Lone Pair···(No-π!)-Heteroarene Noncovalent Interactions: the Janus faced Hydroxyl Group

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Abstract: A comparative study by NMR using designed top pan molecular balances demonstrates that the noncovalent interaction of a hydroxyl group with π-deficient pyrazine and quinoxaline units involves a lone pair···heteroarene interaction which is much stronger and essentially 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] cation[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 a *sine qua non* 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 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 have 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 stabilising the Z-DNA structure was first reported in 1995,[12] and as emphasized subsequently[8b,8h], 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. 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).

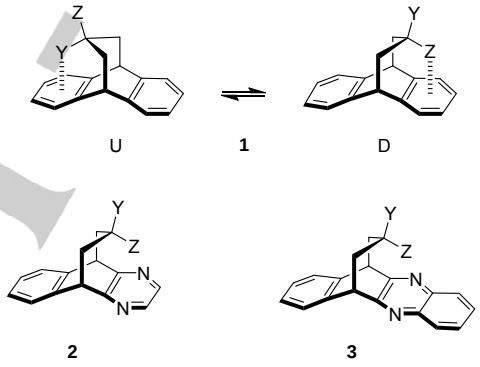

Figure 1. Conformational equilibrium in Z,Y-functionalized molecular balance (**1**). Z denotes the more electronegative substituent. Heteroaromatic balances (**2**) and (**3**) used in the current work.

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 behaviour of the hydroxyl 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 corresponding pyrazines (**2a**) and quinoxalines (**3a**) reveals that the hydroxyl group remains preferentially anchored over the heteroaromatic ring, irrespective of the hydrogen bonding acceptor properties of the solvent. This is in startling contrast with the strong solvent dependence of p_D observed for **1**, **2b** and **3b** (Table 1), the hydroxyl groups of which can form strong but instantaneous hydrogen bonds with the more polar solvents CD_3CN, CD_3OD, Py-d_5 and DMSO-d_6, 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 [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 **3a**-OH,CN (Table 1), the lp···heteroarene interaction outweighs the CN···arene interaction by 0.6 kJ mol^{-1} in deuterochloroform (Table S4, Supporting Information), leading to a $p_D > 50\%$.

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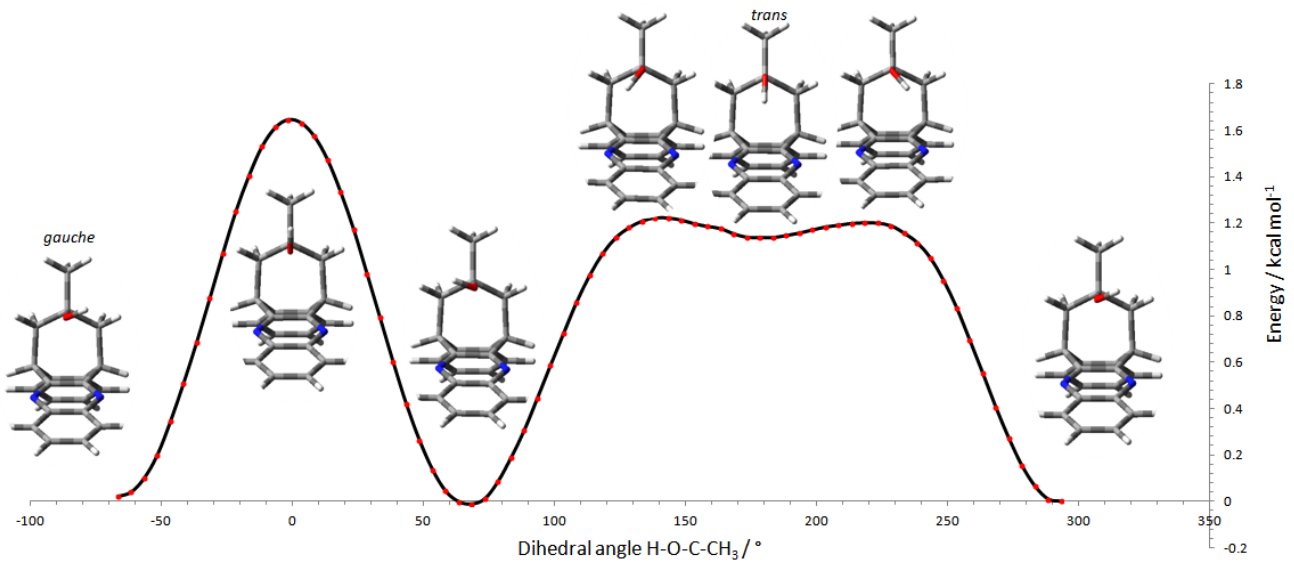


