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Cyanoximes as effective and selective co-crystallizing agents

 Christer B. Aakeröy^a, Debra J. Salmon^a, Michelle M. Smith^a, and John Desper^a
^a Department of Chemistry, Kansas State University, Manhattan, KS, 66506, aakeroy@ksu.edu

Abstract

The ability of cyanoxime-based synthons to act as versatile synthetic tools for the construction of co-crystals is demonstrated through the preparation and structural characterization of seven co-crystals. Cyanoximes can bind effectively to both five-membered and six-membered N-heterocyclic hydrogen-bond acceptors, and they also display selectivity towards the best acceptor (as determined using semi-empirical AM1 calculations) in ditopic compounds.

Introduction

The hydrogen bond is the synthetic tool of choice in crystal engineering in the organic solid state.¹ Although halogen bonds, $\pi\cdots\pi$ interactions, and other non-covalent forces undoubtedly influence solid-state assembly, the hydrogen bond remains of prime importance due to its abundance, strength and directionality.² As crystal engineering moves from fundamental science to the deliberate design and synthesis of functional organic materials with specific pharmaceutical,³ electronic,⁴ or optical⁵ properties it is imperative that we continue to identify and map out the reliability and robustness of supramolecular synthons involving known functional groups.⁶ However, in order to expand the existing synthetic tool box, it is desirable to develop the supramolecular chemistry of new, or less well-known, chemical functionalities.

We previously reported⁷ that aromatic mono cyanoximes readily form co-crystals with symmetric ditopic imidazole-based hydrogen-bond acceptors, producing discrete, trimeric supermolecules. However, before cyanoximes can be fully embraced as a family of reliable and competitive hydrogen-bond donors, considerably more structural data is required. In this study, we set out to examine (a) the versatility of cyanoximes as hydrogen-bond donors and (b) whether a cyanoxime moiety will preferentially bind to the best hydrogen-bond acceptor when faced with an asymmetric ditopic N-heterocyclic molecule. Four different cyanoximes were employed, Scheme 1, all of which can be prepared in good yields by allowing the relevant phenylacetone nitrile to react with methylnitrite.^{7,8} The ready accessibility of suitable starting materials, and the relative ease of synthesis of cyanoximes, add to the potential usefulness of this functional group as a supramolecular synthetic tool.

These four hydrogen-bond donors, **A–D**, were subsequently allowed to react with a series of N-heterocyclic hydrogen-bond acceptors, Scheme 2.

The group of hydrogen-bond acceptors, **1–7**, contains both five-membered and six-membered, symmetric and asymmetric, monotopic and ditopic compounds in order to determine if there are any particular acceptors that are unsuitable as partners for the cyanoximes.

Correspondence to: Christer B. Aakeröy.

Electronic Supplementary Information (ESI) available: CIF files and experimental crystallographic data.

One asymmetric ditopic acceptor, **7**, was employed in order to test the best-donor/best-acceptor guideline for hydrogen-bonding in a competitive situation.^{9,10} The relative ranking of the two acceptor sites, the pyridine moiety and the benzimidazole moiety, can be accomplished using semi-empirical AM1 calculations.^{11,12,13}

Seven of the co-crystallization reactions between **A–D** and **1–7** produced crystals that were suitable for single-crystal X-ray diffraction.

Experimental

5 was purchased from Aldrich and used without further purification. The remaining supramolecular reagents **1**,¹⁴ **2–4**,¹⁰ **6**,¹⁵ **7**¹¹ were synthesized according to previously-reported methods (or slight modifications thereof).

Synthesis of co-crystals

Synthesis of 4-bromophenylcyanoxime 3-bromo-5-methoxypyridine (1:1) A1

4-Bromophenylcyanoxime (20 mg, 0.089 mmol) was dissolved in 1:1 ethanol/ethyl acetate in a 50 mL beaker. A 1:1 ethyl acetate/ethanol solution of **1** (15 mg, 0.080 mmol) was added. Colourless prisms suitable for X-ray crystallography were obtained after four days; mp: 110–115 °C.

Synthesis of 4-bromophenylcyanoxime 1-[(4-bromophenyl)methyl]-2-methylbenzimidazole (1:1) A2

4-Bromophenylcyanoxime (10 mg, 0.044 mmol) was dissolved in ethyl acetate in a 50 mL beaker. A 1:1 ethyl acetate/ethanol solution of **2** (13 mg, 0.043 mmol) was added. Colourless prisms suitable for X-ray crystallography were obtained after one day; mp: 142–145 °C.

Synthesis of 4-bromophenylcyanoxime 1-[(4-bromophenyl)methyl]-benzimidazole (1:1) A3

4-Bromophenylcyanoxime (10 mg, 0.044 mmol) was dissolved in ethyl acetate in a 50 mL beaker. A 1:1 ethyl acetate/ethanol solution of **3** (13 mg, 0.045 mmol) was added. Colourless prisms suitable for X-ray crystallography were obtained after five days; mp: 92–96 °C.

