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Benzotriazole Complexes with Amines and Phenol: Cooperativity Mediated by Induction Effects in the Crystal State

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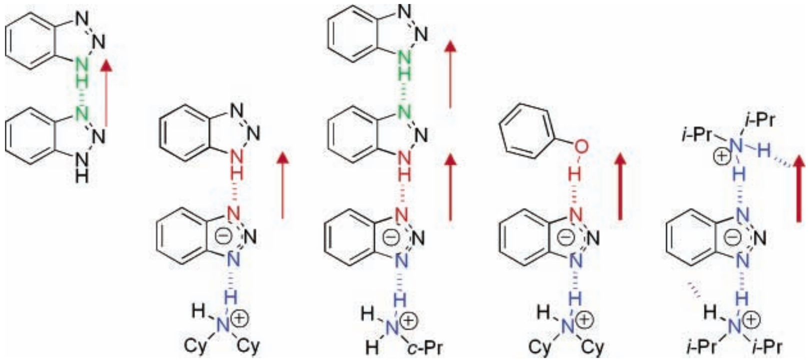
ABSTRACT



Benzotriazole forms complexes of different stoichiometries with amines and phenols. Four of them have been characterized by single-crystal X-ray diffraction. The trends of donor–acceptor hydrogen-bond distances between corresponding molecular entities in the different complexes are related to induction-mediated cooperativity effects.

Despite the widespread interest in benzotriazole (**BTZ**) and its value in organic synthesis, as shown especially by Katritzky's group, no formation of stable crystalline complexes, besides the standard salt formation, has ever been reported in its reactivity with amines and phenols.[1] Herewith, we report on the behavior of **BTZ** with amines and/or phenols and on the determination of the structures of four of them by X-ray crystallography. The study highlighted cooperative effects which have theoretical implications in the biological and medicinal realm, where aromatic nitrogen heterocycles are widely diffused.[2] Cooperative effects are observed in organized structures when the overall energy of a set of weak interactions does not match the sum of energies of the pairwise interactions as independently considered.[3]

Two types of cooperative effects are described, mediated by either conformational or electronic-distribution changes in the implicated structure(s).[4] Recent theoretical and experimental studies support the relevance of this phenomenon in proteins and more generally when amide groups are involved in H-bonding.[5,6] Herewith, it is shown that the **BTZ** amine complexes are a simple model system that gives experimental evidence about the role of long-range polarization effects in intermolecular interactions.[7]

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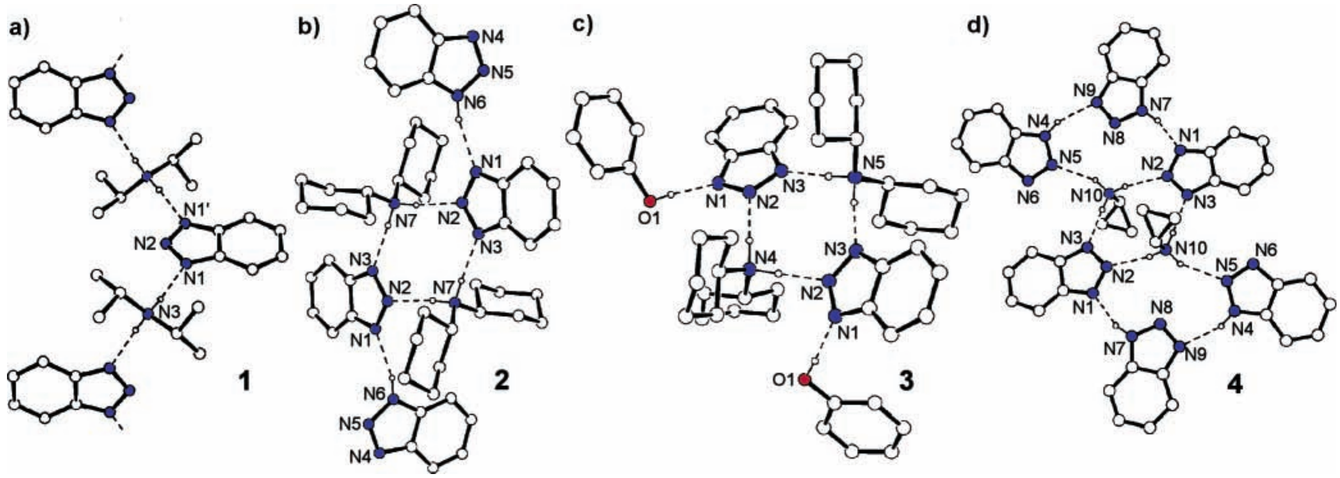

Figure 1. Crystal structures of: (a) **DIP**$^{+}$**·BTZ**$^{-}$ (**1**); (b) **DCH**$^{+}$**·BTZ**$^{-}$**·BTZ** (**2**); (c) **DCH**$^{+}$**·BTZ**$^{-}$**·PhOH** (**3**); (d) **CYP**$^{+}$**·BTZ**$^{-}$**·BTZ**$_2$ (**4**).