Figure 2. Relative M06-2X/6-31+G(d) energy changes on rotation about the C-O bond starting from the *gauche* conformation of **3a**-OH,Me. The structures at extrema of the curve are also shown. Energies of *trans* and eclipsed rotamers relative to that of the *gauche* rotamer are 1.16 and 1.65 kcal mol^{-1},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

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 | 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
Py-d_5	46.3	91.5	95.1	54.5	59.8
DMSO-d_6	43.4	88.4	93.8	45.8	51.6
			OH | 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
Py-d_5	77.5	93.2	96.0	74.6	79.4
DMSO-d_6	64.4	91.8	95.2	65.5	71.0
			OH | 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
Py-d_5	66.4	93.2	95.7	48.9	56.7
DMSO-d_6	57.4	90.0	94.9	41.8	48.3
			OH | 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
Py-d_5	18.8	98.8	87.8	23.9	3.6
DMSO-d_6	20.8	98.0	87.0	24.4	3.0
			OH | 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
Py-d_5	2.0	-	33.1	-	6.1
DMSO-d_6	1.2	-	37.8	-	5.7

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

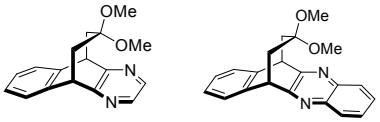
Furthermore, comparison with **1**-OH,CN reveals that the lp···heteroarene interaction is stronger than the OH···arene interaction by 3.3 kJ mol^{-1}. This observation is of significance since the CN···arene interaction is the strongest noncovalent functional group interaction to a benzene ring which 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 & OH,CN. In all cases the hydroxyl group has a freedom of rotation about the C-O bond. Using our previously established NMR protocol,[13b] it was possible to demonstrate for alcohol **3a** that the favoured rotamer of hydroxyl proton around the C-O bond adopts the *gauche* conformation (see Figures S2, S4-S6 and further discussion in Supporting Information).

The conformational energy profile generated from a series of DFT calculations is also in agreement with the NMR results 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 stabilised by an OH…N electrostatic interaction. However, these are still higher in energy than either *gauche* or *trans* rotamers. 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 and further discussion in Supporting Information). 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 using torsional molecular balances,[14] the present study provides, to the best of our knowledge, the first quantifiable measurements which feature both a lone pair interaction of the hydroxyl group and a heteroaromatic ring.

Further substantive evidence for a lone pair···heteroarene interaction comes from the measured populations of conformers in dimethoxy derivatives shown in Figure 3. In both pyrazine **2c**

and quinoxaline **3c**, the OMe-to-heteroarene conformer dominates with the population 88-100% in different solvents (Table S6 in Supporting Information). These experimental results were further supported by DFT calculations (Table S12 in Supporting Information).



2c (population >88%) **3c** (population >94%)

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 polarisation effects with the former characterised either by the Q_{zz} component of the quadrupole moment of 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 is readily appreciated.

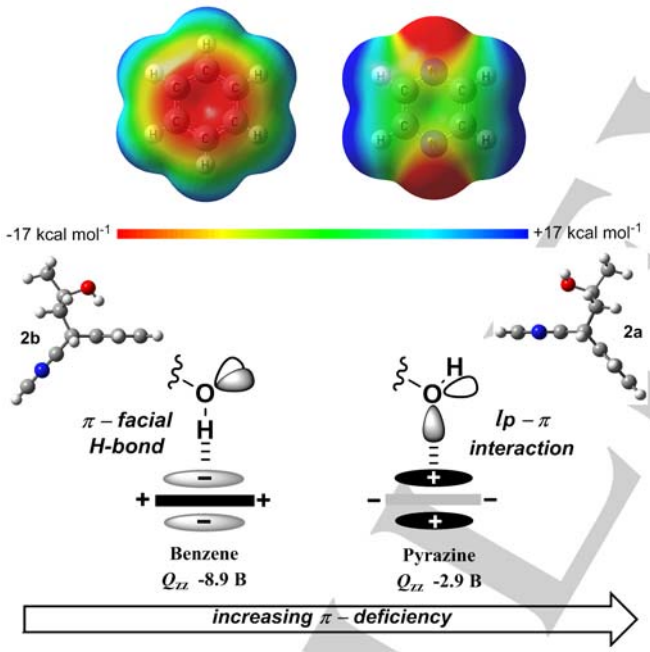


Figure 4. Quadrupole moments (Q_{zz}, in Buckinghams)[11b] and MESPs (from HF/aug-cc-pVQZ calculations) of benzene and pyrazine and their interaction with the hydroxyl group. The preferred conformations of **2a** and **2b** are also shown.