Synthesis of 4-bromophenylcyanoxime 1-[(3-cyanophenyl)methyl]-5,6-dimethylbenzimidazole (1:1) A4

4-Bromophenylcyanoxime (10 mg, 0.044 mmol) was dissolved in ethyl acetate in a 50 mL beaker. A 1:1 ethyl acetate/ethanol solution of **4** (12 mg, 0.046 mmol) was added. Colourless prisms suitable for X-ray crystallography were obtained after five days; mp: 136–140 °C.

Synthesis of 2-fluorophenylcyanoxime 1,2-bis(4-pyridyl)ethylene (2:1) B5

2-Fluorophenylcyanoxime (13 mg, 0.082 mmol) and **5** (13 mg, 0.082 mmol) were dissolved separately in acetonitrile. Slow evaporation over 5 days yielded very thin needles not suitable for X-ray diffraction. Consequently the needles were redissolved in methanol, which produced suitable colorless plates; mp: 167–170 °C.

Synthesis of 3-chlorophenylcyanoxime 1,4-bis[(benzimidazol-1-yl)methyl]benzene (2:1) C6

3-Chlorophenylcyanoxime (8.0 mg, 0.045 mmol) was dissolved in 1:1 ethanol/ethyl acetate in a 50 mL beaker. A 1:1 ethyl acetate/ethanol solution of **6** (15 mg, 0.045 mmol) was added. Fibrous colorless crystals were obtained after 2 days. These were subsequently redissolved in methanol and colorless plates were obtained via slow evaporation after ~ 2 weeks; mp: 175–179 °C.

Synthesis of 4-fluorophenylcyanoxime 1-[(4-pyridyl)methyl]-5,6-dimethylbenzimidazole (1:1) D7

7 (20 mg, 0.084 mmol) was dissolved in ethanol with slight heat. A solution of 4-fluorophenylcyanoxime (15 mg, 0.084 mmol) in ethanol was added and the solution was allowed to evaporate at room temperature. Colourless plates suitable for X-ray crystallography were obtained within 2 weeks; mp: 114–116 °C.

Semi-empirical calculations

In order to rank the hydrogen-bond acceptor sites of **7**, the molecular structure was constructed using Spartan '04 (Wavefunction, Inc. Irvine, CA), and the geometry was optimized using AM1. The results show that the benzimidazole moiety is likely to be a better hydrogen-bond acceptor than the pyridyl site. The former gives an energy of –299 kJ/mol and the latter –274 kJ/mol when the electrostatic potential surface (0.002 e/au isosurface) around each nitrogen atom is allowed to interact with a positive point charge in vacuum as a probe.

Results

The driving force for the synthesis of the co-crystal **A1** is the expected hydrogen bond between the oxime moiety and the pyridyl hydrogen-bond acceptor site, O(17)···N(21); 2.667(6) Å, Figure 1. There is also a relatively short Br(py)···O(oxime) contact of 2.93 Å. The oxime moiety is almost perpendicular to the pyridyl ring, which rules out the presence of any ancillary C–H···N interactions involving the oxime nitrogen atom as an acceptor. A secondary interaction is frequently observed in the synthon comprising a carboxylic acid and a pyridyl moiety.¹⁶

In the crystal structure of **A2**, the main non-covalent interaction is the hydrogen bond between R-OH (oxime) and the benzimidazole acceptor; O···N 2.627(2) Å, Figure 2.

This time, the oxime nitrogen atom is in the plane of the benzimidazole ring but the distance to the nearest potential C–H donor (H15) is too large to be considered as a structure-directing interaction, C···N; 3.69 Å. Neither of the two bromine atoms is engaged in a well-defined non-covalent interaction, and the same is true for the nitrile nitrogen atom. Despite very close similarities in chemical composition between **A2** and **A3**, they belong to different crystal systems and space groups, monoclinic $P2_1/c$ and triclinic $P-1$, respectively. Nevertheless, the driving force for the co-crystal formation in **A3** is still the O–H···N, oxime/benzimidazole, hydrogen bond, Figure 3.

In both **A2** and **A3**, the primary N···O hydrogen bond is short, 2.63 Å, and close to linear. Neither bromine atoms, nor the nitrile nitrogen atom, are engaged in any noteworthy intermolecular interactions. The torsion angle between oxime moiety and benzimidazole ring is approximately 25°.

The crystal structure of the 1:1 co-crystal **A4**¹⁷ shows that the primary intermolecular interaction is the oxime O–H···N(benzimidazole) hydrogen bond, O(47)···N(13); 2.656(7) Å, Figure 4.

There are no noteworthy short intermolecular distances to either of the two CN moieties or to the bromide atom. The oxime moiety is co-planar with the adjacent benzimidazole ring.

The crystal structure determination of **B5**, shows that the outcome is a 2:1 co-crystal with one oxime interacting with each of the two hydrogen-bond sites in the symmetric ditopic acceptor, 1,2-*bis*(4-pyridyl)ethylene, Figure 5. The heterocycle is located on an inversion centre with the symmetry related oxime moieties rotated approx. 30° out of the plane with respect to the

adjacent pyridyl ring. Again, the O-H...N hydrogen bond is short, (O(17)...N(21): 2.628(3) Å) and close to linear.

Neither the nitrile nitrogen atom, nor the oxime nitrogen atom participate in any significant intermolecular interactions.

