# Molecular Complexes, 14. Isomeric Arene Complexes of Caffeine and 1,3,7,9-Tetramethyluric Acid Detected with Toluene. Polar Interactions Inverted with Hexafluorobenzene

Helmut Stamm, Hannelore Jäckel, and Jürgen Stafe

Pharmazeutisch-Chemisches Institut, Universität Heidelberg,
Neuenheimer Feld 364, D-69120 Heidelberg, Germany

Reprint requests to Prof. Dr. H. Stamm. Fax: +49(0)6227/81039. E-mail: bista@web.de

Z. Naturforsch. **58b,** 869 – 876 (2003); received March 19, 2003

Stacking of an arene D on caffeine (**1**) near 7-Me and 8-H is known ($^1$H NMR shifts, $CCl_4$, AUS concept) to yield the same association constant *K* for each signal of **1**. Toluene (**T**) and **1** now yielded the same *K* from 7-Me and 8-H while *K* from 1-Me (and 3-Me) is smaller indicating a minor stacking centre near N-1 that forms both **1T** and $\mathbf{1T_2}$; this $\mathbf{1T_2}$ disturbs computations of *K*. The main stacking centre forms no $\mathbf{1T_2}$ since its **1T** is stabilized by dipole-dipole interaction. Diphenylmethane **Dp**, a substituted **T** that cannot form a dimer of type $\mathbf{T_2}$, does not form $\mathbf{1Dp_2}$. Ethyl of 1-ethyltheobromine (**2**) is proven to stand perpendicular so that the above minor complex can only arise on one face of **2** halving $K_{minor}$ and making the disturbance of computations by $\mathbf{2T_2}$ insignificant; apart from this minor **2T** there are *cis-trans* isomers of the main complex. Stacking of **1** and **2** with larger arenes is discussed in terms of relative molecular sizes under consideration of the perpendicularly placed ethyl group of **2**. Stacking of D near N-3 and N-9 of 1,3,7,9-tetramethyluric acid (**4**) is known. **4** and **T** now provided $K = 0.218$ l mol$^{-1}$ from 3-Me and 9-Me but $K = 0.157$ l mol$^{-1}$ from 1-Me and 7-Me. This and the complex induced shifts *IK* indicate formation of stacking **4T** + $\mathbf{4T_2}$ and of two edge-on **4T** standing on 3-Me and 9-Me under dipole-dipole interaction with a neighbouring oxygen. The oxygens of **4** (and probably of **1**, too) form edge-on complexes with hexafluorobenzene; this underlines the importance of polar effects.

*Key words:* Arene Complexes in $CCl_4$, Formation Constants, Topologies

## Introduction

Complexation of various compounds A with arenes D changes $^1$H NMR shifts of A protons due to the rapid equlibrium between free and complexed A since the complexing D shields the protons of A (complex induced shifts CIS). The formation constant *K* for a rather strong complex AD can be calculated from the experimental shifts $\Delta_0$ when the total concentration $[D_0]$ of D is varied over a sufficiently wide range and is much higher than the total concentration $[A_0]$ of A [1, 2]. With a small *K* the contributions to $\Delta_0$ from non-complexing shielding by excess D must not be ignored. Surrounding D molecules shield AD, free A, and an internal reference giving unreliable results as evident from the usually observed proton dependence of *K*. The AUS method (solvent $CCl_4$, concentrations in mol l$^{-1}$) eliminates the corresponding errors by external referencing and by iterative computations that for each signal of A provide the parameters *K*, *IK* (approximate CIS) and $m_2$ which is composed of a susceptibility correction and of non-complexing shielding of the respective proton in AD [3 – 5]. The basic principle behind $m_2$ was confirmed with more than 30 arenes [6]. The parameters refer to all complexes if more than one is formed. For concise descriptions of method and parameters see [5, 7]. The computer program CA-AUS based on the method of Cresswell and Allred [8] is less sensitive to experimental error than Sc-AUS based on the method of Scatchard [9]. The topology of AD is inferable from *IK* values; the average position of D stacking over A is termed complex centre.

Finding the same parameters from both programs and the same *K* from different signals is a good indicator for the reliability of results in particular with four signals coming of different positions in A. Value and power of the method are shown e. g. by detecting edge-on complexing through a very large *IK* when a stacking interface is too small [10] or by the detection of hindered torsional vibrations in stacking AD [5] and

Table 1. Parameters for complexation of **1** (caffeine) and **T** ($d_8$-toluene)[a]; rounded parameters for complexations of **1**[b] and **2**[c] with **B** ($d_6$-benzene), **T**, **Dp** (diphenylmethane), **Bp** (biphenyl), **N** ($d_8$-naphthalene), **P** (phenanthrene) and **Fa** (fluoranthene).

