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Competing hydrogen-bond donors: phenols vs. cyanooximes

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ARTICLE TYPE

Competing hydrogen-bond donors: Phenols vs. cyanooximes

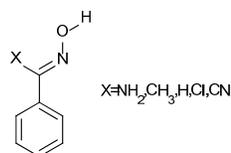
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5 Based on a systematic structural study of co-crystals of a ditopic probe molecule, (Z)-N,4-dihydroxybenzimidoyl cyanide, decorated with an –OH group and a cyanooxime moiety, it has been shown that in a competitive molecular recognition event, the former is the better hydrogen-bond donor. This structural behaviour is reflected by calculated electrostatic potential surfaces of the competing donors, which highlights that electrostatic charge can offer a reliable tool for predicting primary hydrogen-bond preferences.

The oxime moiety is a common chemical functionality often found in pharmaceuticals,^{1,2} agrochemicals,³ organometallics⁴ and in biological materials.⁵ The structural and bio-physical properties of all oximes are directly related to its hydrogen-bond capability, but what sets it apart from most other donor groups is its tunability⁶ which can be readily affected by altering the substituent (–X) on the carbon atom, Scheme 1.



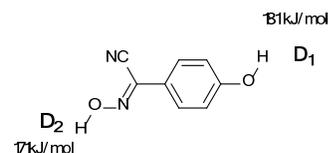
Scheme 1 The oxime moiety

Aldoximes and acetyloximes normally form head-to-head dimers in the solid state through a pair of O–H...N interactions.⁶ However, cyanooximes,⁷ where the oxime nitrogen atom is a particularly weak hydrogen-bond acceptor due to the presence of the electron-withdrawing –CN moiety,^{8,9} tend to act as a single point hydrogen-bond donors similar to an –OH group.¹⁰ The latter functionality is ubiquitous in biological systems, and is also heavily utilized in applications such as templated covalent synthesis,¹¹ nonlinear optics¹² and sensors.¹³ Again, many functions and properties of –OH substituted molecules are directly related to their hydrogen-bond capabilities.

A key requirement for effective supramolecular synthesis and crystal engineering,¹⁴ is a detailed understanding of the structural balance between different synthons, and therefore it is important to establish how potentially competing interactions will manifest themselves in the solid state. It has previously been shown that both cyanooxime moieties¹⁵ and phenolic –OH groups¹⁶ are more effective hydrogen-bond donors than carboxylic acids. The question is, can we establish a reliable ranking of the hydrogen-bond efficiency of these two moieties based upon systematic co-crystallizations of a single molecule that contains both moieties

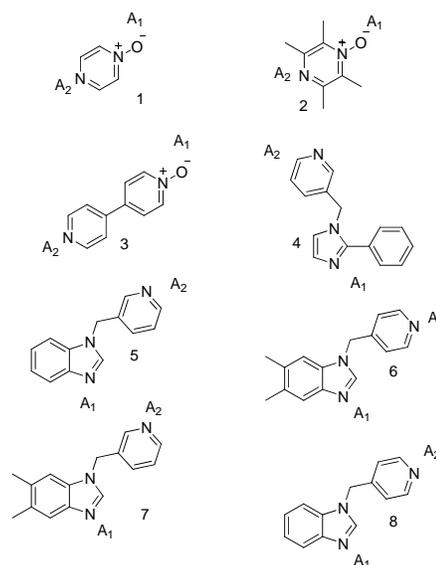
on the same molecular backbone? To address this issue, we synthesized (Z)-N,4-dihydroxybenzimidoyl cyanide as a suitable probe molecule, and co-crystallized it with eight different hydrogen-bond acceptor molecules each equipped with two binding sites of different strength, Scheme 2.

The ranking of the acceptor sites was established using calculated molecular electrostatic potential (MEP) surfaces. Similar calculations were performed on the –OH/oxime probe molecule, and the results show that the hydrogen atom of the –OH moiety carries a higher positive charge than the hydrogen atom of the cyanooxime, and is consequently designated as the better hydrogen-bond donor, D1 (the oxime becomes the second-best donor, D2), Scheme 2.



Scheme 2 (Z)-N,4-dihydroxybenzimidoyl cyanide, PhOx

According to best-donor/best acceptor guidelines for molecular recognition,¹⁷ we would expect that the better donor should bind to the better acceptor on the ditopic molecules employed herein, Scheme 3.



Scheme 3 Eight ditopic acceptors (5-7 were synthesized according to previously published methods.^{15,18})

In each case, A₁ indicates the stronger acceptor and A₂ the weaker hydrogen-bond acceptor site based on calculated MEP values.

