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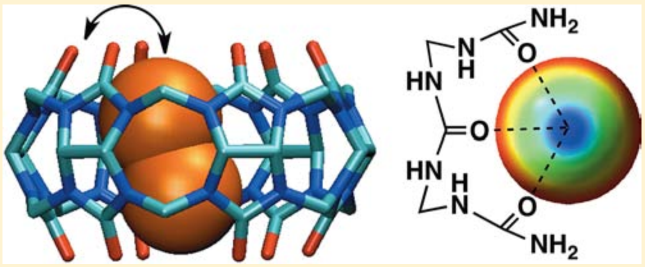
Halogen Bonding inside a Molecular Container

Hamdy S. El-Sheshtawy, Bassem S. Bassil, Khaleel I. Assaf, Ulrich Kortz, and Werner M. Nau*

School of Engineering and Science, Jacobs University Bremen, Campus Ring 1, D 28759 Bremen, Germany

Supporting Information



ABSTRACT: The synthetic macrocycle cucurbit[6]uril forms host–guest inclusion complexes with molecular dibromine and diiodine. As evidenced by their crystal structures, the encapsulated dihalogens adapt a tilted axial geometry and are held in place by two different types of halogen-bonding interactions, one with a water molecule (bond distances 2.83 Å for O···Br and 3.10 Å for O···I) and the other one with the ureido carbonyl groups of the molecular container itself (bond distances 3.33 Å for O···Br and 3.49 Å for O···I). While the former is of the conventional type, involving the lone electron pair of an oxygen donor, the latter is perpendicular, involving the π-system of the carbonyl oxygen (N−C═O···X dihedrals ca. 90°). Such perpendicular interactions resemble those observed in protein complexes of halogenated ligands. A statistical analysis of small-molecule crystal structural data, as well as quantum-chemical calculations with urea as a model (MP2/aug-cc-pVDZ-PP), demonstrates that halogen bonding with the π-system of the carbonyl oxygen can become competitive with the commonly favored lone-pair interaction whenever the carbonyl group carries electron-donating substitutents, specifically for ureas, amides, and esters, and particularly when the lone pairs are engaged in orthogonal hydrogen bonding (*h*X bonds). The calculations further demonstrate that the perpendicular interactions remain significantly attractive also for nonlinear distortions of the O···X−X angle to ca. 140°, the angle observed in the two reported crystal structures. The structural and theoretical data jointly support the assignment of the observed dihalogen–carbonyl contacts as genuine halogen bonds.

INTRODUCTION

Following the detailed description by Guthrie of a complex between molecular diiodine and ammonia in 1863,[1] intermolecular interactions of dihalogens with electron donors have remained a constant source of inspiration for chemists, culminating in the Nobel lecture of Hassel.[2] The poles of heavy dihalogen molecules are electron-deficient (in analogy to iodine and bromine atoms in organic molecules), a peculiarity which gives rise to the so-called halogen bonding to electron donors containing either π-systems or lone pairs on heteroatoms such as oxygen and nitrogen.[3−10] Numerous organic, supramolecular systems have been assembled and described ever since, with the aim to exploit this type of specific intermolecular interaction for applications ranging from crystal engineering to functional materials, anion receptors, and drug design.[11−18]

Recently, there has been a paradigm shift regarding the importance of halogen bonds in biological systems, where on the one hand mainly carbonyl groups serve as donor sites and on the other hand the π-orbital of the carbonyl oxygen is involved in halogen bonding.[19−22] In fact, this has been shown to be exclusively the case for halogen bonds of amide carbonyl groups within proteins.[19] Inspection of the lead structures obtained by screening of a halogen-enriched fragment library in the context of a recent drug discovery study[18] confirms this dihedral preference. This contrasts with the general rule, strictly obeyed in the gas phase,[7,8] that donor atoms carrying both n- and π-orbitals (sp^2-hybridized oxygens and nitrogens) will undergo halogen bonding through the n-orbital, i.e., the lone electron pair. Moreover, while halogen bonds have been shown to display numerous similarities to hydrogen bonds,[6,7] both interactions have recently been demonstrated, again for biomolecules, to be orthogonal in nature, with the n- and π-orbitals of the carbonyl oxygen being involved in hydrogen and halogen bonding, respectively, and frequently even simultaneously.[10,20,21,24] Such special types of "perpendicular"[3] halogen bonds have been referred to as *h*X-bonds in the special case of interactions involving hydrogen-bonded carbonyl oxygens.[24]