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,[11b] who has 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 centre 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 derivatives (**1**) with the diastereoisomeric pyrazines (**2b**) and quinoxalines (**3b**). Within this group, the counterbalancing interaction in our top-pan balance is the intramolecular π-facial hydrogen bond between the hydroxyl 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 trend in non-polar solvents to indicate that the preferred sequence is for placement of an sp^3 hybridised 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 favoured significantly compared to the benzene. This 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 stabilisation of a conformer in which the vinyl plane is approximately parallel to the heteroarene ring in **2b** and **3b** compared to **1**. This orientation has been confirmed by DFT calculations and by experimental NOE measurements (see Figures S6 and S11-S14 in Supporting Information).

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 **3b** overwhelms the competing formation of the π-facial intramolecular hydrogen bond to an arene (for full details see Section 3 in Supporting Information).

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 tertiary fluorides (**2d**, **3d**, **2e** and **3e** in Table S8 in Supporting Information). 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 germinal difluorides **2f** and **3f** were therefore prepared (Table 2).

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
Py-d_5	70.0	73.1
DMSO-d_6	63.5	67.8

[a] Estimated uncertainties are within ±0.9%

The results shown in Table 2 confirm that the preferred site for the fluorine atom is over the pyrazine or quinoxaline ring, with the latter being marginally favoured. 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 may be attributed to the fact that carbon-bonded fluorine in organic

compounds rarely forms strong hydrogen bonds due to 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 hydroxyl oxygen. Nevertheless, fluorine lone pairs are expected to prefer pyrazine or quinoxaline to benzene for a noncovalent attraction due to a more positive MESP above the pyrazine ring compared to 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 (Figures S32-S37, Supporting Information).[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 diastereomers **2a**-OH,CCH and **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.

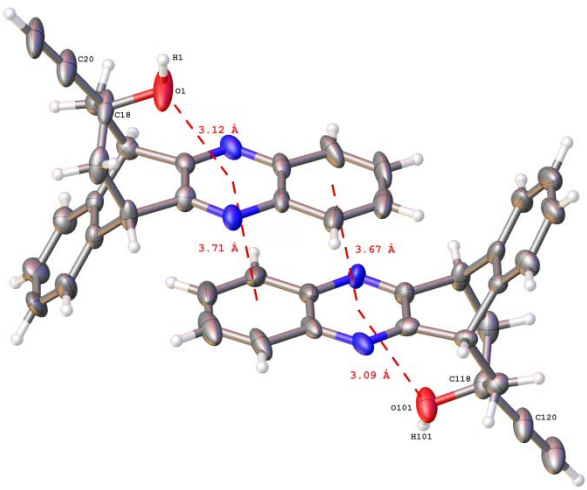


Figure 5. The X-ray structure of **3a**-OH,CCH showing two favourable π···heteroarene interactions between benzene and pyrazine rings of quinoxaline.

In terms of intermolecular interactions, the crystal structure of **2a** is comprised of H-bonded dimers, whilst **3a** is comprised of two crystallographically independent molecules in the asymmetric unit which form H-bonded catemers (see Figures S29 and S31 in Supporting Information). The structure of **3a** 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, 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 hydroxyl group with pyrazine and quinoxaline units is a much stronger and essentially solvent independent attractive force when compared to its behaviour 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 geminal difluorides **2f** and **3f** is also noteworthy, although F(lp)-N(heteroarene) interactions may be expected to be weaker than O(lp)-N(heteroarene) interactions. Finally, selection of terminal alkyne as a counterbalance for the hydroxyl group has led to the discovery of a strong attractive interaction between the alkyne and a quinoxaline, which outweighs the intramolecular hydrogen bond.