The co-crystal **C6**, also comprises an aromatic cyanoxime and a symmetric ditopic hydrogen-bond acceptor, but this time each pyridyl moiety is replaced with a five-membered analogue, a benzimidazole site. Again, the crystal structure determination shows, Figure 6, that the outcome of the reaction is a co-crystal with a 2:1 stoichiometry, as was the case in **B5**.

The heterocycle is located on an inversion centre, and the trimeric supermolecule is constructed via two symmetry related O-H...N hydrogen bonds (O(37)...N(13): 2.615(2)) The oxime moiety is co-planar with the benzimidazole ring, and no additional short intermolecular contacts are observed. Finally, when one equivalent of a **D** is allowed to react with one equivalent of an asymmetric ditopic acceptor, **7**, the result is a 1:1 co-crystal, **D7**. The crystal structure determination allows us to establish binding preference for the single donor moiety; the oxime hydrogen-bond donor interacts with the benzimidazole nitrogen atom, (O(47)-H(47)...N(13) 2.6047(10) Å), Figure 7.

The cyanoxime moiety, the only strong hydrogen-bond donor in this system, selects the better of the two hydrogen-bond acceptors (as determined by a calculation of the electrostatic potential around each atom), whereas the remaining pyridyl moiety, a perfectly good hydrogen-bond acceptor, is left without a partner.

Discussion

This structural study of co-crystals of N-heterocycles and cyanoximes has furnished information that allows us to begin to draw some conclusions about the structural behaviour of the latter functional group. There are four phenylcyanoximes in the CSD,¹⁸ and all of them contain O-H...N (nitrile) hydrogen-bonded catemers. This is in contrast to the structural preference of aromatic aldoxime and acetyloximes which show a preference for dimers that utilize the O-H moiety as a donor, and the oxime nitrogen atom as the hydrogen-bond acceptor. 25 of 32 structures show this arrangement and seven of 32 structures contain OH...N(oxime) catemers.¹⁹ This change in pattern preference may come about because the nitrile moiety is a better hydrogen-bond acceptor, -224 kJ/mol (N-nitrile) vs. -125 kJ/mol (N-oxime) as indicated by AM1 calculated electrostatic potential, Scheme 3). This makes the cyanoxime hydrogen-bond donor more inclined to interact with the nitrile moiety, than with the oxime nitrogen atom. This behaviour is in accordance with the best-donor/best-acceptor guideline.

There is only one example of a non-solvated pyridylcyanoxime,²⁰ and in this case, the O-H...N hydrogen bond involves the pyridyl nitrogen atom as the acceptor site. In addition to the seven structures presented herein, there are a further eight published examples of co-crystals that combine a phenylcyanoxime hydrogen-bond donor and a N-heterocyclic compound as the hydrogen-bond acceptor (ten benzimidazoles, three imidazoles, and two pyridines). The cyanoxime hydrogen-bond donor seems equally adept at interacting with a N-heterocyclic compound regardless of the geometry (five-membered vs. six-membered) of the acceptor site. Again, this is not necessarily surprising since the oxime moiety is a single-point donor (it does not rely on an ancillary acceptor atom), which makes it less sensitive to the precise geometry of the acceptor site, as long as the lone-pair on the nitrogen atom is accessible.

Based on existing structural information from the CSD,¹⁸ the carboxylic acid moiety is more likely than an oxime site to be co-planar with an aromatic N-heterocycle (when they form an O-H...N hydrogen bond). This indicates that the C=O moiety of the carboxylic acid is a better

hydrogen-bond acceptor (for a C–H donor) than is the nitrogen atom of the oxime moiety. An alternative explanation could be that oximes are more likely to be sterically hindered from approaching an aromatic heterocycle in a co-planar manner. However, a space-filling representation of the co-planar supermolecule in **C6** suggests that there is no obvious steric factor that would make it less likely for an oxime to be co-planar with a heterocycle, than it would be for an aromatic carboxylic acid, Fig. 8

Although there are very few structures available that probe the potential hydrogen-bond selectivity of cyanoximes, both **D7** and the previously reported co-crystal of **D** and the 3-pyridyl isomer of **7**, form 1:1 co-crystals with an asymmetric ditopic ligand where the oxime binds to the better of the two hydrogen-bond acceptors, the benzimidazole moiety. More information is obviously required before we can confidently discuss the possible limitations of the best-donor/best-acceptor for predicting synthon-preferences of cyanoximes but, at this, stage, the simple charge-based approach seems to offer a useful guideline.

In a comparative structural and spectroscopic study of co-crystals between phenyloximes R–C=N–OH (where R = H, Me, or CN) and N-heterocyclic hydrogen-bond acceptors, cyanoximes were shown to be more effective co-crystallizing agents,⁷ and this could be directly related to the superior hydrogen-bond donor ability of the oxime –OH moiety in the latter family.