We have now succeeded in isolating host–guest assemblies with diiodine and dibromine being positioned in the cavity of a synthetic macrocycle, the barrel-shaped cucurbituril.[25−31] In these complexes, the dihalogen is held in place by a "conventional" halogen bond with a water molecule and a perpendicular one with the π-orbital of the carbonyl oxygen at the portal of the host. The latter interactions fall in the range of bond distances and angles accepted for halogen bonds in biological molecules.[19−21,24] A joint experimental and theoretical analysis reveals that the O···X interactions are attractive, which is a prerequisite, according to the recent definition, to classify them as halogen bonds.[32]

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RESULTS AND DISCUSSION

In the course of direct and competitive host−guest titrations, we observed that cucurbit[6]uril (CB6, Figure 1), the parent cucurbituril,[25−31] forms a surprisingly stable complex with molecular diiodine in aqueous solution; its binding constant [$K = (1.4 \pm 0.2) \times 10^6$ M^{-1}] falls at the upper end of those observed for binding of neutral, hydrophobic molecules with CB6,[33−35] and it has a higher affinity for iodine than traditional macrocycles such as cyclodextrins or crown ethers.[36−46] The experimental structure of the CB6·I_2 complex in the solid state (see Figure 2 and Supporting Information) immediately directed our attention toward halogen bonding. The comparison of bond distances and angles typical for both "conventional" and perpendicular halogen bonds (Figure 2) showed that the $H_2O\cdots I_2$ interaction at the lower CB6 portal has a bond distance of 3.10(2) Å and an I−I···O bond angle of 177.5(1)° and is therefore a prototype for a conventional halogen bond in terms of bond length and linearity in general[3] and for water molecules in particular.[47] In contrast, the interaction between the dihalogen and the carbonyl groups at the upper rim of CB6 establishes an example for a nonbiological, "small molecule" analogue of a perpendicular halogen bond, which involves the carbonyl oxygen π-orbital.[19−21] Whereas π-halogen bonding is common for alkenes and aromatics as donors, it has only been implicated for heteroatoms in sterically congested thio- and selenocarbonyl compounds.[3,48] For aldehydes and ketones, in particular, several examples of halogen bonding exist in the solid state[49−54] and a few in solution,[55−57] in the gas phase,[58,59] and in silico,[60−62] but they involve invariably the carbonyl oxygen lone pairs. Important to note, the carbonyl oxygens interacting with diiodine form also hydrogen bonds to lattice water molecules (average O···O hydrogen-bonding distance ca. 2.77 Å, $C{=}O\cdots OH_2$ bond angle ca. 114°, $N{-}C{=}O\cdots O$ dihedral ca. 40°, and I···O···O angle ca. 123°). Accordingly, the carbonyl oxygens in the CB6·I_2 complex interact simultaneously but approximately orthogonally with a halogen and a hydrogen atom. The interactions can accordingly be considered as a synthetic equivalent of the *h*X halogen bonds hitherto observed exclusively in biological systems.[19−21,24]

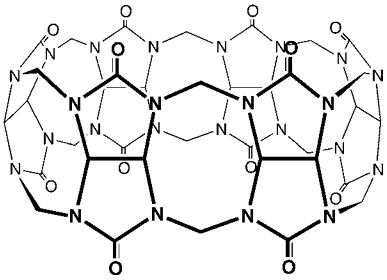

Figure 1. Molecular structure of cucucurbit[6]uril (CB6).