| A-D | $K$ (l mol$^{-1}$) | $10^2IK$ (max. deviation) (ppm) 1-Me of **1** 1-$CH_2$ of **2** | 3-Me | 7-Me | 8-H |
|---|---|---|---|---|---|
| **1-T**[d] | 0.065 – 0.099 | 36.8 – 58.7 | | | |
| | 0.093 – 0.105 | | 40.5 – 44.6 | | |
| | 0.130 ± 0.004[e] | | | 150.5 (5.3) | 177.6 (2.7) |
| **1-Dp**[f] | 0.222 | 15 | 32 | 202 | |
| **1-B** | 0.116 | 22 | 30 | 175 | 173 |
| **2-T** | 0.107 | 16 | 26 | 185 | 206 |
| **2-B** | 0.092 | 9 | 27 | 189 | 206 |
| **1-Bp**[f] | 0.246 | 40 | 50 | 196 | |
| **1-N** | 0.287 | 39 | 50 | 219 | 232 |
| **2-N** | 0.266 | 28 | 40 | 237 | 240 |
| **1-P**[f] | 0.585 | 57 | 83 | 240 | |
| **2-P**[f] | 0.502 | 47 | 66 | 239 | |
| **1-Fa**[f] | 0.906 | 62 | 85 | 230 | |
| **2-Fa**[f] | 0.688 | 58 | 73 | 224 | |

[a] Three experimental series; [b] taken from [5, 6]; [c] taken from [7]; [d] average $10^2\,m_2$ (max. deviation) (ppm l mol$^{-1}$): 1-Me 4.7 (0.2), 3-Me 6.3 (0.1), 7-Me 7.20 (0.04), 8-H 5.77 (0.04); [e] saturation fraction ([AD] / [$A_0$]) = 0.05 – 0.54; [f] signals of 8-H are hidden under signals of D.

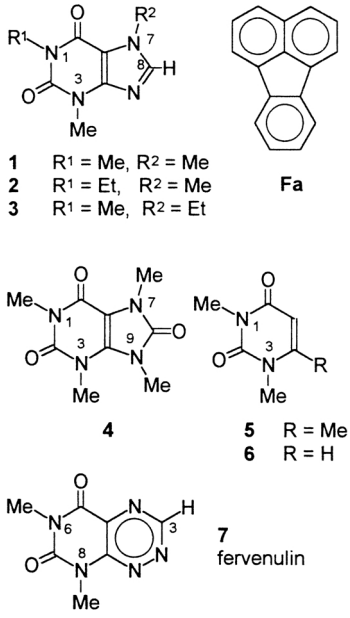


Fig. 1. Constitutions and numbering of **1 – 7** and of **Fa**.

last not least by a novel way to detect isomeric complexes that usually cannot be detected [11]. When D is toluene T one may find both AT and $AT_2$, the latter by an increased $IK$. $AT_2$ might be considered to arise from A and the toluene dimer $T_2$, a stacking dimer with antiparallel T dipoles [12]. Isomeric complexes with T are detectable when one of them profits from a dipole-dipole attraction in AT that prevents formation of the corresponding $AT_2$ (stacking of three dipoles) [5].

Complexing of caffeine (**1**, Fig. 1) found early interest for various reasons. The solubility of polycyclic arenes in water, *e.g.* of the carcinogenic 3,4-benzopyrene, is increased by **1** [13]. Studies of the complex with benzene revealed the usual problems [14] and were finally [15] interpreted by the formation of both 1:1 and 1:2 complexes. The AUS method subsequently showed with 17 arenes [16, 17] that only 1:1 complexes are formed whose complex centre is near 7-Me and 8-H. This centre is in accord with the direction of the dipole moment of **1** [18] as well as with the formation of an intermolecular hydrogen bond from =CH (position 8) to a carbonyl oxygen both in the crystal [19] and in $CD_3COCD_3$ [5]. The same centre was found (5 arenes) for complexes of 1-ethyltheobromine (**2**, Fig. 1) [20]. This picture is now completed by a weak second centre.

## Results and Discussion

Results obtained with $d_8$-toluene **T** by means of computer program CA-AUS [1 – 3, 7] are presented in Tables 1 and 2; the program Sc-AUS provided practically the same results unless a deviation is noted. $^1$H NMR results proving the postulated Et conformation in **2** are given in the text. Symbols used are: **B** = $d_6$-benzene, **Bp** = biphenyl, **Dp** = diphenylmethane, **N** = $d_8$-naphthalene, **P** = phenanthrene, **Fa** = fluoranthene, **Hx** = hexafluorobenzene. The Figures and the term complex centre refer to an average position of D that may undergo vibrations and other motions.

### *Complexes of caffeine (**1**) and of 1-ethyltheobromine (**2**)*

**1** and **T** provided (Table 1) the same $K$ for 7-Me and 8-H while the other computations are unusually sensitive to experimental scatter. Both $K$ and $IK$ values from 1-Me and 3-Me extend over a broad range each and the $K$ values are distinctly smaller than $K$ obtained from 7-Me and 8-H. Both findings are most pronounced for 1-Me. The 1:1 model is clearly sufficient for the complex centre near N-7 and C-8 (Fig. 2: A, solid hexagon) described for 17 complexes of **1**; this centre can attach **T** under extra-stabilization by dipole-dipole attraction (Fig. 2: B) and does not form $\mathbf{1T_2}$. But