While evaluating the capability of **BTZ** to act as a catalyst in amidation reactions, it was observed that mixtures of **BTZ**, dicyclohexylamine (**DCH**), and phenol (**PhOH**) in isopropyl acetate led to the formation of a precipitate that emerged to be the **DCH·BTZ·PhOH** complex.[8] To gain more information on the influence of **BTZ**, a series of amines were added to an IPAC solution of **BTZ**.[9] For some of the amines, colorless precipitates were observed and ^{1}H NMR analysis of the crystals revealed a variety of **BTZ·amine** salts displaying different stoichiometries, though the 1:1 ratio was prevailing in the majority of cases.

Crystals suitable for X-ray diffraction were grown for diisopropylamine, **DIP·BTZ** (**1**), dicyclohexylamine, **DCH·BTZ**$_2$ (**2**), **DCH·BTZ·PhOH** (**3**), and the cyclopropylamine, **CYP·BTZ**$_3$ (**4**), quaternary complex. The structures of the complexes, as determined by single-crystal X-ray diffraction, are illustrated in Figure 1. Their H-bond parameters are in Table 1.

Structure analysis revealed a common feature in all the complexes: the amines are protonated by **BTZ** to produce ammonium benzotriazolates (**AMM**$^{+}$**·BTZ**$^{-}$), and the side nitrogen of **BTZ**$^{-}$ opposite to **AMM**$^{+}$ acts as a second hydrogen-bond-acceptor site, giving rise to the variety of complexes shown in Figure 1.[10] Furthermore, in all the complexes, except **1**, the central nitrogen atom of **BTZ**$^{-}$ (N2) participates in the formation of the final complex through the formation of ion-pair dimers across a ring of hydrogen bonds. However, the distances involving this central nitrogen atom are generally longer than those involving the side nitrogen atoms, in agreement with the electron density distribution of **BTZ**$^{-}$ which brings more negative charge on its side nitrogen atoms.

Figure 2 reports the variation of the hydrogen-bond distances between the **AMM**$^{+}$ ion and the side nitrogen of **BTZ**$^{-}$ (blue line) as well as between the **BTZ**$^{-}$ and the second **BTZ** molecule (as in **2** and **4**) or the extra hydrogen-bond donor (as in **3**) (red line). The π system of the central **BTZ**$^{-}$ brings transmission through the complex and allows for the interactions to be mutually influenced. For example, the comparison between **2** and **3** shows that **PhOH** in **3** leads to a stronger hydrogen bond than **BTZ** in **2**; i.e., a shorter **BTZ**$^{-}$**·PhOH** decreases the **BTZ**$^{-}$ electronic density and as a consequence lengthens the **DCH**$^{+}$**·BTZ**$^{-}$ ion-pair distance. Conversely, the weaker **BTZ**$^{-}$**·BTZ** interaction of **2** allows for a shorter **DCH**$^{+}$**·BTZ**$^{-}$ ion-pair distance and consequently a stronger bond. In other words, the variation of the negative charge in the **BTZ**$^{-}$ anion due to the relocation

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(8) To a solution of **PhOH** (10 g, 0.106 mol) and **DCH** (19.3 g, 0.106 mol) in isopropyl acetate (100 mL) was added **BTZ** (12.6 g, 0.106 mol). To the obtained white slurry was added isopropyl acetate (100 mL), and the solution was heated to reflux. After complete solubilization of the precipitate, the mixture was slowly cooled to room temperature. At ca. 60 °C, the formation of colorless crystals began. The precipitate was filtered obtaining the **DCH·BTZ·PhOH** complex (36.2 g, 86% yield).

(9) A 1:1 **BTZ·**amine precipitate was observed for diisopropylamine, pyrrolidine, morpholine, (−)-*S*-phenylethylamine, cyclohexylamine, and benzylamine. A 2:1 **BTZ·**amine precipitate was found for dicyclohexylamine, monoethanolamine, isopropylamine, and diisobutylamine. A 3:1 **BTZ·**amine precipitate was detected for cyclopropylamine. No precipitate was observed for triethylamine, ethyldiisopropylamine, diethylamine, imidazole, diphenylamine, benzylethylamine, and *R*-(−)-2-amino-1-ethanol.

(10) The anionic character of **BTZ**$^{-}$ is supported by the equivalence of its two N−N bond distances.