The observed interaction between the CB6 carbonyl groups and I_2 perfectly matches the ideal dihedral angle requirement for carbonyl oxygen π-halogen bonds ($N{-}C{=}O\cdots I$ dihedral angle is 87°−91°),[19] while the $C{=}O\cdots X$ bond angle of 80°−83° falls at the lower end of the angles encountered in biological systems (80°−150°).[19] The macrocyclic confinement imposes also a sizable variation from the linearity rule of halogen bonding (O···X−X bond angle is 131°−148°).[3,19] Similar deviations due to structural confinement are observed in biological systems,[10,19,47] where the distribution has even two maxima, one near 160°−170° and another one near 145°−150°.[19] Quantum-chemical calculations of the electrostatic potential maps[4,5,19] (Figure 3) nicely visualize the so-called σ-hole at the two poles of the heavy dihalogens, the region of

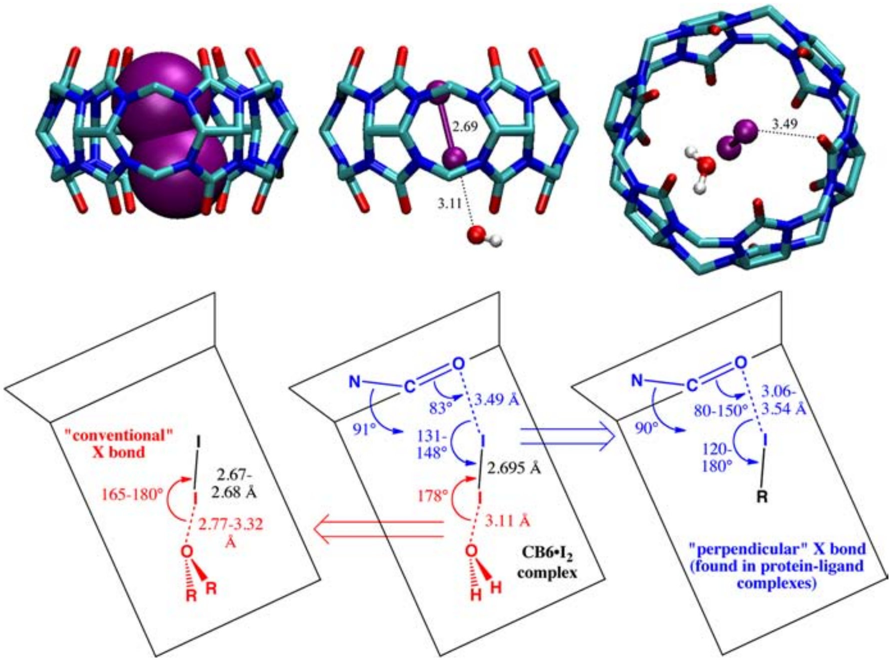

Figure 2. (Top) Views of the single-crystal XRD structure of the CB6·I_2 complex, showing the van der Waals surface of iodine inside the cavity (left), the halogen bonding with a water molecule near the lower portal (center), and the carbonyl−halogen contact at the upper portal (right). (Bottom) Schematic representation of bond lengths and angles for the two distinct interactions (red and blue) in the CB6·I_2 complex (center) in comparison to those in conventional halogen bonds (lone pair of an sp^3 oxygen interacting with I_2, left; data from refs 3, 45, 46) and in "perpendicular" ones (π-orbital of an sp^2 oxygen from a carbonyl group, right; parameters for bond lengths and angles from refs 19, 24, 47, 64, 65).

