Arene Interactions

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Noncovalent Functional-Group–Arene Interactions**

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In recent years, it has become increasingly clear that the planar aromatic ring plays a vital three-dimensional role in chemical and biological recognition by virtue of its ability to participate in noncovalent interactions.[1] Since a detailed understanding of protein–ligand interactions involving aromatic rings is essential for drug design and lead optimization, considerable research effort has been devoted to studies involving such phenomena as aryl–aryl interactions,[2] the behavior of aromatic rings as hydrogen-bond acceptors,[3] and their marked affinity for cationic species.[4] In qualitative terms, the quadrupolar model of aromatic systems[5] has proven to be the most popular in terms of providing a simple unifying theoretical basis upon which these different types of interaction can be considered. In this model, an aromatic ring is viewed as a quadrupole with the positive charge distributed around the edges and the negative charge located above and below the plane of the ring. A variety of elegant approaches, including structural database mining,[6] measurements of gas-phase complexes,[7] and computational modeling,[8] all provide corroboration for this simple picture.

Nevertheless, in terms of an even more rational approach for the design of new drugs, asymmetric ligands, and sensors, there is a clear need for a much more quantifiable estimation of the strength, distance, and angular dependence of the intermolecular forces acting between individual functional groups and aromatic rings. The vitally important but often neglected influence of the solvent on such noncovalent interactions should also be taken into account. Since the interaction energies are small, such data are relatively difficult to obtain and special care must accordingly be taken in the design of suitable model systems which allow their observation and evaluation. The pioneering work on the molecular torsion balance by Wilcox and co-workers[1a,2d] provides an exemplary approach to the problem of quantifying such weak interactions, and recent studies by Diederich and co-workers[9a] and by Hunter and Cockroft[9b] confirm the power of this method.

Consideration of the above requirements suggested to us that a detailed study of the conformational equilibria in suitably functionalized dibenzobicyclo[3,2,2]nonane (BCN) derivatives would provide a useful probe as shown in Figure 1.

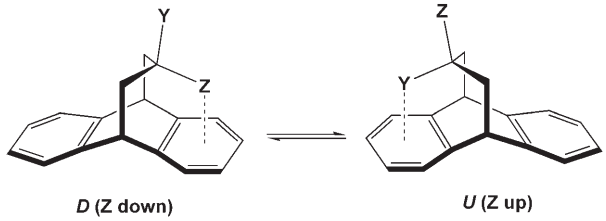

Figure 1. Conformational equilibrium in Z,Y-functionalized dibenzobicyclo[3,2,2]nonanes. Z denotes the more electronegative substituent. The dotted line highlights the possibility of noncovalent interaction between the aromatic ring and the substituents Y or Z.

Both the aromatic rings and the functional groups of the BCN derivatives are spatially confined but do not suffer from any further undesirable conformational flexibility which often impedes evaluation of measured results. Moreover, the substituents on the central carbon atom of the bridge are brought into close proximity with the centers of the aromatic rings and hence interaction energies are large enough to measure. In essence, so many of the structural features are the same on both sides of the equilibrium between conformers *D* and *U*, that the dibenzopropanoanthracene skeleton can function as a highly sensitive balance for comparison of the relative strengths of the interaction between aromatic rings and various functional groups. Note that, in contrast to more conformationally mobile systems, such as that designed by Wilcox,[1a,2d] the two functional groups on the central carbon atom of the bridge can only adopt a unique trajectory towards the aromatic ring, thereby precluding functional-group–arene interactions which would certainly be observed in more

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Supporting information for this article (including further details of infrared spectroscopy, X-ray analyses, NMR-spectroscopy coupling constants *J* and solvent dependence studies) is available on the WWW under http://www.angewandte.org or from the author.

flexible models. Herein we report the results of our preliminary studies of the conformational equilibria in such systems.

