Conformational Analysis

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Noncovalent Lone Pair···(No-π!)-Heteroarene Interactions: The Janus-Faced Hydroxy Group**

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Abstract: *A comparative study using NMR spectroscopy and designed top-pan molecular balances demonstrates that the noncovalent interaction of a hydroxy group with π-deficient pyrazine and quinoxaline units involves a lone pair–heteroarene interaction which is much stronger and solvent independent when measured relative to the classical π-facial hydrogen bond to a benzene ring. Alkyl fluorides also prefer the heteroarene rings over the benzene ring. The attractive interaction between a quinoxaline and a terminal alkyne is also stronger than the intramolecular hydrogen bond to an arene.*

Noncovalent interactions[1] involving aromatic rings are essential elements for molecular recognition in a vast array of chemical and biological processes. Consequently, quantifiable information on such phenomena as π stacking[2] and cation–π[3] and anion–π[4] interactions, the ability of an arene to act as a hydrogen-bond acceptor,[5] and solvation[6] are now regarded as essential for the rational design of organocatalysts and drugs. The conformational analysis of designed molecular balances[2d,7] with limited degrees of freedom has proven to be a particularly powerful tool for probing the strength of the intramolecular variants of such weak interactions with precise control over the geometry of interacting partners. Nevertheless, we were intrigued to note that there is a relative dearth of quantifiable information using such molecular balances to probe noncovalent interactions with heteroaromatic systems, especially given the overwhelming preponderance of such compounds in the pharmaceutical and agrochemical industries.

In light of the above, we elected to study noncovalent functional-group interactions involving pyrazine and quinoxaline nuclei as prototypical heteroaromatic systems and to compare them with the parent benzene ring. The selection of these electron-deficient units was also made because of their potential ability to attract a lone pair (lp) of electrons.[8] Within the last decade, following on from theoretical studies,[4b,9] the related area of anion–π interactions has witnessed explosive growth.[4a,10,11] The significance of the attractive lp–π interaction in stabilizing the Z-DNA structure was first reported in 1995,[12] and as emphasized subsequently,[8b,h] is now gaining recognition as a new supramolecular bond.

As shown in Figure 1, we have previously introduced[13] the dibenzobicyclo[3.2.2]nonane framework **1** as the pivotal element of a top-pan molecular balance for quantifiable comparison of functional group–arene interactions in a range of solvents through variation of the two substituents (Y and Z) and determination of the conformational population [up (U) or down (D)] of the more electronegative substituent (Z) by NMR spectroscopy. We have used similar models to compare arene versus alkene interactions.[13c] Accordingly, the present study required construction of the differentiated systems **2** and **3** (Figure 1).

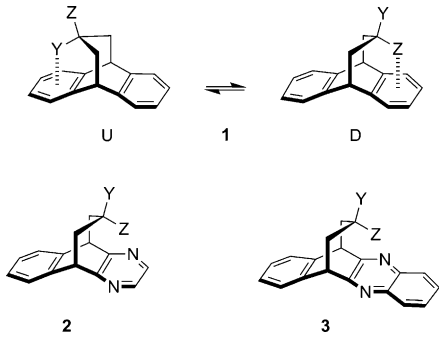

Figure 1. Conformational equilibrium in Z,Y-functionalized molecular balance **1**. Z denotes the more electronegative substituent. Heteroaromatic balances **2** and **3** used in the current work.

In the first instance, given the well-known propensity for formation of a π-facial hydrogen bond to a benzene ring, we chose to examine the behavior of the hydroxy group. The results for both diastereoisomers of a series of tertiary alcohols and two quinoxaline cyanohydrin derivatives, together with those from the original dibenzo systems are collected in Table 1. Comparative inspection with the conformational populations for the pyrazines **2a** and quinoxalines **3a** reveals that the hydroxy group remains preferentially anchored over the heteroaromatic ring, irrespective of the hydrogen-bond acceptor properties of the solvent. This result is in startling contrast to the strong solvent dependence of p_D observed for **1**, **2b**, and **3b** (Table 1), the hydroxy groups of which can form strong but instantaneous hydrogen bonds with

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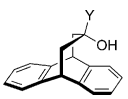
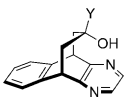
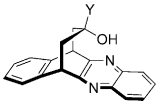
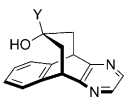
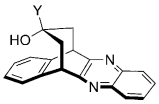
Table 1: Populations of the OH_{down} conformer (p_D, in %) in molecular balances **1**, **2**, and **3** shown in Figure 1.[a]