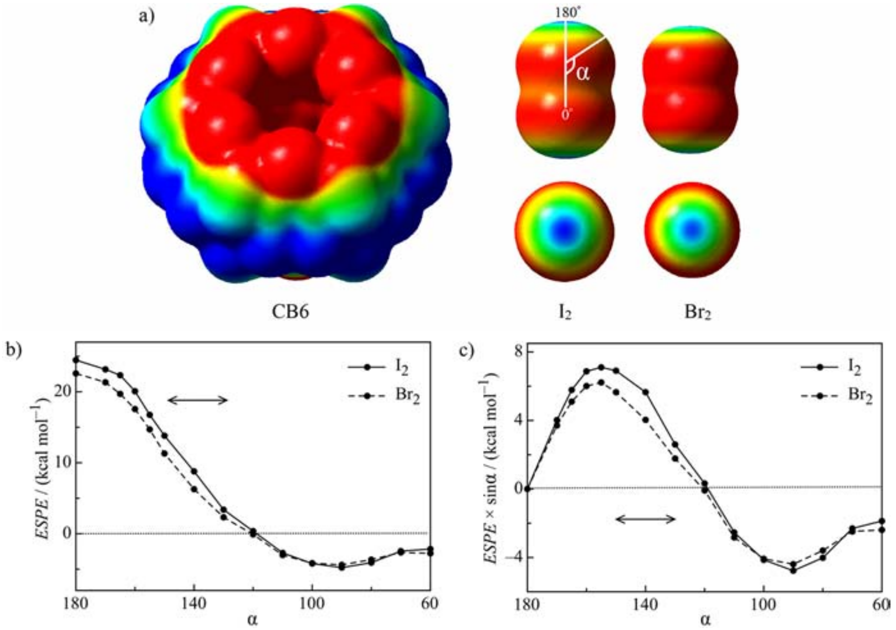

Figure 3. (a) Electrostatic potential maps for CB6 (HF/6-31G* level of theory) and for I_2 and Br_2 (HF/aug-cc-pVDZ-PP level of theory); the red to blue color range spans −5.0 to +25.0 kcal mol^{-1}. Plots of (b) the electrostatic potential energy and (c) the surface-weighted (factor sinα) electrostatic potential energy for I_2 (solid line) and Br_2 (dashed line) against the polar angle (α, defined on top) (cf. ref 63). The double arrows mark the range of O···X−X angles encountered in the crystal structures.

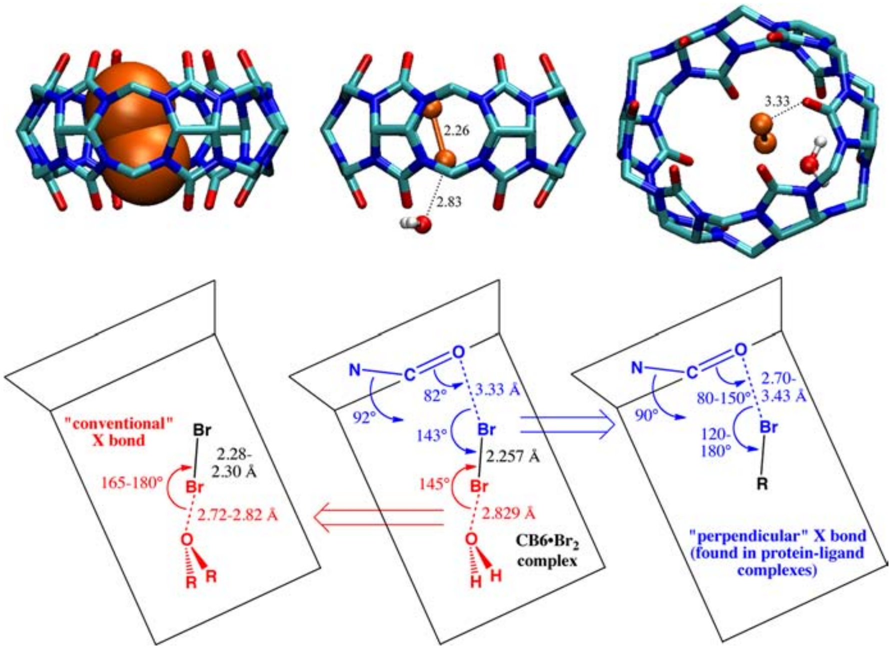

Figure 4. (Top) Views of the single-crystal XRD structure of the CB6·Br_2 complex, showing the van der Waals surface of bromine inside the cavity (left), the halogen bonding with a water molecule near the lower portal (center), and the carbonyl−halogen contact at the upper portal (right). (Bottom) Schematic representation of bond lengths and angles for the two distinct interactions (red and blue) in the CB6·Br_2 complex (center) in comparison to those in conventional halogen bonds (lone pair of an oxygen interacting with Br_2, left; data from ref 3) and in "perpendicular" ones (π-orbital of an sp^2 oxygen from a carbonyl group, right; parameters for bond lengths and angles from refs 19, 24, 47, 64, 65).