The required family of derivatives was generated from symmetrical ketone **1** (Scheme 1), which was prepared from the Diels–Alder adduct **2** by ring expansion and samarium diiodide deoxygenation of **3**. We initially wanted to gain some insight into the capacity of the aromatic ring of these derivatives to function as a hydrogen-bond acceptor. The existence of such π-facial hydrogen bonds is now well established and recent evidence[1b] indicates that it may well play an important role in biological systems.

A series of infrared studies for the alcohols **4**, **5**, and **6** in a range of solvents (Table S1 in the Supporting Information) provided strong initial evidence for both of the tertiary alcohols to form a π-facial intramolecular hydrogen bond which could partially survive even in pyridine solution, where strong solvent–solute hydrogen bonding should prevail.

We then turned to the problem of quantifying the conformational equilibria of the propano-bridged anthracenes using dynamic NMR spectroscopy. However, the interconversion energy barriers are rather small and the usual approach of reaching the slow-exchange limit on the NMR timescale by operating at low temperature failed. Only time-averaged spectra were obtained at 163 K in carbon disulfide or fluorotrichloromethane. In the ^{13}C NMR spectrum of the symmetrically substituted spiro cyclopropane derivative **12**, however, a severely broadened resonance was detected at 163 K at approximately $\delta = 14$ ppm in a $CFCl_3$/CD_2Cl_2 (4:1) solution. A 50:50 peak ratio would be expected at very low temperatures owing to the symmetry of the molecule and, indeed, two separate peaks with equal intensity and linewidth were detected in the solid-state ^{13}C cross-polarization magic-angle-spinning (CP-MAS) NMR spectrum for the cyclopropane methylene carbon atoms at $\delta = 9.2$ and 20.2 ppm at ambient temperature. Using these values as boundary values in the slow-exchange region, and assuming that the coalescence temperature in the solution state is less than 163 K, the interconversion energy barrier was estimated to be less than 27 kJ mol^{-1}.

An alternative approach was therefore used, based on the fact that equilibrium constants can be calculated using the experimentally determined averaged coupling constants if the J couplings in both conformers are known. In the case of two-site equilibrium, the populations of conformers D and U (p_D and $p_U = 1 - p_D$) can be calculated using $\bar{J} = J^D p_D + J^U p_U$, where $\bar{J}$ is the measured averaged coupling constant (either $^3\bar{J}_{H_AH_X}$ or $^3\bar{J}_{H_BH_X}$; Figure 2, Table 1) whereas J^D and J^U are corresponding boundary couplings in conformers D and U, respectively.

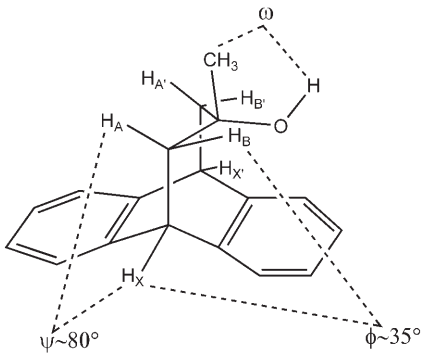
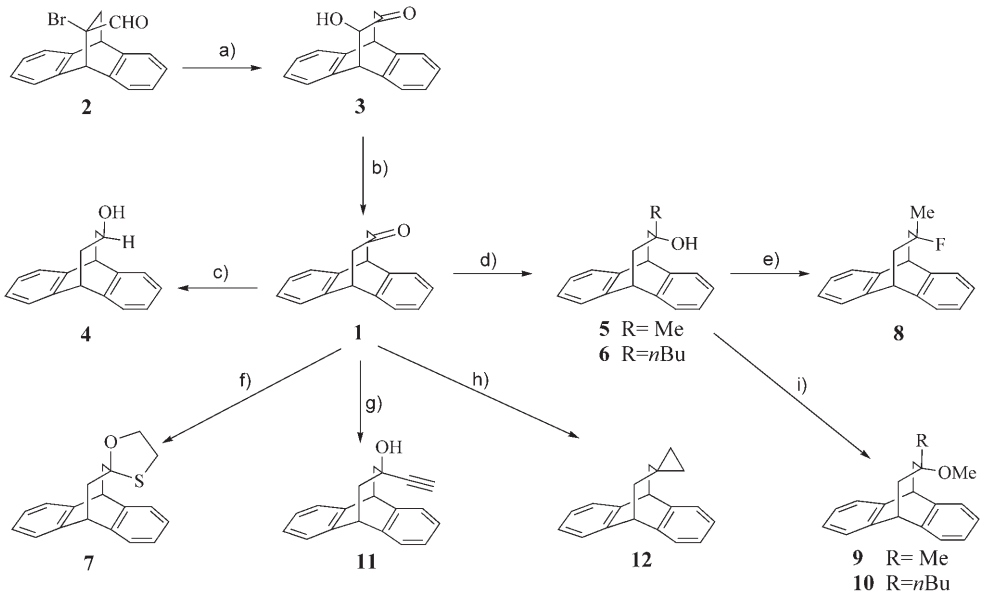