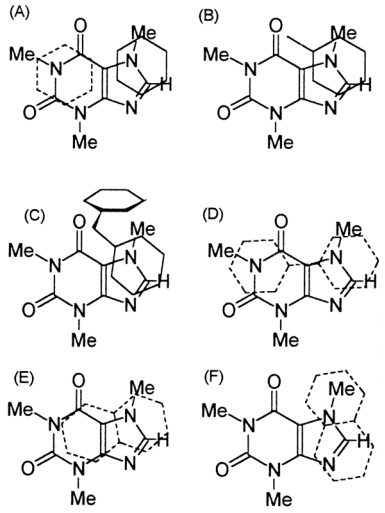


Fig. 2. (A) Main (solid hexagon) and minor complex centre of **1**, (B) dipole-dipole stabilization with **T**, (C) **1Dp** with combined stacking + tilted edge-on complexing, (D) **Bp** covers both stacking centres of **1**, (E) **N** cannot cover both stacking centres of **1**, (F) one rotamer of the main complex of **1N**.

this model is definitely insufficient for 1-Me pointing to a minor complex centre near N-1 (Fig. 2: A, dashed hexagon) that is unsuited for dipole-dipole attraction of **T**. Thus, both **T** and $\mathbf{T_2}$ are attached to this centre under in-plane rotation and this $\mathbf{T_2}$ disturbs the computation of parameters for 1-Me and less so for 3-Me and probably even of *IK* for 7-Me (see below). Moreover, the presence of two isomeric complexes means that the calculated $IK_i$ (= $IK_{i,total}$) for proton group *i* is equal to the sum $IK_{i,1}\ K_1/K_{total} + IK_{i,2}\ K_2/K_{total}$ where subscripts 1 and 2 refer to complexes 1 and 2. $IK_{i,n}$ can be very small or even zero and depends as usual on the distance to the shielding D of complex n and hence on the distance to the stacking centre n. This makes the low $10^2$ *IK* values for 1-Me throughout Table 1 better compatible with the formation of a minor complex near N-1. The somewhat higher values for 3-Me come of both minor and main complex; the centre of the latter is closer to 3-Me than to 1-Me. On the other hand partial or complete suppression of complex 2 should augment the ratio $K_1/K_{total}$ of complex 1 as well as those *IK* values that come mainly of 1. This is demonstrated below with complexes of **2**.

Diphenylmethane **Dp** is a dipole analogue of **T** whose substituted methyl group by rotation prevents formation of stacking $\mathbf{Dp_2}$ and hence of $\mathbf{1Dp_2}$. Indeed (Table 1), **1Dp** provides the same *K* from all protons. One may expect a *K* value that is twice that one of **1T** since in any concentration of D there are twice as many phenyl rings with **Dp** than with **T**. This doubled *K* is not reached because rotation of the benzyl group is hindered in complexed **Dp**. For a discussion of *IK* values **1Dp** may conveniently be compared with **1B** (Table 1) and then the $10^2$ *IK* values resemble each other except for 7-Me that in **1Dp** seems much too great for stacking with a **B**-like D. However, this great *IK* can easily arise when the non-stacking phenyl of the dipole-dipole stabilized main complex forms (Fig. 2: C) a tilted edge-on complex on 7-Me.

The above interpretation for the **1T** results is also confirmed by comparison with **1B** and **2T** (Table 1). Dipole-dipole attraction makes the main complex of **1T** more stable than **1B** explaining the greater *K*. The presence of $\mathbf{1T_2}$ should increase $10^2$ *IK* of 1-Me and 3-Me for **1T** relative to **1B**; this seems to be verified despite the uncertainty of these *IK* values for **1T**. As for 7-Me and 8-H one would expect no significant difference between **1B** and **1T**; the smallness of $10^2$ *IK* for 7-Me of **1T** relative to **1B** and its maximal deviation point to an *IK* computation that is slightly disturbed by $\mathbf{1T_2}$ in contrast to the *IK* computation for 8-H that has a somewhat larger distance to the minor centre.

Replacing Me at the minor centre of **1** by Et in **2** always decreases *K* (Table 1). Both faces of the planar molecule **1** may attach a D molecule although not simultaneously. With **2** rotation of Et about the N-C bond is hindered so that Me of Et protrudes from one molecular face as already expected from the reported [21] behaviour of **1** and **2** in water; both compounds dimerize but a tetramere is formed by **1** only. Hindered rotation is also indicated by the chemical shifts for **2** as compared to the isomeric 7-ethyltheophylline **3** (Fig. 1). Et in **3** can rotate without hindrance and its $CH_2$ signal is only 0.29 ppm downfield of 7-Me in **1** quite as expected. The $CH_2$ signal of Et in **2** is 0.63 ppm downfield of 1-Me in **1** indicating the perpendicular conformation that holds the $CH_2$ protons near the flanking oxygens. This conformation is unambigously corroborated by the temperature dependence (*cf.* [5]) of signals. Cooling (+25 °C to −15 °C) a solution of **2** in $CCl_4$ makes signals go downfield by 0.044 ppm (8-H), 0.021 ppm (7-Me), 0.006 ppm (3-Me) and upfield by 0.021 ppm ($CH_2$) and 0.0006 ppm (C-Me). The upfield shift for $CH_2$ results from hindered torsional vibrations of Et making the $CH_2$ protons come less close to the molecular plane whose mean angle to the CH bonds is 30°. This is the first example for the temperature

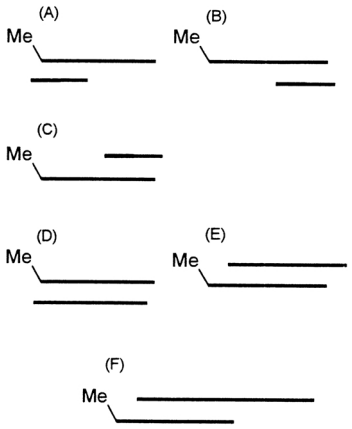


Fig. 3. Complexes of **2**, schematic view along the molecular plane of **2**. (A) Minor complex with small D, (B,C) isomeric main complexes of about equal strength with small D, (D,E) two isomeric complexes when D (*e. g.* **P**) reaches the size of **2**, (F) the weaker one of the two complexes with a D (*e. g.* **Fa**) whose size exceeds the size of **2**.

dependence of a $CH_2R$ substituent standing vertically to the molecular plane.