Table 1 MEP (AM1) values of acceptors **1-8**

Acceptor	A ₁ /kJmol ⁻¹	A ₂ /kJmol ⁻¹
1	-266	-232
2	-287	-255
3	-294	-249
4	-290	-279
5	-292	-262
6	-301	-269
7	-296	-261
8	-291	-268

The charges bear the units of potential as they are calculated based on the maxima and minima of a calculated molecular electrostatic potential surface which represents the points of highest and lowest charge on the molecule.

MEP surfaces were constructed using Spartan '06 (Wavefunction, Inc. Irvine, CA). All molecules were geometry optimized using AM1, with the maxima and minima in the electrostatic potential surface (0.002 e au⁻¹ isosurface) determined using a positive point charge in vacuum as a probe.

Ditopic acceptors **1-8** were co-crystallized with **PhOx** by combining the relevant reactants in methanol in a 1:1 ratio, followed by slow evaporation. Five co-crystals suitable for single crystal X-ray diffraction were obtained.

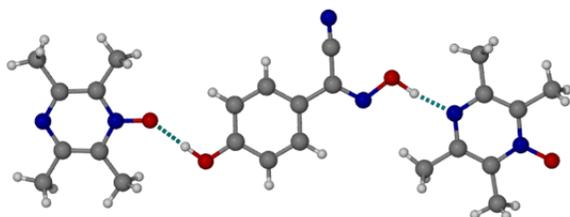


Fig 1 The primary hydrogen bonds in the crystal structure of **PhOx:2**

The crystal structure determination of **PhOx:2** shows that in the resulting 1:1 co-crystal, the best donor, the –OH moiety, forms a hydrogen bond to the N-oxide oxygen atom, the best acceptor, (O14...O21 2.6631(15) Å, O14-H14...O21 176(2)°), and the second-best donor, cyanooxime, engages in a hydrogen bond with the pyridyl nitrogen atom, the second-best acceptor, (O17...N24 2.7223(16) Å, O17-H17...N24 170(2)°), Fig 1.

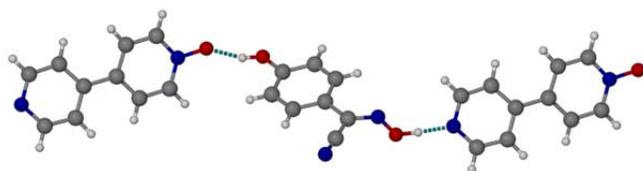


Fig 2 The primary hydrogen bonds in the crystal structure of **PhOx:3**

In the crystal structure of **PhOx:3**, also a 1:1 co-crystal, the –OH moiety forms a hydrogen bond to the N-oxide oxygen atom, (O14...O21 2.6052(19) Å, O14-H14...O21 163(2)°), and

cyanooxime, interacts with the pyridyl nitrogen atom, (O17...N31 2.665(2), O17-H17...N31 176(2)°), Fig 2

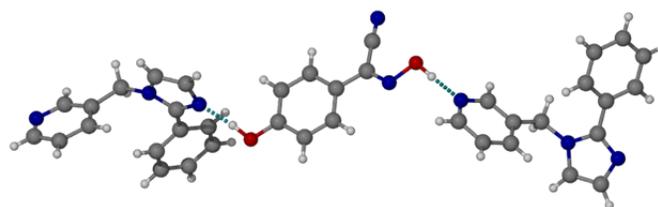


Fig 3 The primary hydrogen bonds in the crystal structure of **PhOx:4**

The 1:1 co-crystal of **PhOx:4** shows that the –OH moiety of **PhOx** interacts with the imidazole site, (O44...N13 2.6685(15) Å, O44-H44...N13 169(2)°), leaving D2, the cyanooxime, to form an O-H...N hydrogen bond with the pyridyl nitrogen atom (O47...N21 2.6536(14) Å, O47-H47...N21 176(2)°), Fig 3.

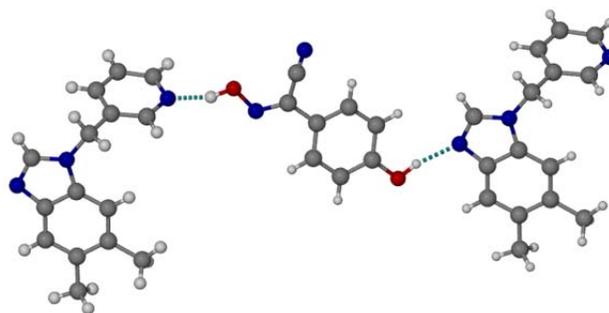


Fig 4 The primary hydrogen bonds in the crystal structure of **PhOx:7**

The structure determination of **PhOx:7** shows that in the resulting 1:1 co-crystal D1, the –OH site, binds to A1, the benzimidazole site, (O44...N13 2.7405(14) Å, O44-H44...N13 166(2)°), with D2 seeking out A2 (O47...N31 2.6474(14) Å, O47-H47...N31 161(2)°), Fig 4.