positive charge density that allows the halogen to serve as an electron pair acceptor in halogen bonds. Importantly, although the electrostatic potential of the dihalogens is largest at an angle of 180°, it remains significantly electropositive near the experimentally observed O···I−I angle of ca. 140°.[63] This is an important prerequisite for classifying the associated electrostatic interactions as being halogen-bonding in nature.[9]

Crystallographic evidence for halogen bonds between I_2 and oxygen donors is very rare,[3] with one complex for 1,4-dioxane and two for α-cyclodextrins being known;[45,46] the last two do not involve, however, halogen bonding within a host−guest complex but rather between two adjacent host−guest complexes. The bond distance of 3.490(9) Å (70% occupancy) lies at the upper end of O···I halogen bonds (the sum of the van der Waals radii is 3.50−3.53 Å)[66,67] but is very similar to the value of 3.4 Å found in several protein–iodine interactions.[47,68,69] For example, 3,5-diiodosalicylic acid forms a complex with human serum albumin with a 3.46 Å I···O═C halogen bond,[70] which has been considered to contribute to both stabilization and structure.[10] The observation of two symmetrically disordered positions (each ca. 15%, in our refinement) displaying very similar interactions with the two adjacent carbonyl oxygens, i.e., comparable bond lengths (ca. 3.50 Å) and angles, confirms the tendency of the upper iodine pole to be attracted by the carbonyl oxygens (these are of the ureido type and therefore biomimetic to peptide amide carbonyls, i.e., both are N–C═O···I interactions). As a result, iodine is centered but tilted inside CB6 (the CB and I_2 axes have an intersection angle of 12.9°) and "leans" against three carbonyl oxygens (Figure 2).

The possibility that halogen atom contacts are the result of a dense crystal packing (minimization of repulsion) rather than specific attractive forces must always be considered.[23,71−73] The deep immersion of dihalogens within a rigid macromolecular cavity provides a particularly fortunate situation in this respect, because the packing within the void can be separated, in a good approximation, from the packing of the surrounding crystal lattice. Taking into account Rebek's rule for related host–capsule complexes,[74,75] the packing coefficient of I_2 within CB6 (50% versus an ideal value of 55–68% in condensed phases) points to a rather loose fit in comparison to other CB6 complexes.[33] This and the fact that the shortest intercomplex atomic distance of the iodine at the upper rim is to an equatorial hydrogen of another distant CB6 (3.47 Å; see crystal packing in Supporting Information) rule out repulsive forces as the underlying reason for the observed close host–guest contact. In fact, if repulsive host–guest interactions were dominant, the diiodine guest would need to adapt a centrally symmetric position on the CB axis, equidistant to all six carbonyl oxygens. The interaction between the upper iodine and the oxygen atoms must consequently be attractive by nature, even if weakly. In fact, a strongly stabilizing interaction between the ureido carbonyls and iodine is not expected because the binding constants of simple dialkylureas (and similarly amides) with iodine are only ca. 10 M^{-1} (in heptane).[57] Nevertheless, these can be sufficient to be structure-determining, certainly in the solid state. Characteristic for a weak donor–halogen interaction,[76] the I–I bond in the CB6 complex [2.694(4) Å] is only marginally longer than in the gas phase (2.681 Å),[77] identical to the I–I bond length in ether solution (2.694 Å),[77] but longer than in the previously reported I–I···O complexes (2.67–2.68 Å).[45,46]