The protruding Me of Et prevents stacking over N-1 so that this stacking is possible only from the opposite face (Fig. 3: A) making the *K* contribution from the minor complex of **2** half that one of **1**. In this way and assuming that $K_{main}$ does not change on going from **1** to **2** one can calculate $K_{main}$ and $K_{minor}$ from the data of Table 1. $K_{main}$ is 0.068 l mol$^{-1}$ for **1B** and **2B** but 0.084 l mol$^{-1}$ for **1T** and **2T** indicating a substantial dipole-dipole extra stabilization. $K_{minor}$ = 0.023 l mol$^{-1}$ for **2T** is obviously too small to seriously disturb the computations of $K_{total}$ by $\mathbf{2T}_2$. Since the two faces of **2** are unequal there are *cis-trans* isomers of the main complex (Fig. 3: B, C) so that on the whole three isomeric complexes can arise. $K_{main}$ of a **2** complex as calculated above is composed of $K_{main,B}$ and $K_{main,C}$ that are equal or nearly so. A partial suppression of the minor complex as *e. g.* with **2B** decreases its proportional contribution to $K_{total}$ as well as to those *IK* values that come predominantly of the main complexes. Indeed, $10^2$ *IK* of 7-Me and 8-H are always greater (Table 1) for the complex with **2** than for the complex with **1** except for a large condensed D (**P**, **Fa**). The latter case is discussed below.

It is clear that now with all arene complexes of **1** the detected minor centre has to be considered. **1** and biphenyl **Bp** (Table 1) provide a *K* value that is slightly more than twice the *K* of **1B**. In analogy to **Dp** one may perhaps consider **Bp** to form both complexes of Fig. 2 (A) with each ring of **Bp** doubling *K* without changing *IK* values. However, additive stabilization by complexing of one **Bp** with both stacking centres of **1** (Fig. 2: D) appears more likely and is supported by the *IK* values since each $10^2$ *IK* is greater than that one of **1B** by about 20 ppm. In contrast to **1Bp** (Fig. 2: D) the molecular dimensions (Fig. 2: E) of **1N** (Table 1) do not enable a two-centres stacking. Formation of main (Fig. 2: F) and minor complexes of **1N** and **2N** (Table 1) analogous to **1B** and **2B** is compatible with all $10^2$ *IK* values, in particular with the high values of 7-Me and 8-H that reflect the strong shielding by **N** in the main complexes. Moreover, an argument against two-centres stacking comes of very similar $K_{minor}$ values when calculated as described above: 0.024 l mol$^{-1}$ for **2B**, 0.023 l mol$^{-1}$ for **2T** and 0.021 l mol$^{-1}$ for **2N**; the oxygens of **1** seem to repel a larger D. A minor complex may be absent with **P** or **Fa** and their main complexes have large contact interfaces resulting in strong dispersion forces. **P** reaches the size of **1** so that **2P** practically forms only the two complexes of Fig. 3 (D, E), the protruding Me (Fig. 3: E) makes **2P** weaker than **1P** by 0.083 l mol$^{-1}$. This size effect is much stronger (0.470 l mol$^{-1}$) for **2Fa** (Fig. 3: F) and **1Fa** since the size of **Fa** is definitely larger than the size of **1**.

*Complexes of 1,3,7,9-tetramethyluric acid (**4**)*

The main stacking centre of **1** is blocked in **4** (Fig. 1) by an oxygen atom that, however, makes each complex of **4** markedly stronger than the corresponding complex of **1**, the more so the larger D is (Table 2) as may be expected from a more centralized stacking. In a previous report 3-Me and 9-Me of **4** gave by far the largest *IK* values (Table 2); this was ascribed to stacking over a centre close to N-3 and N-9 (Fig. 4: A) [22]. This description of the complexation is incomplete since **4** and **T** (Table 2) now provided *K* = 0.218 l mol$^{-1}$ from 3-Me and 9-Me but *K* = 0.157 l mol$^{-1}$ from 1-Me and 7-Me clearly indicating more than one kind of complexes. The former *K* is greater than the total *K* for **4B** (Table 2) and must also be the total *K* as is corroborated by results from the shift difference method [4]. The $\Delta_0$ differences 3-Me/1-Me, 3-Me/7-Me, 9-Me/1-Me and 9-Me/3-Me provided *K* = 0.222 l mol$^{-1}$ (max. deviation 0.012 l mol$^{-1}$). By analogy to other **T** complexes follows that one type of complex forms both **4T** and $\mathbf{4T}_2$ while the other type forms only **4T**. Formation of the same type of complex with **T** and $\mathbf{T}_2$ does