In summary, cyanoximes have considerable potential as effective co-crystallizing agents. As single-point hydrogen-bond donors they should be, based on the electrostatic potential surfaces around their acidic protons, comparable to, (if not better than) carboxylic acids, they are synthetically readily available, and they also tend to be soluble in a wide range of solvents, which facilitates solution-based co-crystal synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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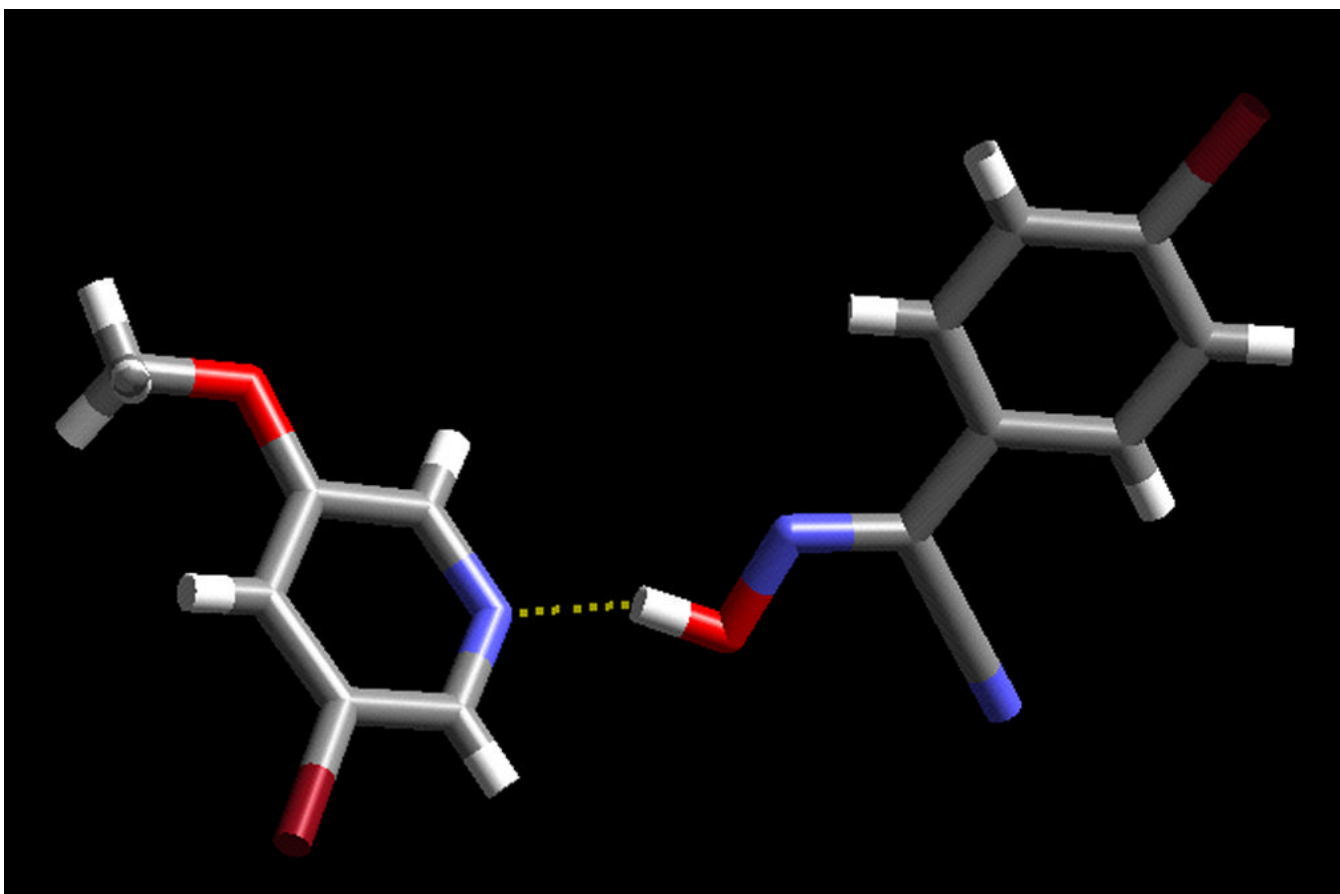


Figure 1.
Dimer connected through an O-H...N hydrogen bond in the crystal structure of **A1**.

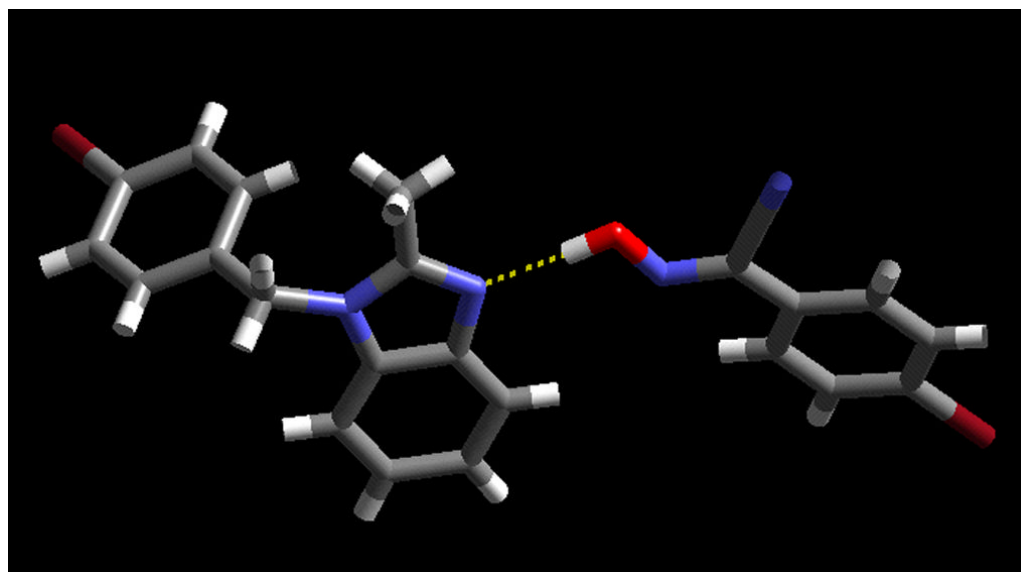


Figure 2.
The primary O-H···N hydrogen bond between the oxime and the benzimidazole moieties in the crystal structure of **A2**.