Solvent	**1**	**2a**	**3a**	**2b**	**3b**
					
			OH | Y = Me		
$CDCl_3$	93.5	90.4	93.5	89.0	92.1
C_6D_6	91.0	89.3	93.2	85.6	87.9
CD_3CN	76.5	89.8	94.7	74.3	79.9
CD_3OD	52.2	90.3	94.4	61.0	65.4
[D_5]pyridine	46.3	91.5	95.1	54.5	59.8
[D_6]DMSO	43.4	88.4	93.8	45.8	51.6
			OH | Y = Et		
$CDCl_3$	98.5	93.0	95.1	91.8	95.3
C_6D_6	96.7	92.6	94.9	90.6	93.9
CD_3CN	88.9	94.3	96.0	85.5	89.7
CD_3OD	75.9	92.6	95.4	76.9	80.5
[D_5]pyridine	77.5	93.2	96.0	74.6	79.4
[D_6]DMSO	64.4	91.8	95.2	65.5	71.0
			OH | Y = CH=CH_2		
$CDCl_3$	93.5	89.3	93.8	77.9	82.8
C_6D_6	91.3	90.0	93.7	76.2	80.3
CD_3CN	80.0	91.0	94.9	62.8	69.9
CD_3OD	64.6	92.0	95.4	45.5	49.6
[D_5]pyridine	66.4	93.2	95.7	48.9	56.7
[D_6]DMSO	57.4	90.0	94.9	41.8	48.3
			OH | Y = C≡CH		
$CDCl_3$	50.2	89.0	76.2	40.1	15.1
C_6D_6	39.3	92.0	79.0	33.6	10.0
CD_3CN	29.8	96.3	83.0	30.7	6.4
CD_3OD	17.1	100.0	87.3	25.6	1.4
[D_5]pyridine	18.8	98.8	87.8	23.9	3.6
[D_6]DMSO	20.8	98.0	87.0	24.4	3.0
			OH | Y = C≡N		
$CDCl_3$	24.8	–	56.2	–	26.9
CD_3CN	2.7	–	47.0	–	12.8
CD_3OD	0.0	–	29.9	–	5.4
[D_5]pyridine	2.0	–	33.1	–	6.1
[D_6]DMSO	1.2	–	37.8	–	5.7

[a] Based on the accuracy of NMR *J* coupling measurements (±0.05 Hz, see the SI). The uncertainty in the p_D values is estimated to be within ±0.9%.

the more polar solvents CD_3CN, CD_3OD, [D_5]pyridine, and [D_6]DMSO, thus leading to decreased p_D values (for detailed discussion of solvent effects for OH-to-arene conformers, including dependence of p_D on the hydrogen-bond acceptor parameter β, see Ref. [13c]). The relatively high strength of the lp···heteroarene interaction is also mirrored in the measured populations for the two diastereoisomeric cyanohydrin derivatives. Thus, for $\mathbf{3a}_{OH,CN}$ (Table 1), the lp···heteroarene interaction outweighs the CN···arene interaction by 0.6 kJ mol^{-1} in $CDCl_3$ (see Table S4 in the Supporting Information, SI), thus leading to a p_D value of greater than 50%. Furthermore, comparison with $\mathbf{1}_{OH,CN}$ reveals that the lp···heteroarene interaction is stronger than the OH···arene interaction by 3.3 kJ mol^{-1}. This observation is of significance since the CN···arene interaction is the strongest noncovalent functional group interaction to a benzene ring we have measured.[13c]

Note that the models chosen (Table 1) incorporate steric constraints, so that the OH group is oriented either towards the arene or heteroarene ring. The steric constraints are introduced in a controlled manner, by relaxing them in the sequence OH, Et > OH, Me > OH, CH=CH_2 > OH, C≡CH and OH, CN. In all cases the hydroxy group has a freedom of rotation about the C–O bond. By using our previously established NMR protocol,[13b] it was possible to demonstrate for the alcohol **3a** that the favored rotamer of the hydroxy proton around the C–O bond adopts the *gauche* conformation (see Figures S2 and S4–S6 and further discussion in SI).

The conformational energy profile generated from a series of DFT calculations is also in agreement with the NMR results, thus confirming that the *gauche* rotamer is preferred in **2a** and **3a** compared to the *trans* rotamer (Figure 2). The two conformations shown on either side of the *trans* rotamer in Figure 2 are likely to be stabilized by an OH···N electrostatic interaction. However, these are still higher in energy than either the *gauche* or *trans* rotamer. The interproton distances estimated from NOESY spectra are also in agreement with the geometry of the *gauche* rotamer predicted by DFT calculations (see Figures S2, S4–S6). By ruling out OH···π and OH···N interactions, the above results provide compelling presumptive evidence for a strong and dominant interaction of the oxygen lone pair with the heteroaromatic ring. Although several recent reports of lone pair–arene interactions have been measured by NMR spectroscopy using torsional molecular balances,[14] the present study provides, to the best of our knowledge, the first quantifiable measurements which feature a lone pair interaction of a hydroxy group and a heteroaromatic ring.