Table 2. Parameters for complexation of **4** (tetramethyluric acid) with **T** ($d_8$-toluene)[a] and with **Hx** (hexafluorobenzene); rounded parameters[b] for complexations of **4** with **B** ($d_6$-benzene), **Bp** (biphenyl), **N** ($d_8$-naphthalene) and **P** (phenanthrene).

| A-D | $K$ (l mol$^{-1}$) (max. dev.) {from shift differences}[c] ⟨deviating Sc-AUS results⟩ | | $10^2 IK$ (ppm) (max. deviation) ⟨deviating Sc-AUS results⟩ | | | |
|---|---|---|---|---|---|---|
| | | | 1-Me | 3-Me | 7-Me | 9-Me |
| **4-T**[d] | 0.157 (0.007) | | 23.8 (0.4) | | 25.0 (0.1) | |
| | 0.218 (0.004)[e] | | | 152.1 (0.8) | | 156.2 (1.5) |
| **4-B** | 0.165 | {0.164} | 17 | 158 | 19 | 161 |
| **4-Bp** | 0.506 | {0.509} | 41 | 155 | 44 | 159 |
| **4-N** | 0.750 | {0.733} | 29 | 198 | 33 | 216 |
| **4-P** | 2.084 | {2.053} | 50 | 210 | 56 | 223 |
| **4-Hx**[f] | 0.0960 (0.0036) | | 52.6 | 43.4 | 54.9 | 29.0 |
| | ⟨0.0808⟩ | | ⟨66.2⟩ | | | |
| | ⟨0.0861⟩ | | | ⟨48.0⟩ | | |

[a] Two experimeental series; [b] taken from [22]; [c] obtained from shift ($\Delta_0$) differences [4] of Me signals 3/1, 3/7, 9/1, 9/7; [d] average $10^2\ m_2$ (ppm l mol$^{-1}$) (max. deviation): 1-Me 4.0 (0.1), 3-Me 5.2 (0.1), 7-Me 4.8 (0.1), 9-Me 5.3 (0.2); [e] saturation fraction ([AD] / [$A_0$]) = 0.14-0.67; [f] one experimental series; saturation fraction = 0.05–0.40; $10^2\ m_2$ (ppm l mol$^{-1}$): 1-Me 5.76, 3-Me 2.49, 7-Me 5.76, 9-Me 2.97; deviating $10^2\ m_2$ (ppm l mol$^{-1}$) from Sc-AUS: 1-Me 5.34, 3-Me 2.36.

not necessarily disturb the computations as long as the experimental shifts $\Delta_0$ contain no contributions from an isomeric 1:1 complex; this was previously shown with 4-nitrobenzaldehyde [5] and may also be expected when such contributions are small.

$10^2\ IK$ values for 3-Me and 9-Me mainly come of a complex type forming only **4T** since they are a bit smaller (4%, 3%) than those of **4B** (Table 2). $10^2\ IK$ for 1-Me and 7-Me are enlarged (40%, 32%) relative to **4B** showing that here both **4T** and **4T$_2$** arise. The seperate edge-on (see below) $K_e$ for the complex type that forms only **4T** and shields only 3-Me and 9-Me is 0.061 l mol$^{-1}$ (the difference between both $K$ in Table 2); it is smaller than $K$ (0.157 l mol$^{-1}$) obtained from 1-Me and 7-Me which have very small $IK$ values. The two complex types with **T** should generally be found in Table 2 except for complexing with **Hx**; so, the following discussion is not restricted to the results with **T**.

The main complex ($K_{st}$ = 0.157 l mol$^{-1}$) with **T** is the stacking complex (Fig. 4: A) which was previously described for **4B**, **4Bp**, **4N** and **4P**; it gives rise to nearly all (see below) of $IK$ for 1-Me and 7-Me as well as to a substantial part of $IK$ for 3-Me and 9-Me.

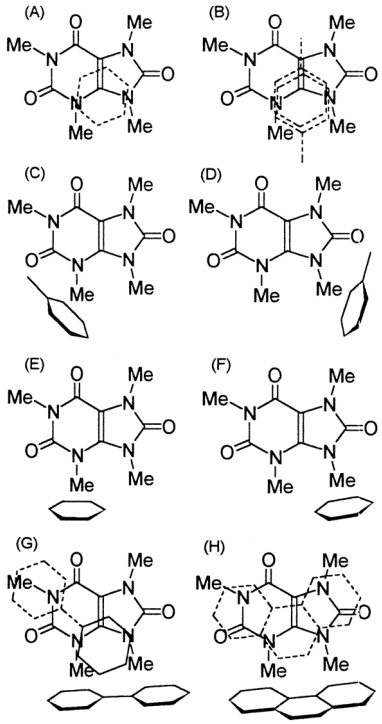


Fig. 4. Complexes of **4**. (A) Main stacking centre of **4**, (B) **4T**$_2$ with in-plane rotating **T**$_2$, (C, D) two isomeric edge-on **4T** with dipole-dipole interaction, (E, F) two isomeric edge-on **4B**, (G) edge-on **4Bp** and in-plane rotation of stacking **4Bp** (the dashed hexagon circling around), (H) edge-on **4P** and stacking **4P**.