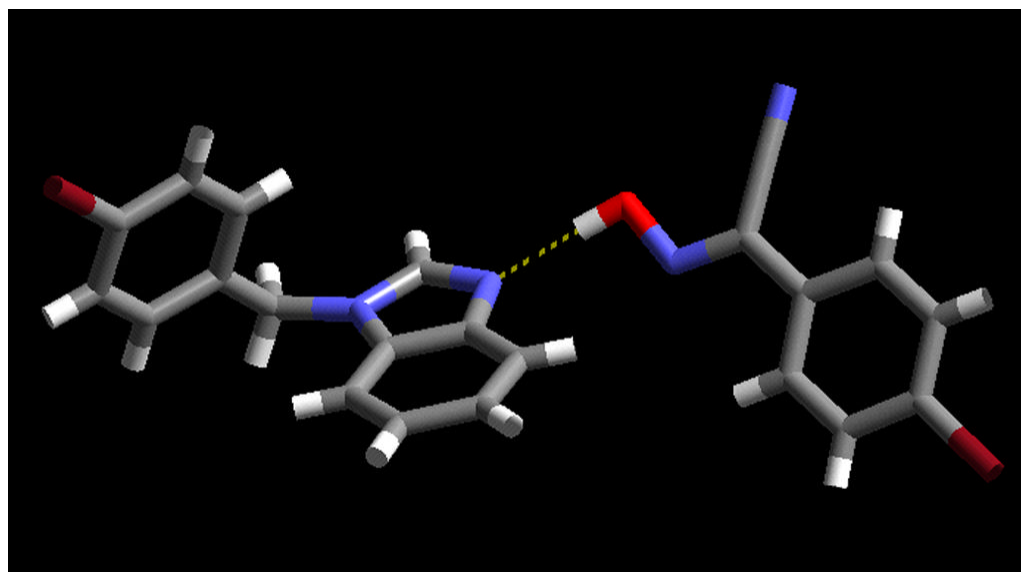


Figure 3.
The primary O-H...N hydrogen bond between the oxime and the benzimidazole moiety in the crystal structure of **A3**.