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Keywords: Conformational analysis · Molecular balances · NMR spectroscopy · Non-covalent interactions · Lone pair · π-interactions

[1] a) H.-J. Schneider, *Angew. Chem., Int. Ed.* **2009**, *48*, 3924-3977; *Angew. Chem.,* **2009**, *121*, 3982-4036. b) H. Adams, C. A. Hunter, K. R. Lawson, J. Perkins, S. E. Spey, C. J. Urch, J. M. Sanderson, *Chem. Eur. J.* **2001**, *7*, 4863-4877. c) L. M. Salonen, M. Ellermann, F. Diederich, *Angew. Chem. Int. Ed.* **2011**, *50*, 4808-4842; *Angew. Chem.,* **2011**, *123*, 4908-4944. d) E. Persch, O. Dumele, F. Diederich, *Angew. Chem. Int. Ed.* **2015**, *54*, 3290-3327; *Angew. Chem.* **2015**, *127*, 3341-3382. e) F. Biedermann, W. M. Nau, H.-J. Schneider, *Angew. Chem. Int. Ed.* **2014**, *53*, 11158-11171; *Angew. Chem.* **2014**, *126*, 11338-11352.

[2] a) C. A. Hunter, J. K. M. Sanders, *J. Am. Chem. Soc.* **1990**, *112*, 5525-5534. b) F. Cozzi, M. Cinquini, R. Annunziata, T. Dwyer, J. S. Siegel, *J. Am. Chem. Soc.* **1992**, *114*, 5729-5733. c) J. H. Williams, *Acc. Chem. Res.* **1993**, *26*, 593-598. d) S. Paliwal, S. Geib, C. S. Wilcox, *J. Am. Chem. Soc.* **1994**, *116*, 4497-4498.

[3] a) V. P. Santarelli, A. L. Eastwood, D. A. Dougherty, R. Horn, C. A. Ahern, *J. Biol. Chem.* **2007**, *282*, 8044-8051. b) H. Ihm, S. Yun, H. G. Kim, J. K. Kim, K. S. Kim, *Org. Lett.* **2002**, *4*, 2897-2900. c) J. C. Ma, D. A. Dougherty, *Chem. Rev.* **1997**, *97*, 1303-1324. d) P. Lakshminarasimhan, R. B. Sunoj, J. Chandrasekhar, V. Ramamurthy, *J. Am. Chem. Soc.* **2000**, *122*, 4815-4816. e) D. A. Dougherty, *Acc. Chem. Res.* **2013**, *46*, 885-893.

[4] a) H. T. Chifotides, K. R. Dunbar, *Acc. Chem. Res.* **2013**, *46*, 894-906. b) M. Mascal, A. Armstrong, M. D. Bartberger, *J. Am. Chem. Soc.* **2002**, *124*, 6274-6276. c) P. Gamez, T. J. Mooibroek, S. J. Teat, J. Reedijk, *Acc. Chem. Res.* **2007**, *40*, 435-444. d) D.-X. Wang, M.-X. Wang, *J. Am. Chem. Soc.* **2012**, *135*, 892-897. e) B. P. Hay, V. S. Bryantsev, *Chem. Commun.* **2008**, 2417-2428. f) O. B. Berryman, D. W. Johnson, *Chem. Commun.* **2009**, 3143-3153. g) A. Frontera, P. Gamez, M. Mascal, T. J. Mooibroek, J. Reedijk, *Angew. Chem., Int. Ed.* **2011**, *50*, 9564-9583; *Angew. Chem.,* **2011**, *123*, 9736-9756. h) P. Ballester, *Acc. Chem. Res.* **2012**, *46*, 874-884.

[5] a) S. Burley, G. Petsko, *Science* **1985**, *229*, 23-28. b) M. Hirota, K. Sakaibara, H. Suezawa, T. Yuzuri, E. Ankai, M. Nishio, *J. Phys. Org. Chem.* **2000**, *13*, 620-623. c) T. Steiner, G. Koellner, *Journal of Molecular Biology* **2001**, *305*, 535-557.

[6] a) C. A. Hunter, *Angew. Chem. Int. Ed.* **2004**, *43*, 5310-5324; *Angew. Chem.,* **2004**, *116*, 5424-5439. b) K. B. Muchowska, C. Adam, I. K. Mati, S. L. Cockroft, *J. Am. Chem Soc.* **2013**, *135*, 9976-9979. c) I. K. Mati, C. Adam, S. L. Cockroft, *Chem. Sci.* **2013**, *4*, 3965-3972. d) S. L. Cockroft, C. A. Hunter, *Chem. Commun.* **2009**, 3961-3963.