This $K_{st}$ includes formation of stacking **4T**$_2$ (Fig. 4: B) from **4** and **T**$_2$. The other complex type throughout Table 2 is T-shaped (dipole moment of **4** [23]: 3.21 debye) either standing with 3-Me and 9-Me on the same D (see below) or, with a small D (**B**, **T**), consisting of two complexes since either 3-Me or 9-Me will stand on D. Both **4T** of this edge-on type must be stabilized by dipole-dipole interactions (Fig. 4: C, D) else edge-on **4T$_2$** should also arise. These two edge-on **4T** do not give full edge-on shieldings since each **T** is not exactly on top of the rotating Me. In contrast, the two edge-on **4B** (Fig. 4: E, F) not only can reach the maximal edge-on shielding, but they also somewhat shield the neighbouring Me, i. e. the complex on 3-Me (Fig. 4: E) somewhat shields 9-Me and vice versa. Considering these different edge-on topologies the finding that $IK$ values of 3-Me and 9-Me of **4T** are slightly smaller than those of **4B** may be a real difference. The maximal shielding reported for a Me standing on **B** ($10^2\ IK$ =

289 ppm) was found for 6-Me in the edge-on complex of 1,3,6-trimethyluracil **5** (Fig. 1) [20]. A similarly high value may be expected for the separate edge-on *IK* values $IK_{e,3}$ and $IK_{e,9}$ of **4B** (Fig. 4: E, F) although their contributions to $IK_{total}$ for 3-Me and 9-Me (Table 2) will be very small. The main complex with **T** and with **B** will have practically the same $K_{st}$.

For **4Bp** (Table 2) one may expect (see **1Bp** above) a stacking *K* of about 0.314 l mol$^{-1}$ (the doubled $K_{st}$ of **4B**), so *K* = 0.506 l mol$^{-1}$ indicates a substantial increase of the edge-on *K* that may come of the additive effect shown in Fig. 4 (G). The relatively high *IK* values for 1-Me and 7-Me are in accord with an in-plane rotation of stacking **Bp** (indicated by the dashed hexagon of **Bp** in Fig. 4: G) that will increase dispersion forces and also somewhat contribute to *K*. The increase of *K* in the sequence **4B**<**4Bp**<**4N**<**4P** is clearly more pronounced than in the analogous sequence of Table 1. This is probably caused by both complex types of **4** that cannot be fused into a single complex in contrast to the isomeric complexes of **1** where two-centres stacking is possible with a larger D. An increase of stacking *K* in the sequence **B**<**N**<**P** is a general phenomenon and need not be discussed in detail. For edge-on *K* a similar effect is known from 1,3-dimethyluracil (**6**) that stands with 1-Me and 6-H on D [20]: **6B** 0.079 l mol$^{-1}$, **6Bp** 0.282 l mol$^{-1}$ (less reliable than usual), **6N** 0.235 M$^{-1}$, **6P** 0.446 M$^{-1}$. **N** should better fit in edge-on complexing than **Bp** (Fig. 4: G) and stacking **4N** is certainly stronger than stacking **4Bp**. Both types of complexing are undoubtedly much stronger in **4P** (Fig. 4: H) explaining its rather high *K*. All $K_{total}$ values of Table 2 (except **4T**) are corroborated using $\Delta_0$ differences [4].

The ratio $R_{iso} = K_{main}/K_{minor}$ is unknown, a rather reliable estimate is available for **4T** only. $R_{iso}$ is 2.57 for **4T** and much greater for **4B** (see above) making edge-on **4B** difficult to detect; one may consider $R_{iso} < 2$ for **1T** and **1B**. Summarising, for the isomeric complexes of **4** there was a lucky coincidence of stacking $\mathbf{4T}_2$ and a good $R_{iso}$ as well as negligible edge-on contributions to $IK_{total}$ for 1-Me and 7-Me owing to dipole-dipole interactions (Fig. 4: C, D). So far the only way to detect isomeric complexes was complexation with **T**. A certain motive to suspect a mixture of stacking and edge-on complexes may now be seen in a strong increase of *K* when going from **B** to **P** or another condensed D as *e. g.* reported [24] for complexes of fervenulin (**7** in Fig. 1) whose *K* is 0.178 l mol$^{-1}$ with **B**, 0.976 l mol$^{-1}$ with **N**, 2.22 l mol$^{-1}$ with **P** and 3.41 l mol$^{-1}$ with **Fa**. This suspection is supported by a $10^2$ *IK* value of **7N**. $10^2$ *IK* for 3-H is 79.0 ppm for **7B** but 68.0 ppm for **7N** pointing to edge-on complexes on 3-H whose contributions to the total *IK* is smaller for **7N** than for **7B** due to a great predominance of stacking **7N**. $10^2$ *IK* for 6-Me (72.3 ppm) of **7N** is practically equal to that one of **7B** (71.1 ppm). By analogy with the minor complex of **1B** this points to a minor stacking complex of **7B** near N-6 that is absent in **7N** since **N** of the main complex near N-8 may also cover the minor centre.