Figure 2. Tertiary alcohol **5**, with torsional angles ϕ, ψ, and ω indicated, and the location of hydrogen atoms defined for coupling constants.



Scheme 1. Reagents: a) KOH, THF–H_2O, 58%; b) SmI_2, THF, 69%; c) $NaBH_4$, THF, MeOH, 92%; d) RLi, $CeCl_3$, THF, 93% for **5**, 75% for **6**; e) $O(CH_2CH_2)_2NSF_3$, THF, 71%; f) 1) $HC(OMe)_3$, MeOH, *p*-toluenesulfonic acid, 59%; 2) 2-mercaptoethanol, *p*-toluenesulfonic acid, 51%; g) 1) $Me_3SiC{\equiv}CH$, *n*BuLi, $CeCl_3$, THF, 71%; 2) [nBu$_4$N]F, THF, 87%; h) 1) $TiCl_4$, CH_2I_2, Zn, THF, 75%; 2) Et_2Zn, CH_2I_2, Et_2O, 85%; i) KH, DMSO, Me_2SO_4, 84% for **9**, 81% for **10**.

The conformational populations as established by NMR spectroscopy in $CDCl_3$ as solvent are displayed in Table 1, and for clarity the conformers shown in Scheme 1 represent the major conformer in each case. Comparison of these results, even from a qualitative standpoint, reveals several features of considerable interest and relevance for functional-group interactions with the aromatic ring. Thus, for alcohols **4**–**6**, predominantly one conformer was detected in $CDCl_3$ solution. Consequently, the estimated free-energy difference between the two possible conformers is more than 6 kJ mol^{-1} at

Table 1: Population ratios and free energy differences between *U* and *D* conformers of BCNs in $CDCl_3$ at 298 K.[a]

Compound	Z	Y	$^3\bar{J}_{H_BH_X}$ [Hz]	$^3\bar{J}_{H_AH_X}$ [Hz]	p_D/p_U[b]	$\Delta G°$ [kJ mol^{-1}][c]
4	OH	H	7.4	1.1	7:93	6.4
5	OH	Me	6.8	1.4	94:6	−7.9
6	OH	*n*Bu	6.8	1.3	94:6	−7.9
7	OCH_2	SCH_2	5.8	2.6	24:76	2.9
8[d]	F	Me	6.2	1.8	96:4	−7.9
9	OMe	Me	5.3	2.8	70:30	−2.1
10	OMe	*n*Bu	6.5	1.7	88:12	−4.9
11	OH	C≡CH	4.2	3.9	48:52	0.2

[a] Based on variable-temperature and solvent measurements, boundary $^3J_{HH}$ values used were 7.9 and 0.9 Hz for **4** and 7.3 and 1.1 Hz for disubstituted derivatives. [b] Assuming that the boundary values are accurate within ±0.3 Hz, the error of population measurements can be estimated as ±5%. The agreement between population values calculated using two different $^3J_{HH}$ coupling constants for each compound was within 0–2%. [c] The free energy difference, $\Delta G° = -RT\ln(p_D/p_U)$, is defined such that a negative value corresponds to the more stable *D* conformer. [d] $^3J_{HF}$ coupling constants were used, which vary over significantly larger range than the $^3J_{HH}$ values; the calculated[10] boundary values were 36 and 4 Hz.

