which is hardly ever able to compete with entropic effects in normal solution conditions and concentrations. However, when the aromatic groups have been prearranged as in the protein or nucleic acid structures or supported by dipole-dipole interactions as in the nucleic acids, the interaction may have a significant effect on the stability and the arrangement of the structure.

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