From $^1$H NMR studies in $CDCl_3$ Temussi *et al.* [25] deduced a tilted topology between edge-on and stacking for complexes of **4** that can make little use of all forces which stabilize either stacking or T shaped complexes. Their supporting CIS calculations for **4B** were based on the ring current effect in the narrower sense ignoring the diamagnetic anisotropy of the non-delocalized cyclohexatriene (*cf.* the discussion in [6]). Nevertheless, the tilted topology may be considered an ingenious hybrid of stacking and edge-on complexes described above.

*Complexation with hexafluorobenzene (Hx). Polar effects in non-complexing shielding.*

Polar effects predominate in weak AD complexes [5, 7]. The carbon skeleton of an arene D carries negative partial charge that is attracted by positive partial charges in the A molecule. When all hydrogen atoms of D are replaced by fluorine the carbon skeleton carries positive partial charge rather attracting negative partial charges in A. Such reversal of a polarity effect is already known for a simple dipole molecule [6]. The Me groups of chloroisobutene CLIB (Fig. 5: D) behave differently when D is added; *cis*-Me (relative to Cl) shows a strictly linear shift dependence on $[D_0]$ with every investigated arene in contrast to the non-linear dependence with *trans*-Me that points to complexing of this positive pole with D. With **Hx** the behaviour of the Me groups is reversed (Fig. 5: D).

When complexing of **4** with **Hx** was investigated in the usual manner already the experimental shifts $\Delta_0$ indicated an inverted behaviour since for each $[D_0]$ the $\Delta_0$ values decreased in the sequence 7-Me $\approx$ 1-Me > 3-Me > 9-Me quite in contrast to the sequence 9-Me > 3-Me $\gg$ 7-Me > 1-Me for the other complexes in Table 2. The obtained parameters (Table 2) show that the greatest *IK* is much smaller than the greatest *IK* of **4B** even considering the ring current effect of **Hx** that

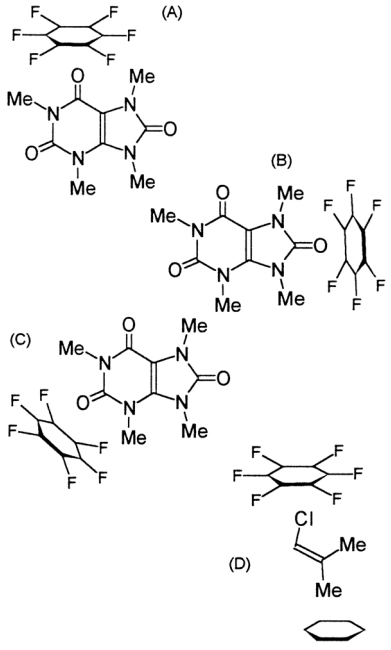


Fig. 5. Complexing with **Hx**. (A), (B) and (C) show complexing of **4**, (D) complexing of CLIB both with **B** and with **Hx**.

is 73% of **B** [6]. With only rather small differences the *IK* values decrease in the sequence 7-Me ≈ 1-Me > 3-Me > 9-Me in contrast to the sequence 9-Me ≥ 3-Me ≫ 7-Me > 1-Me for the other complexes of Table 2. This is best interpreted by formation of isomeric edge-on complexes on each oxygen of **4** as shown in Fig. 5 (A-C). Then 9-Me (Fig. 5: B) and 3-Me (Fig. 5: C) are shielded in one complex only but 1-Me (Fig. 5: A, C) and 7-Me (Fig. 5: A, B) are shielded in two isomeric complexes explaining their greater *IK* values. Formation of one of those complexes seems to change the charge distribution in **4** so much that practically only 1:1 complexes arise. The discrepancy between two CA-AUS and Sc-AUS results in Table 2 shows that the reliability of results is less than usual as may be expected from the smallness of *K* and *IK* values. The saturation fraction [AD] / [$A_0$] is 0.05 – 0.43 and a large part of each $\Delta_0$ is made up of non-specific shielding: the contribution to $\Delta_0$ by complexing is 34 – 47% except for the 48 – 60% of 3-Me that profits from a very small $m_2$. Part of this handicap arises from the upper limit of [$D_0$] that is < 8.71 mol $l^{-1}$ (pure **Hx**); pure **B** has [$D_0$] > 11 mol $l^{-1}$. Nevertheless, these results not only underline the importance of polar effects but they also demonstrate the role of polar effects for $m_2$ that was shortly [3, 6] considered (as $a_2$) in the development of the AUS concept. The sequence of $10^2$ $m_2$ (Table 2) is 1-Me ≥ 7.Me ≫ 9-Me > 3-Me in contrast to **4B** that in this sequence provided [22] the values 4.8, 5.2, 6.1, 5.9 ppm $mol^{-1}$.