298 K. Since the hydroxy group of the secondary alcohol **4** points away from the aromatic ring, the π-facial hydrogen bond which can be formed in the second conformation is not sufficiently strong to compensate for the van der Waals radius of oxygen relative to hydrogen. The tertiary alcohols **5** and **6** however prefer to adopt the opposite conformation and, in these cases, the smaller van der Waals radius of oxygen compared to the methyl group is certainly dominant. This feature is also seen in the fluoride **8** and the ethers **9** and **10**, where both conformers are significantly populated.

Given the importance of arene interactions with sulfur atoms in biological systems,[1b,11] the observed preference in hemithioketal **7** for the sulfur atom to point towards the aromatic ring in preference to the smaller oxygen atom is of special interest. In this conformation the S···C(Ar) distances are in the range of 3.2–4.2 Å. We note that the stabilizing effect of sulfur–arene interactions at distances of 3.5–4.9 Å are known[11] and have been attributed to such factors as the availability of empty 3d orbitals on sulfur and/or its enhanced polarizability.[1b]

The solvent dependence of noncovalent interactions is of particular interest, since the energy of a weak noncovalent interaction is of similar magnitude to that of solvation. For dibenzobicyclo[3,2,2]nonanes, modulation of the observed equilibria can be achieved through interaction of solvent molecules in two distinct areas, namely either in the region of the concave surface (internal free volume), or more importantly by the exposure of the two functional groups on the central carbon atom of the bridge to the solvent. The preliminary results for some solvent dependence measurements are summarized in Table S3 in the Supporting Information.

For the tertiary alcohol **5**, solvation can be dominated by interaction of the hydroxy group with solvent hydrogen-bond acceptors which can efficiently counterbalance the energies involved in the π-facial intramolecular hydrogen bond. Moreover, in terms of the existence of a π-facial intramolecular hydrogen bond in the tertiary alcohol **5**, further evidence was obtained from detailed NMR spectroscopy studies by investigating the coupling constants $^4J_{HH}(CH_3,OH)$ and $^3J_{CH}(CH_3,OH)$, NOEs, and the temperature dependence of the hydroxy chemical shift. A marked preference for the proton of the hydroxy group to point towards the aromatic ring in the π-hydrogen bonded conformer was found in both [D_8]toluene ($^4J_{HH} = 0.8$ and $^3J_{CH} = 6.3$ Hz) and [D_{12}]cyclohexane ($^4J_{HH} = 1.1$ and $^3J_{CH} = 7.5$ Hz) solutions. A relatively weak temperature dependence of -1 ppb K^{-1} was detected for **5** in C_6D_{12} compared to -7 ppb K^{-1} measured for alcohol **4**. These results suggest inter- and intramolecular-type hydrogen bonding in **4** and **5**, respectively. By way of contrast however, a single-crystal X-ray diffraction study of **5** reveals that both conformers are present in the unit cell. Moreover, as shown in Figure 3, the hydroxy group of the central conformer

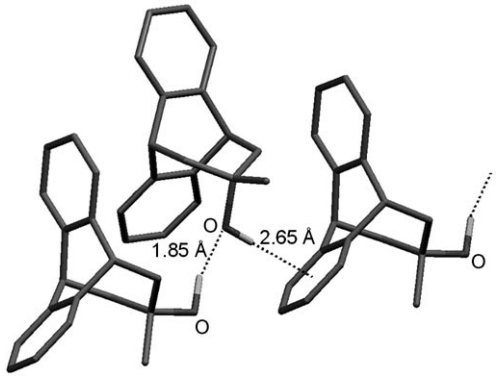


Figure 3. The arrangement of the hydroxy groups in alcohol **5** from an X-ray analysis. Hydrogen atoms not attached to oxygen omitted for clarity. Broken lines represent hydrogen bonds.

is involved in two simultaneous interactions with an intermolecular OH···O hydrogen bond to a second molecule and with the hydrogen atom not involved in the first interaction being directed towards the center of one of the aromatic rings of the third adjacent molecule. Clearly, these observations serve as a warning in terms of extrapolation of data from the solid state into solution.