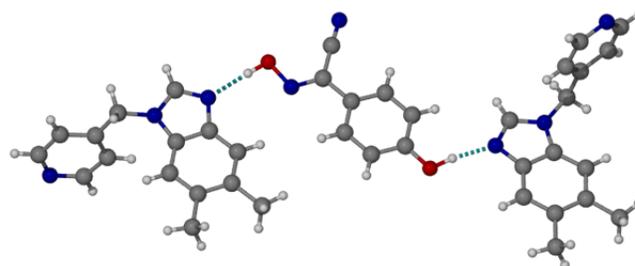


Fig 5 The primary hydrogen bonds in the crystal structure of **PhOx:6**

Finally, the crystal structure determination of **PhOx:6** produced the only outlier in this series. First, the stoichiometry is unexpected with a **PhOx** to **6** ratio of 1:2. Second, both donor sites form hydrogen bonds to the better acceptor, the imidazole moiety, O74...N43 2.6990(12) Å, O74-H74...N43 167(2)° and O77...N13 2.7627(12) Å, O77-H77...N13 178(2)° with D1 and D2, respectively, Fig 5.

The overall picture that emerges from these five crystal structures is that when a hydrogen-bond preference is expressed by the two donors on **PhOx** (which happens in four of five cases)

the primary molecular recognition events can be rationalized using a ranking based on MEP surface calculations. Furthermore, in a competition between an aromatic –OH moiety and a cyanooxime, the former is likely to be more competitive for the best available hydrogen-bond acceptor. The appearance of a 1:2 co-crystal were both D1 and D2 bind to the imidazole moiety on a neighbouring molecule, in preference to the pyridyl moiety, strengthens the argument that charge is the dominating factor driving the formation of hydrogen bonds in a multi-functional system. It could have been argued that the cyanooxime group has an inherent geometric preference for a pyridyl moiety as this type of hydrogen is formed in the first four crystal structures. However, as a cyanooxime...imidazole O-H...N hydrogen bond is present in the crystal structure of **PhOx:6**, there is nothing to suggest that a geometric bias is responsible for the consistent structural patterns that were found. Furthermore, acceptor **6**, which is the only compound that produces a 1:2 co-crystal, carries a charge on its A1 site of -301 kJ/mol which is greater than that found on the corresponding site in any of the other acceptors. This may explain why both donors in **PhOx** are keen to form hydrogen bonds to the same acceptor in **6**, resulting in a 1:2 stoichiometry. The calculated pK_a value of phenylcyanooxime, 7.80¹⁹, is lower than that of phenol, 9.86¹⁸, which underscores that acidities do not provide reliable indicators of relative hydrogen-bond strength when comparing different chemical moieties.

There are no relevant crystal structures in the CSD that can be used to augment the data in this study, and although we have to rely on a relatively small number of data points, it is clear that when a molecule that carries both an –OH group as well as a cyanooxime moiety is confronted with two hydrogen-bond acceptor sites of different strength, the outcome is likely to result in a hydrogen-bond between the –OH moiety and the best acceptor site, leaving the cyanooxime to bind to the second-best acceptor. It should also be pointed out that hydrogen bonds, even though they have considerable strength and directionality, are relatively weak and reversible, which means that synthon polymorphism²⁰ and synthon crossover²¹ is always a possibility in crystal engineering. However, even though exceptions are to be expected, it is still of considerable value to be able to identify patterns of behaviour as such trends provide excellent starting points for further studies that can validate or refine early observations.

Synthesis of (Z)-N,4-dihydroxybenzimidoyl cyanide, PhOx

10 g of NaOH was dissolved in 250 ml of methanol. 2.0 g (15.0 mmol) of 2-(4-hydroxyphenyl)acetonitrile was dissolved in 50 ml of methanol and added to the NaOH solution and allowed to stir for 1 hour. Methyl nitrite was bubbled through the solution over 30 minutes. The resulting solution was allowed to stir at room temperature for 48 hours. Methanol was removed under reduced pressure and the remaining solid was dissolved in 100 ml of water and cooled in an ice bath. The pH was then slowly lowered to pH=2 with 6 M HCl. The precipitate was filtered off and washed with ice water. 1.58 g of pure product was obtained. (Yield 65%) M.p.: 160-165 °C ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 6.89 (d, *J*=8.59 Hz, 2 H) 7.55 (d, *J*=8.98 Hz, 2 H) 10.13 (br. s., 1 H) 13.29 (br. s., 1 H)

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Notes and references

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