With an even smaller *K* than *K* of **4Hx**, *i. e.* with less than three carbonyl groups in A, complexing with **Hx** is probably beyond the limits of the method but complexation can be detected by an inversion of polarity effects relative to common arenes. The sequence of *IK* values 8-H ≈ 7-Me ≫ 3-Me > 1-Me for complexes of **1** (Table 1) is already reflected in the sequence of $\Delta_0$ for each [$D_0$], *e. g.* 0.112, 0.110, 0.041, 0.028 ppm for the smallest [$D_0$] of **1B** [16] and 1.529, 1.570. 0.781, 0.607 ppm for the largest [$D_0$]. We now find that the signals of **1** ($CCl_4$, internal TMS) go upfield on addition of **Hx** ([$D_0$] ∼ 2.90 mol $l^{-1}$) by 0.005 ppm (8-H), 0.003 ppm (7-Me), 0.067 ppm (3-Me) and 0.095 ppm (1-Me) in accord with isomeric edge-on complexes standing on each oxygen atom so that 3-Me is shielded by **Hx** on 2-CO, 1-Me both by **Hx** on 2-CO and **Hx** on 6-CO while 7-Me and 8-H are not shielded at all. The shielding increases to 0.172 ppm (3-Me) and 0.198 ppm (1-Me) with [$D_0$] = 8.71 mol $l^{-1}$.

## General conclusions concerning weak complexes

Isomeric complexes may sometimes play a substantial role. The role of dipoles is usually underestimated, too. Unexpected or uncomprehensible results obtained from the correctly performed AUS method should be taken as real findings that deserve further analysis even for a single anomaly.

## Experimental Section

For procedures, instrument, external reference, further details, computer programs CA-AUs and Sc-AUS see [3, 5, 8, 16]. The accuracy of $\Delta_0$ was ≤ 0.0016 ppm; temperature was 30.0± 0.3 °C. [$A_0$] was kept constant in each experimental series of n (12 – 18) solutions with rather evenly distributed concentrations [$D_0$]. [A]$_0$ was 0.002 – 0.008 mol $l^{-1}$ for **1T**, near 0.0022 mol $l^{-1}$ for **4T** and 0.00537 mol $l^{-1}$ for **4Hx**. For further procedures and for the temperature dependence of shifts (internal TMS) (see [5]).

[1] W. B. Person, J. Am. Chem. Soc. **87**, 167 (1965).
[2] D. A. Deranleau, J. Am. Chem. Soc. **91**, 4044 (1969).
[3] H. Stamm, W. Lamberty, J. Stafe, J. Am. Chem. Soc. **102**, 1529 (1980).
[4] W. Lamberty, H. Stamm, J. Stafe, J. Phys. Chem. 87, 1589 (1983).
[5] H. Stamm, H.-O. Strumm, K.-H. Loebel, H. Jäckel, U. Hoffmanns, S. Bethke, G. Schilling, J. Chem. Soc., Perkin Trans. **2**, 2089 (2001).
[6] H. Stamm, H. Jäckel, J. Am. Chem. Soc. **111**, 6544 (1989).
[7] H. Stamm, H.-O. Strumm, H. Jäckel, G. Schilling, B. Beijer, S. Bethke, Z. Naturforsch. **57b**, 1305 (2002).
[8] C. J. Cresswell, A. L. Allred, J. Phys. Chem. **66**, 1469 (1962); J. Homer, P. J. Huck, J. Chem. Soc. (A) 227 (1968); K. L. Gammon, S. H. Smallcomb, J. H. Richards, J. Am. Chem. Soc. **94**, 4573 (1972).
[9] G. Scatchard, Ann. N. Y. Sci. **51**, 660 (1949); R. Foster, C. A. Fyfe, Trans. Faraday Soc. **61**, 1626 (1965).
[10] H. Jäckel, H. Stamm, J. Phys. Chem. **94**, 3495 (1990).
[11] R. Foster, Organic Charge-Transfer Complexes, chapter 6.C.4, Isomeric 1:1 Complexes, Academic Press, London (1969).
[12] C. Chipot, R. Jaffe, B. Maigret, D. A. Pearlman, P. A. Kollman, J. Am. Chem. Soc. **118**, 11217 (1996).
[13] H. Weil-Malherbe, Biochem. J. **40**, 351 (1946); J. Eisenbrand, G. Becker, Dtsch. Lebensmitt.-Rundsch. **63**, 139, 342 (1967).
[14] M. W. Hanna, A. Sandoval, Biochim. Biophys. Acta **155**, 433 (1968); M. W. Hanna, D. G. Rose, J. Am. Chem. Soc. **94**, 2601 (1972).
[15] S. Andini, L. Ferrara, P. A. Temussi, F. Lelj, T. Tancredi, J. Phys. Chem. **83**, 1766 (1979).
[16] H. Stamm, J. Stafe, Z. Naturforsch. **36b**, 1618 (1981).
[17] H. Jäckel, H. Stamm, Chem.-Ztg. **1130**, 81 (1989).
[18] H. Weiler-Feilchenfeld, Z. Neiman, J. Chem. Soc. B, 596 (1970).
[19] J. Sutor, J. Chem. Soc., 1105 (1963).
[20] H. Stamm, H. Jäckel, J. Phys. Chem. **94**, 3495 (1990).
[21] D. E. Guttman, T. Higuchi, J. Pharm. Sc. **46**, 4 (1957).
[22] H. Jäckel, H. Stamm, Z. Naturforsch. **41b**, 1461 (1986).
[23] H. Weiler-Feilchenfeld, E. D. Bergmann, Isr. J. Chem. **6**, 823, 824 (1968).
[24] H. Jäckel, H. Stamm, Arch. Pharm. (Weinheim) **321**, 213 (1988).
[25] A. Donessi, L. Paolillo, P. A. Temussi, J. Phys. Chem. **80**, 279 (1976).