[7] a) B. Bhayana, C. S. Wilcox, *Angew. Chem. Int. Ed.* **2007**, *46*, 6833-6836; *Angew. Chem.,* **2007**, *119*, 6957-6960. b) S. L. Cockroft, C. A. Hunter, *Chem. Commun.* **2006**, 3806-3808. c) L. Yang, C. Adam, G. S. Nichol, S. L. Cockroft, *Nat. Chem.* **2013**, *5*, 1006-1010. d) A. Nijamudheen, D. Jose, A. Shine, A. Datta, *J. Phys. Chem. Lett.* **2012**, *3*, 1493-1496. e) P. Cornago, R. M. Claramunt, L. Bouissane, J. Elguero, *Tetrahedron* **2008**, *64*, 3667-3673. f) P. Li, C. Zhao, M. D. Smith, K. D.

Shimizu, *J. Org. Chem* **2013**, *78*, 5303-5313. g) C. Zhao, R. M. Parrish, M. D. Smith, P. J. Pellechia, C. D. Sherrill, K. D. Shimizu, *J. Am. Chem. Soc.* **2012**, *134*, 14306-14309. h) W. R. Carroll, C. Zhao, M. D. Smith, P. J. Pellechia, K. D. Shimizu, *Org. Lett.* **2011**, *13*, 4320-4323. i) I. K. Mati, S. L. Cockroft, *Chem. Rev. Soc.* **2010**, *39*, 4195-4205. k) F. R. Fischer, W. B. Schweizer, F. Diederich, *Angew. Chem. Int. Ed.* **2007**, *46*, 8270-8273; *Angew. Chem.* **2007**, *119*, 8418 - 8421. l) F. R. Fischer, P. A. Wood, F. H. Allen, F. Diederich, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 17290-17294. m) H. Gardarsson, W. B. Schweizer, N. Trapp, F. Diederich, *Chem. Eur. J.* **2014**, *20*, 4608-4616.

[8] a) b. W. Gung, Y. Zou, Z. Xu, J. C. Amicangelo, S. Ma, H. C. Zhou, *J. Org. Chem.* **2008**, *73*, 689-693. b) M. Egli, S. Sarkhel, *Acc. Chem. Res.* **2007**, *40*, 197-205. c) T. J. Mooibroek, P. Gamez, *CrystEngComm* **2012**, *14*, 1027-1030. d) J. P. Gallivan, D. A. Dougherty, *Org. Lett.* **1999**, *1*, 103-106. e) X. Fang, X. Yuan, Y.-B. Song, J.-D. Wang, M.-J. Lin, *CrystEngComm* **2014**, *16*, 9090-9095. f) T. Korenaga, T. Shoji, K. Onoue, T. Sakai, *Chem. Commun.* **2009**, 4678-4680. g) J. C. Amicangelo, D. G. Irwin, C. J. Lee, N. C. Romano, N. L. Saxton, *J. Phys. Chem. A* **2013**, *117*, 1336-1350. h) T. J. Mooibroek, P. Gamez, J. Reedijk, *CrystEngComm* **2008**, *10*, 1501-1515.

[9] a) D. Quiñonero, C. Garau, C. Rotger, A. Frontera, P. Ballester, A. Costa, P. M. Deyà, *Angew. Chem., Int. Ed.* **2002**, *41*, 3389-3392. b) I. Alkorta, I. Rozas, J. Elguero, *J. Am. Chem. Soc.* **2002**, *124*, 8593-8598.

[10] S. Matile, A. Vargas Jentzsch, J. Montenegro, A. Fin, *Chem, Soc. Rev.* **2011**, *40*, 2453-2474.

[11] a) Y. Zhao, C. Beuchat, Y. Domoto, J. Gajewy, A. Wilson, J. Mareda, N. Sakai, S. Matile, *J. Am. Chem. Soc.* **2014**, *136*, 2101-2111. b) S. E. Wheeler, J. W. G. Bloom, *Chem. Commun.* **2014**, *50*, 11118-11121.

[12] M. Egli, R. V. Gessner, *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 180-184.

[13] a) W. B. Motherwell, J. Moïse, A. E. Aliev, M. Nič, S. J. Coles, P. N. Horton, M. B. Hursthouse, G. Chessari, C. A. Hunter, J. G. Vinter, *Angew. Chem. Int. Ed.* **2007**, *46*, 7823-7826; *Angew. Chem.,* **2007**, *119*, 7969-7972. b) A. E. Aliev, J. Moise, W. B. Motherwell, M. Nic, D. Courtier-Murias, D. A. Tocher, *Phys. Chem. Chem. Phys.* **2009**, *11*, 97-100. c) A. E. Aliev, J. R. T. Arendorf, I. Pavlakos, R. B. Moreno, M. J. Porter, H. S. Rzepa, W. B. Motherwell, *Angew. Chem. Int. Ed.* **2015**, *54*, 551-555; *Angew. Chem*. **2015**, *127*, 561-565.