Further substantive evidence for a lone pair–heteroarene interaction comes from the measured populations of conformers for the dimethoxy derivatives shown in Figure 3. In both the pyrazine **2c** and quinoxaline **3c**, the MeO–heteroarene conformer dominates with a population of 88–100% in different solvents (Table S6). These experimental results were further supported by DFT calculations (Table S12).

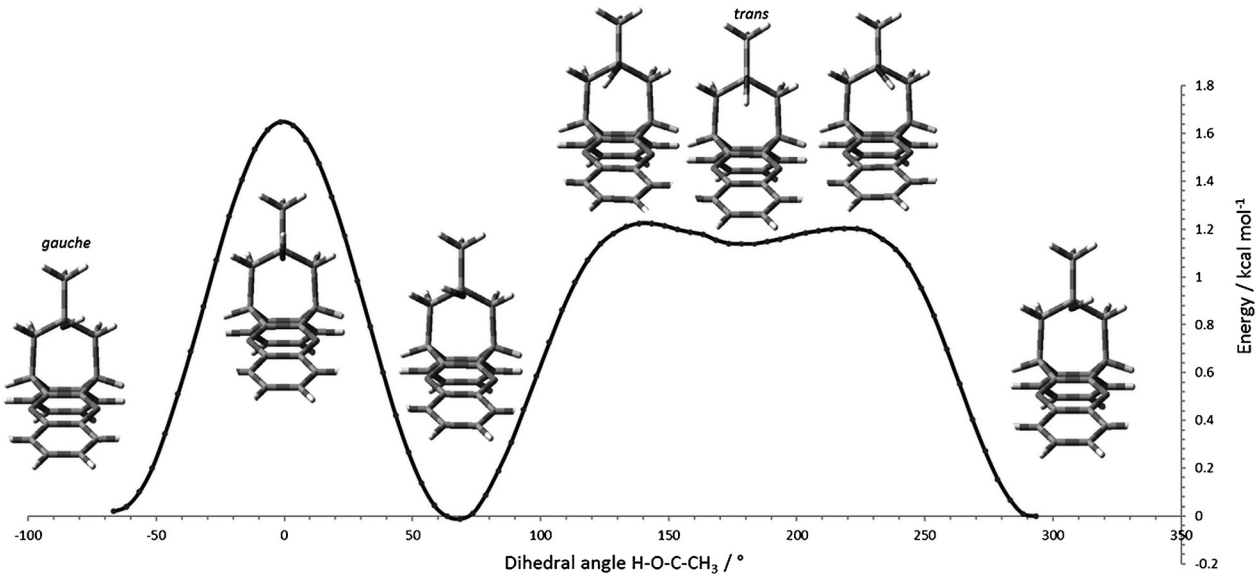


Figure 2. Relative M06-2X/6-31+G(d) energy changes upon rotation about the C–O bond starting from the *gauche* conformation of **3a**$_{OH,Me}$. The structures at extrema of the curve are also shown. Energies of *trans* and eclipsed rotamers relative to that of the *gauche* rotamer are 1.16 and 1.65 kcal mol^{-1}, respectively. The results of similar calculations for other molecules are included in Table S10 and Figures S15–S30.

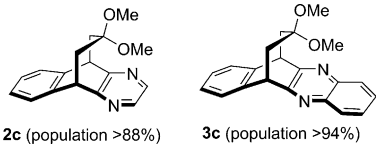


Figure 3. Preferred conformers of dimethoxy ketal derivatives **2c** and **3c**.

The quantifiable measurements[15] reported above are of interest to theoretical chemists who wish to find a rigorous explanation for noncovalent interactions of anions and lone pairs with aromatic rings. At the present time, the traditional viewpoint is to invoke a combination of electrostatic and inductive polarization effects with the former characterized either by the Q_{zz} component of the quadrupole moment of either the arene or heteroarene, or by the molecular electrostatic potential (MESP).[11b,16] In this way, as shown in Figure 4, the propensity for formation of a π-facial hydrogen bond to a benzene ring and a lp–heteroarene interaction to a pyrazine clearly reveals the Janus-faced character of the hydroxy group.