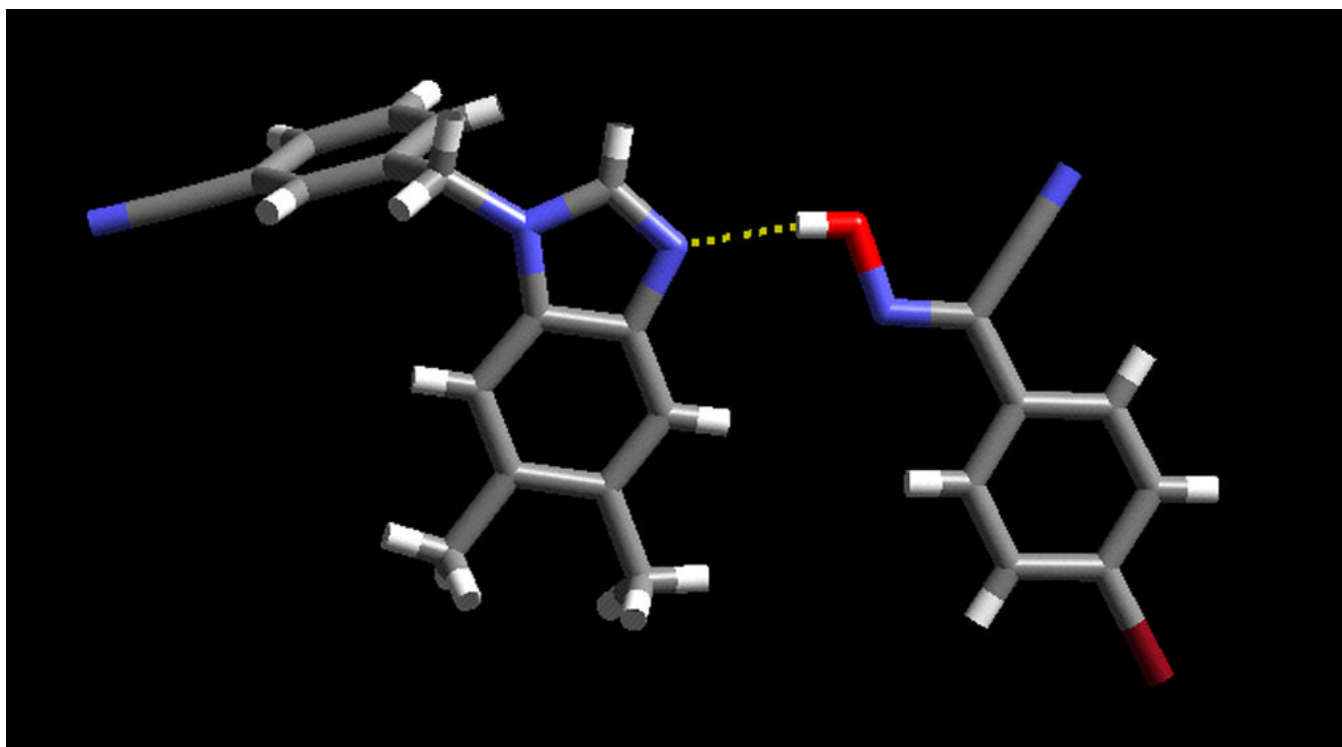


Figure 4.
The primary O-H...N hydrogen bond between the oxime and the benzimidazole moiety in the crystal structure of **A4**.

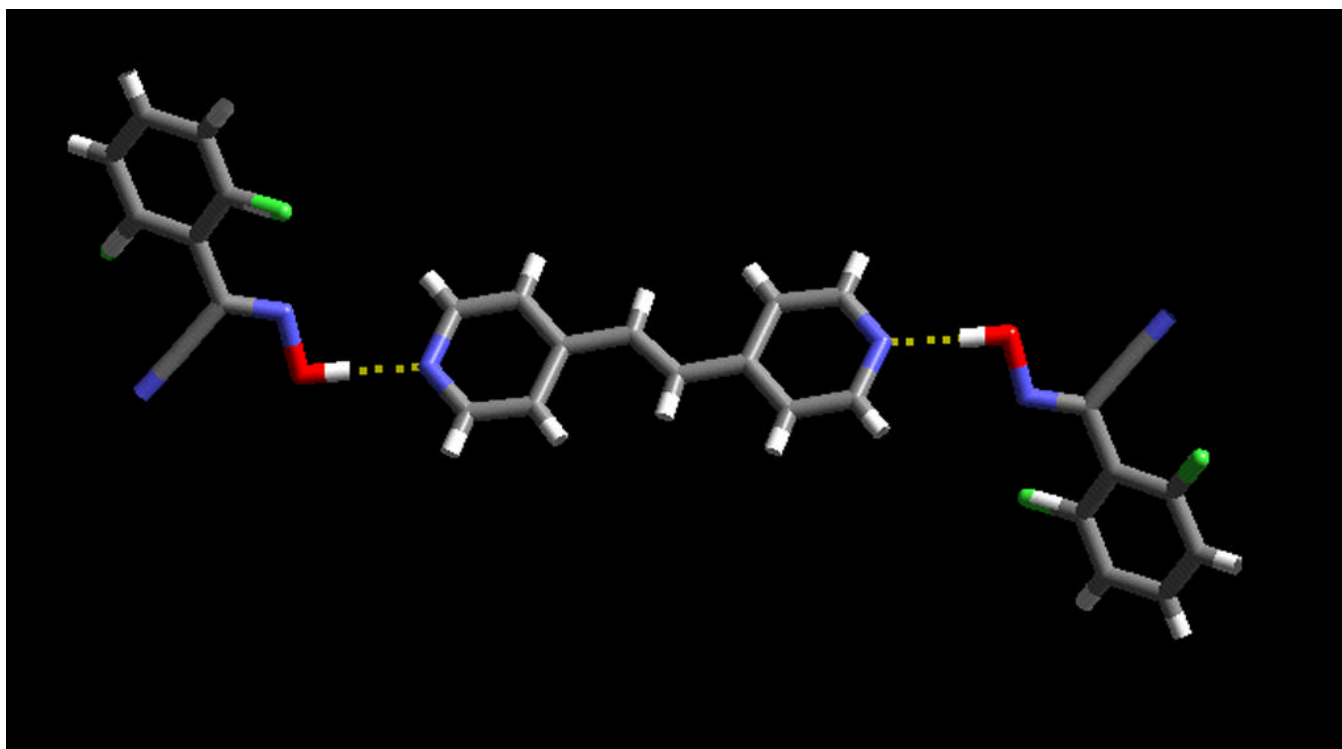


Figure 5. Trimeric supermolecule connected through O-H...N hydrogen bonds in the crystal structure of **B5**.