Table 1. H-Bond Parameters for the Complexes[a]

complex	type of H-bond	donor (D−H)	acceptor (A)	distance (Å) D···A
DIP^{+}·BTZ^{-} (**1**)	**DIP^{+}···BTZ^{-}**	N3−H	N1	2.8839(17)
DCH^{+}·BTZ^{-}·BTZ (**2**)	**BTZ···BTZ^{-}**	N6−H	N1	2.8023(18)
	DCH^{+}···BTZ^{-}	N7−HA	N3	2.8314(16)
	DCH^{+}···BTZ^{-}	N7−HB	N2	2.8617(18)
DCH^{+}·BTZ^{-}·PhOH (**3**)	**PhOH···BTZ^{-}**	O1−H	N1	2.710(3)
	DCH^{+}···BTZ^{-}	N5−H	N3	2.861(2)
	DCH^{+}···BTZ^{-}	N4−H	N2	2.856(2)
CYP^{+}·BTZ^{-}·BTZ$_2$ (**4**)	**BTZ···BTZ^{-}**	N7−H	N1	2.717(2)
	CYP^{+}···BTZ^{-}	N10−HC	N3	2.841(3)
	CYP^{+}···BTZ^{-}	N10−HB	N2	2.942(3)
	BTZ···BTZ	N4−H4	N9	2.789(3)
	CYP^{+}···BTZ	N10−HA	N5	3.038(3)

[a] D−H···A angles are in the range 150−177°. Full details are in the Supporting Information.

given by the extra hydrogen donor influences the strength of the ion-pair bond.

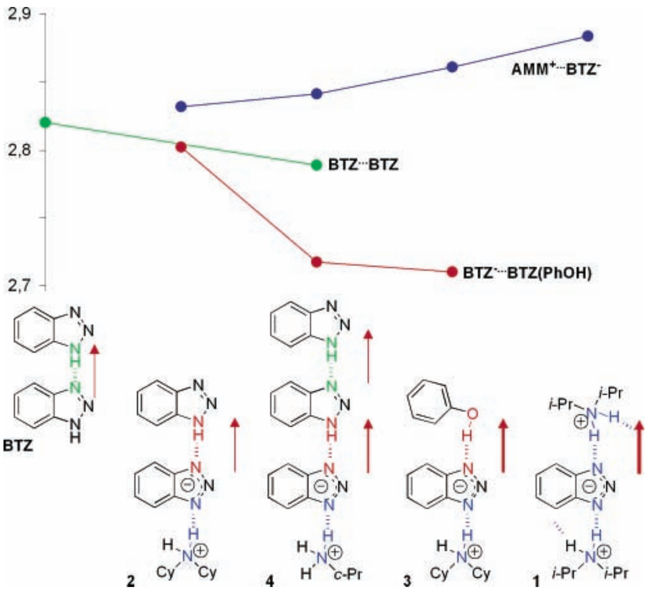

Figure 2. Donor−acceptor H-bond distances in crystalline **BTZ**[9] and in complexes **1**−**4**. Red arrows indicate the displacement of negative charges due to the formation of H-bonds.

In line with this rationale, the negative charge of **BTZ^{-}** is additionally reduced in the case of **1** where the **BTZ^{-}** is hydrogen bonded on both sides with a positively charged species thus lengthening the **DIP^{+}·BTZ^{-}** bond.

Complex **4** displays four nonequivalent molecular moieties, thus allowing the analysis of a system in which two **BTZ** molecules are hydrogen bonded to the ion pair. The **BTZ·BTZ^{-}** distance is shorter in comparison with the corresponding distance in complex **2**. This fact is due to the capability of the terminal **BTZ** to polarize the central **BTZ**. This results also in a diminished electron density in **BTZ^{-}** and a longer distance in the ion pair compared to **2**. Thus, the additional **BTZ** molecule affects the whole set of interactions. The polarization also works reversely. The shorter **BTZ·BTZ** distance in **4**, as compared to that occurring in the crystal structure of pure **BTZ**,[11] further supports the polarization effects (green line). Figure 2 shows the effect of the different molecules hydrogen bonded to **BTZ^{-}**. Moving through the blue line, a lengthening of the **AMM^{+}·BTZ^{-}** bond can be observed, induced by the different lateral moieties, whereas a shortening of the **BTZ^{-}···BTZ** distance (red line) is observed on going from **2** to **4** due to the presence of an extra molecule of **BTZ**. Such an effect could not be presumed on considering the pairwise interactions independently.

To the best of our knowledge, ammonium benzotriazolate complexes have never been reported so far. These salts constitute a case study of cooperativity as the interactions at both sides of **BTZ^{-}** are mutually influenced. In addition to the ion pairs, neutral molecules may also take part in these complexes through hydrogen bonds (as in **2**, **3**, and **4**) and modulate the interactions. Our findings might be related to the long-range effects observed in enzymes involving histidine residues in the catalytic site, where changes in the electrostatic distribution at more than 10 Å distance influence the catalytic activity.[12]

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Supporting Information Available: Crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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