Following on from initial calculations of the electrostatic potentials of the parent azines by Almlöf et al.[17a] in 1973, and an extended study by Murray and Politzer,[17b] it was clearly stated that, for pyrazine and other azines: "Due to the electron-withdrawing power of these nitrogens, nothing remains of the negative potentials that are found above and below the ring in benzene". Most recently, the various contributions to the positive electrostatic potentials of azines have been beautifully dissected by Wheeler and Bloom,[11b] who concluded that the ability of azines to bind anions, and hence presumably to interact with lone pairs, is due to the proximity of a greater amount of nuclear charge near the ring center as a consequence of the heteroatoms, and does not involve changes in π-electron density. Clearly, the current terminology of anion–π and lp–π interactions is very unfortunate indeed.

Our attention was then directed towards comparison of the derivatives **1** with the diastereoisomeric pyrazines **2b** and quinoxalines **3b** (Table 1). Within this group, the counterbalancing interaction in our top-pan balance is the intramolecular π-facial hydrogen bond between the hydroxy group and a benzene ring, and the measured populations follow the normal solvent dependence. Interest therefore lies in comparing the weaker interactions of the saturated and unsaturated alkyl groups with the aromatic or heteroaromatic rings. For the saturated alkyl groups (Me and Et) there is a small

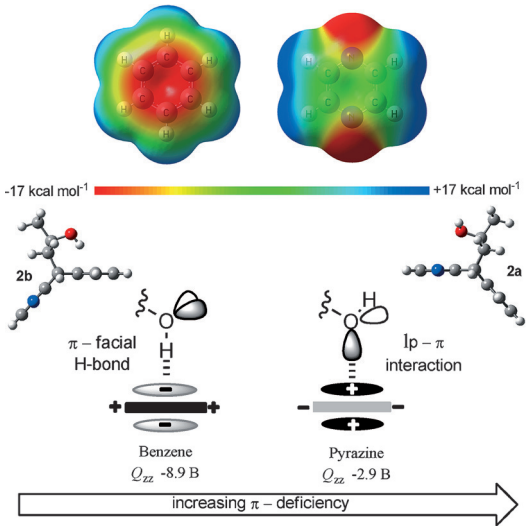


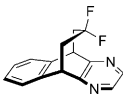
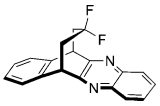
Figure 4. Quadrupole moments (Q_{zz}, in Buckinghams)[11b] and MESPs (from HF/aug-cc-pVQZ calculations) of benzene and pyrazine and their interaction with the hydroxy group. The preferred conformations of **2a**$_{OH,Me}$ and **2b**$_{OH,Me}$ are also shown.

trend in nonpolar solvents to indicate that the preferred sequence is for placement of an sp^3-hybridized carbon atom firstly over pyrazine and quinoxaline rings, and then the benzene. For the vinyl group, this difference is amplified considerably and in all solvents the pyrazine and quinoxaline are favored significantly compared to the benzene. This preference may be a reflection of the alkene acting as a π donor for the π-deficient heteroaromatic ring. Such a π vinyl–heteroarene interaction is expected to lead to stabilization of a conformer in which the vinyl plane is approximately parallel to the heteroarene ring in **2b** and **3b** compared to that in **1**. This orientation has been confirmed by DFT calculations and by experimental NOE measurements (see Figures S6 and S11–S14).

With regard to acetylenic alcohols (Table 1), it was surprising to note that the noncovalent interaction of the terminal alkyne with the quinoxaline ring in $\mathbf{3b}_{OH,C\equiv C}$ overwhelms the competing formation of the π-facial intramolecular hydrogen bond to an arene (for full details see Section 3 in SI).

Finally, given that the selective incorporation of one or more fluorine atoms is a proven stratagem within the pharmaceutical and agrochemical industries[18] we have also prepared both diastereomers of the tertiary fluorides $\mathbf{2}_{F,Me}$ and $\mathbf{3}_{F,Me}$ (see structures of **2d**, **3d**, **2e**, and **3e** in Table S8 in SI). However, tertiary fluorides did not show significant changes in conformational populations on changing the orientation from F-to-arene to F-to-heteroarene (Table S8). For meaningful comparison of the arene versus heteroarene preferences, the geminal difluorides **2f** and **3f** were therefore prepared (Table 2). The results shown in Table 2 confirm that

Table 2: Populations (in %) of conformers **2f** and **3f**.[a]

Solvent	**2f**	**3f**
		
$CDCl_3$	71.2	76.3
C_6D_6	75.6	71.9
CD_3CN	62.6	66.4
CD_3OD	75.5	81.0
[D_5]pyridine	70.0	73.1
[D_6]DMSO	63.5	67.8