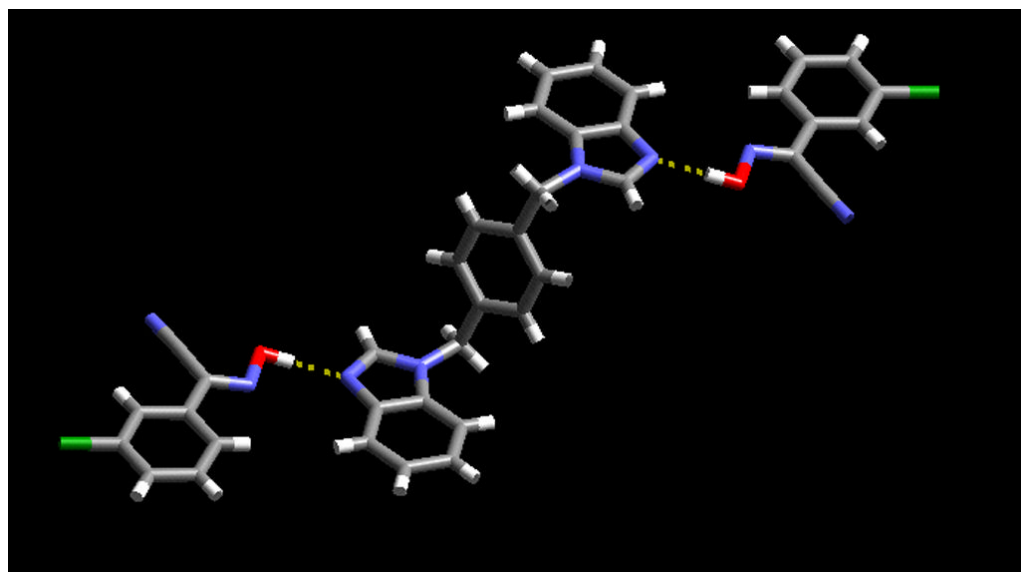


Figure 6.
Trimeric supermolecule in the crystal structure of **C6**.

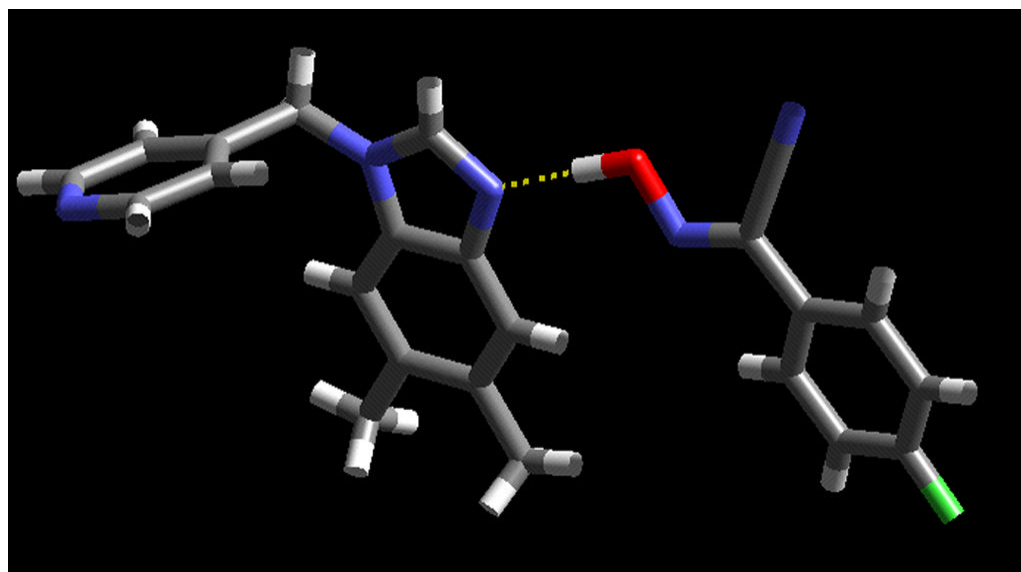


Figure 7.
Dimer in the crystal structure of **D7**.