Since the stabilization of a hydroxy group by a fluorine atom is a proven stratagem in the pharmaceutical industry,[12] comparison of the tertiary alcohol **5** with the fluoride **8** is especially instructive. Most notably, there are no strong solvent–solute or solute–solute hydrogen-bonding interactions for the conformer in which the fluorine atom is exposed to solvent, which is in agreement with studies suggesting that F···H close contacts are extremely rare.[13] There is in fact an increased population of conformer *D* on increasing solvent polarity, from 77% in C_6D_{12} to 97% in CD_3CN. Thus, in situations where a π-facial hydrogen bond contributes to molecular recognition, replacement by a fluorine atom should be very beneficial.

The behavior of **11** proved to be very intriguing. Approximately equal populations of both conformers were found in $CDCl_3$ at 298 K, whereas the *U* conformer dominated in the

other solvents. The single-crystal X-ray structure of **11** showed two conformers, **11***Dt* and **11***Dg*, in a 70:30 ratio. Because of the difficulties in modeling the disorder present in **11***Dg*, the major conformer **11***Dt* is considered. The torsion angles ϕ and ψ (shown for **5** in Figure 2) are 42 and 74°, respectively, which are in accordance with those found in the other compounds in this series. Deviations of the torsional angle ω and the bond angle C–C≡C (both 169°) from 180° are likely to arise from difficulties in modeling the disorder present. Despite the complexity of the data involved, the analysis revealed an unusual "head-to-tail" dimer formed by a pair of C≡C–H···π interactions between two molecules of **11***Dt* in the single crystal (Figure 4). Interestingly, in the solution NMR spectroscopy studies of **11** in $CFCl_3/CD_2Cl_2$, a very significant shift of the signal for the acetylene proton occurred on cooling the sample from 295 K ($\delta = 2.07$ ppm) to 163 K ($\delta = 0.51$ ppm). Based on the anisotropy of the ring current effect, the upfield shift that was detected agrees well with the relative orientation of the acetylene proton relative to the aromatic ring shown in Figure 4.

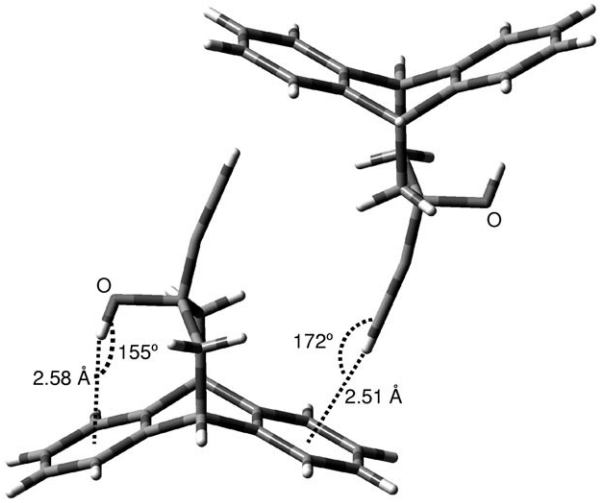


Figure 4. A dimeric arrangement of two **11***Dt* molecules from an X-ray analysis. The distances and the angles for the two close contacts of the centroids of the aromatic rings with protons (OH···π and C≡C–H···π) are highlighted with dotted lines.

In conclusion, the less conformationally mobile dibenzobicyclo[3,2,2]nonane scaffold provides an interesting probe for investigation of weak noncovalent arene interactions which are vital for chemical and biological recognition. The model was used to study solvation and such important interactions as a geometrically defined O–H···π(Ar) hydrogen bonding, and thus provide comparative insights into the effectiveness of replacing such a π-hydrogen-bonded hydroxy group by a fluorine atom, or to establish the arene affinity of sulfur as opposed to oxygen.

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