[a] Estimated uncertainties are within ±0.9%.

the preferred site for the fluorine atom is over either the pyrazine or quinoxaline ring, with the latter being marginally favored. In terms of solvent dependence, it is of interest to note that there is no direct correlation either with the dielectric constant (ε) of the solvent or with the hydrogen-bond acceptor parameters (β). This lack of correlation may be attributed to the fact that carbon-bonded fluorine in organic compounds rarely forms strong hydrogen bonds because of its low polarizability and tightly contracted lone pairs.[19] For the same reason, lone pairs of fluorine are likely to form weaker lp–heteroarene attractions than those of the hydroxy oxygen atom. Nevertheless, fluorine lone pairs are expected to prefer pyrazine or quinoxaline to benzene for a noncovalent attraction because of a more positive MESP above the pyrazine ring compared to that of the benzene ring, resulting from changes in the charge distribution, as illustrated in Figure 4.

Throughout our studies, single-crystal X-ray diffraction studies have also provided additional insights (see Figures S32–S37).[20] Although we have previously noted that extrapolation of data from the solid state to solution can be misleading,[13] the fact that all five structures reported herein also reflect the major conformation observed in solution provides further evidence for the strength of these intramolecular noncovalent interactions. Thus, for the diastereomers $\mathbf{2a}_{OH,CCH}$ and $\mathbf{3a}_{OH,CCH}$ the OH group is oriented towards the heteroarene rings, with intramolecular oxygen···centroid(heteroarene) distances of 3.22 Å and 3.12 Å respectively, and for **2e** and **3f**, F···centroid(heteroarene) distances of 3.13 Å and 3.17 Å, respectively.

In terms of intermolecular interactions, the crystal structure of $\mathbf{2a}_{OH,CCH}$ comprises hydrogen-bonded dimers, whilst $\mathbf{3a}_{OH,CCH}$ comprises two crystallographically independent molecules in the asymmetric unit which form hydrogen-bonded catemers (see Figures S32 and S34). The structure of $\mathbf{3a}_{OH,CCH}$ is further stabilized by a beautiful π acid···π base parallel sandwich pairing of two quinoxaline rings, as illustrated in Figure 5. This finding is in agreement with the charge distributions shown in Figure 4, thus reinforcing further the importance of electrostatic interactions of lone pairs and π clouds with heteroarenes.

In conclusion, the quantitative data reported herein provide compelling evidence that the noncovalent lp–heteroarene interaction of the hydroxy group with pyrazine and quinoxaline units is a much stronger and essentially solvent independent attractive force when compared to its behavior as a π-facial hydrogen-bond donor for the π-basic benzene ring. The preference for a fluorine atom to reside over the heteroaromatic ring in **2f** and **3f** is also noteworthy, although F(lp)–N(heteroarene) interactions may be expected to be

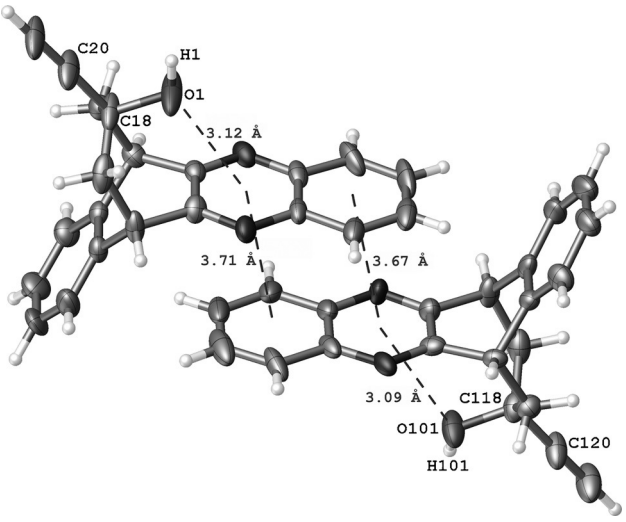


Figure 5. The X-ray structure of $\mathbf{3a}_{OH,C\equiv CH}$ showing two favorable π–heteroarene interactions between the benzene and pyrazine rings of quinoxaline.[21]

weaker than O(lp)–N(heteroarene) interactions. Finally, selection of a terminal alkyne as a counterbalance for the hydroxy group led to the discovery of a strong attractive interaction between the alkyne and quinoxaline, and it outweighs the intramolecular hydrogen bond.

Keywords: conformational analysis · heterocycles · NMR spectroscopy · noncovalent interactions · π interactions

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