[14] a) C. C. Forbes, A. M. Beatty, B. D. Smith, *Org. Lett.* **2001**, *3*, 3595-3598. b) B. W. Gung, X. Xue, H. J. Reich, *J. Org. Chem.* **2005**, *70*, 7232-7237. c) R. Annunziata, M. Benaglia, F. Cozzi, A. Mazzanti, *Chem. Eur. J.* **2009**, *15*, 4373-4381.

[15] a) T. Lu, S. E. Wheeler, *Org. Lett.* **2014**, *16*, 3268-3271. b) A. Bauzá, D. Quiñonero, P. M. Deyà, A. Frontera, *Comput. Theor. Chem.* **2012**, *998*, 20-25. c) X. Fang, X. Yuan, Y. B. Song, J. D. Wang, M. J. Lin, *CrystEngComm* **2014**, *16*, 9090-9095. d) P. Arranz-Mascarós, C. Bazzicalupi, A. Bianchi, C. Giorgi, M.-L. Godino-Salido, M.-D. Gutiérrez-Valero, R. Lopez-Garzón, M. Savastano, *J. Am. Chem. Soc.* **2012**, *135*, 102-105.

[16] S. E. Wheeler, K. N. Houk, *J. Chem. Theory Comput.* **2009**, *5*, 2301-2312.

[17] a) J. Almlöf, B. Roos, U. Wahlgren, H. Johansen, *J. Elect. Spetrosc. Rel. Phenom.* **1973**, *2*, 51-74. b) J. S. Murray, J. M. Seminario, P. Politzer, *J. Mol. Struct. (Theochem)* **1989**, *187*, 95-108.

[18] a) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881-1886. b) T. Vagt, M. Salwiczek, B. Koksch in *Fluorine in Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications* (Eds.: V. Gouverneur, K. Müller), Imperial College Press, London, 2012.

[19] For detailed discussion of C-F…H hydrogen bonds see: a) P. A. Champagne, J. Desroches, J. F. Paquin, *Synthesis* **2015**, *47*, 306-322. b) H. J. Schneider, *Chem. Sci.* **2012**, *3*, 1381-1394.

[20] For recent examples of noncovalent interactions in solid pyrazines and quinoxalines see: a) B. Machura, A. Świtlicka-Olszewska, R. Kruszyński, T. Groń, M. Oboz, H. Duda, *Polyhedron*, **2013**, *62*, 158-168. b) J. C. Castillo, R. Abonia, J. Cobo, C. Glidewell, *Acta Crystallogr. C* **2013**, *69*, 544-548. c) S. Rajković, U. Rychlewska, B. Warżajtis, D. P. Ašanin, M. D. Živković, M. I. Djuran, *Polyhedron*, **2014**, *67*, 279-285. d) Y. Wang, H. Li, W. Wu, Y. Lu, *Comput. Theor. Chem.* **2012**, 1025, 1-6.

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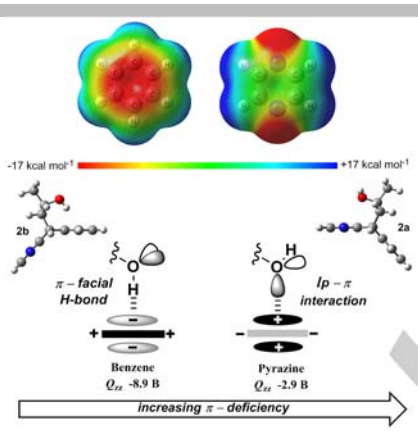
A comparative study shows that the noncovalent interaction of a hydroxyl group with pyrazines and quinoxalines involves a lone pair···heteroarene attraction which is stronger and solvent independent when measured relative to the π-facial hydrogen bond to a benzene ring. Organic fluorides also prefer the heteroarene ring over benzene. The attraction between a quinoxaline and a terminal alkyne is stronger than the intramolecular OH···arene bond.



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Noncovalent Interactions of Heteroarenes with Lone Pairs, the Hydroxyl Group, Fluorine and a Terminal Alkyne.