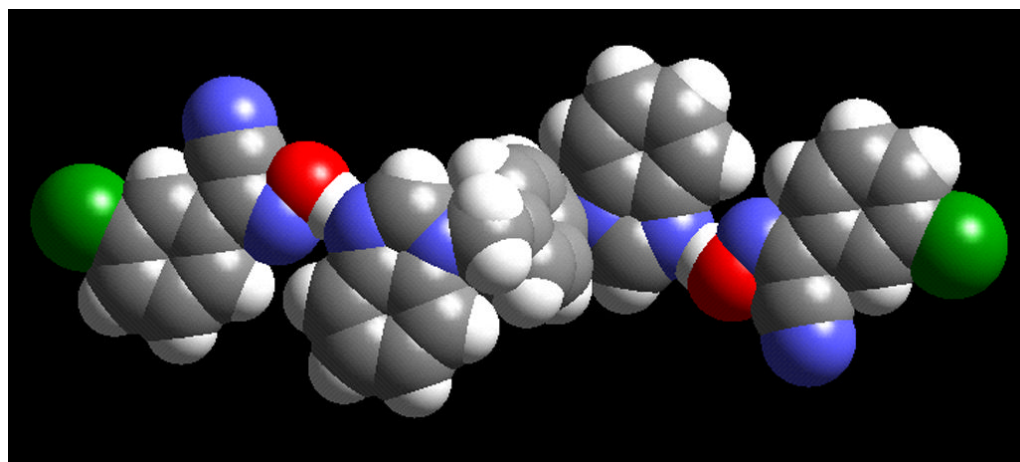
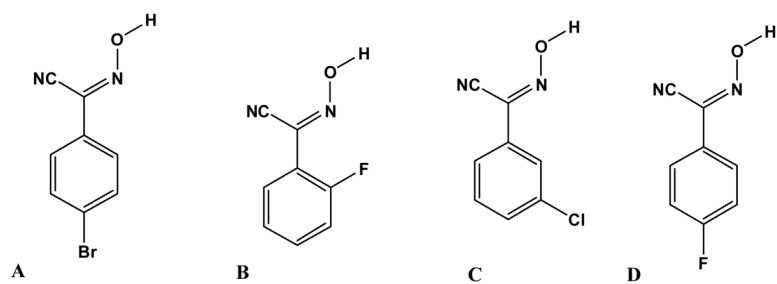
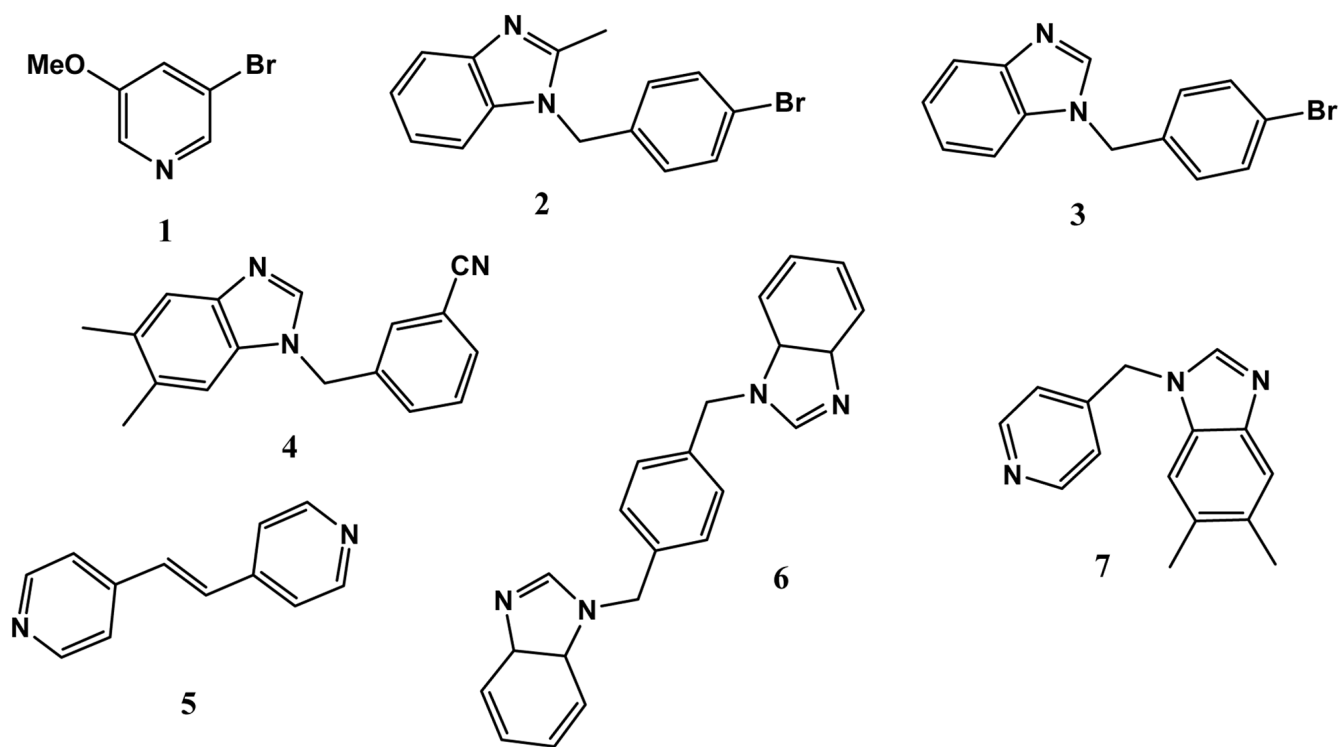
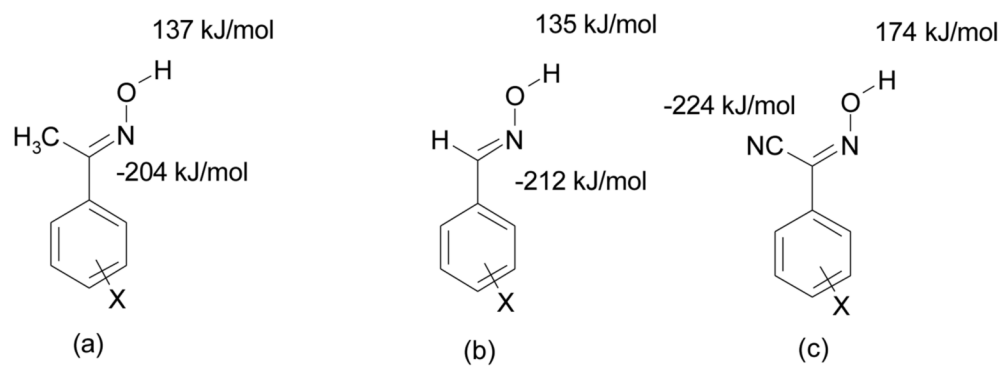


Figure 8. The oximes on either side of the bis-benzimidazole molecule in the crystal structure of **C6** are able to approach in a co-planar manner.

**Scheme 1.**



Scheme 2.

**Scheme 3.**

Molecular electrostatic potential data (maxima and minima) for three generic oximes (a) acetyloximes, (b) aldoximes, and (c) cyanoximes.