When crystals of CB6 were grown in the presence of dibromine, XRD analysis revealed a homologous CB6·Br_2 host–guest complex in one out of three macrocycles of the asymmetric unit (Figure 4). Note, again, that only very few structures of Br_2 complexes with organic molecules are known.[3] In contrast to the CB6·I_2 structure, Br_2 is not centered in the cavity but also tilted relative to the axis of the macrocycle and disordered over two symmetry-related, slipped-parallel positions (see Supporting Information). The CB6·Br_2 complex showed a similar halogen-bonding pattern as in the case of the CB6·I_2 complex (Figure 4), namely, a conventional halogen bond to a water molecule at the lower rim and a perpendicular carbonyl–halogen contact at the upper rim. The latter interaction can again be classified as an attractive one, leaning on the arguments advanced above for the CB6·I_2 complex and supported by an even lower packing coefficient of 39% for CB6·Br_2. Particularly conclusive, even though Br_2 (or the H_2O···Br_2 cluster) is a much smaller guest than I_2 (or the H_2O···I_2 cluster), the upper halogen seeks again close contact to the oxygen rim.

The refined Br–Br bond length in the CB6 complex [2.257(5) Å] was very similar to that of Br_2 in different phases (2.28–2.31 Å)[78] and those in its complexes with acetone (2.28 Å) and 1,4-dioxane (2.30 Å), two examples of conventional halogen bonds with oxygen lone pairs.[3] The bond distance between Br_2 and the water molecule [2.83(2) Å] is also similar to those observed in the known complexes (2.82 Å for acetone and 2.72 Å for 1,4-dioxane),[3] while the Br–Br···OH_2 bond angle of 145° deviates from linearity. The bond length of 3.331(10) Å between Br_2 and the CB6 carbonyl oxygen is again below the sum of the van der Waals radii of 3.35–3.37 Å[66,67] and can accordingly be assigned as a perpendicular C═O···Br contact in a synthetic organic system, supported by the perfectly matching N–C═O···Br dihedral angle (92°), a C═O···Br bond angle of 82°, and a O···Br–Br bond angle of 143°, which are all within the known broad ranges.[10,19,47] The O···Br distance compares well with that of perpendicular Br···O halogen bonds in biological systems (3.17 ± 0.16 Å).[24,47,65] Finally, although the carbonyl oxygen involved in the bromine contact does not participate in hydrogen bonding, the lone pairs of this oxygen are coordinated electrostatically to two separate sodium counter cations (O···Na distances are 2.433(11) Å and 2.675(14) Å, respectively), which appears to establish an alternative orthogonality motif.

Intrigued by the fact that perpendicular halogen bonds with carbonyls are common for proteins and that similar interactions can also be observed for cucurbiturils as synthetic hosts, we raised the question whether the amide donor functionality, N–C═O, is essential to promote these peculiar interactions. We have first engaged in a database search (Cambridge Crystallographic Data Centre) to identify the abundance and occurrence of perpendicular halogen bonds with carbonyls in synthetic systems, even though they may not have been identified as such in the related studies. Setting the bond distance cutoffs as 3.35 Å for C═O···Br and 3.50 Å for C═O···I, we identified 899 and 407 hits, respectively, of which only 4% and 1%, respectively, met the angular criteria for perpendicular halogen bonds (see Supporting Information). Strikingly, all carbonyls involved in perpendicular halogen bonding were substituted with mesomerically electron-donating substituents, i.e., only ethers, amides, and ureas formed perpendicular halogen bonds with iodine, while for bromine also one *α*,*β*-unsaturated ketone was found. Among 1306 structures, only a single "regular" ketone, R–CH_2–CO–CH_2–R, was found to engage in a perpendicular halogen bond in the solid state. Evidently, amido and ureido groups have an intrinsic preference for perpendicular halogen bonding, while regular carbonyl groups have a preference for halogen bonding through their lone pairs.

The biomolecular work by Auffinger et al.[19] has already stimulated computational studies on halogen bonding with carbonyl groups. However, for the previously selected "protein models", formaldehyde and acetone,[60−62] perpendicularly halogen-bonded structures have not been identified as a minimum, but only planar ones with a conventional halogen bond to the carbonyl oxygen lone pair. Very recently, halogen bonding to an amide has been investigated in computational detail.[79] We selected urea as a common computational model for both cucurbituril ureido and peptide amide groups (see Supporting Information) and performed calculations at recommended high levels of theory and basis sets (MP2/aug-cc-pVDZ-PP).[13,61,62] As can be seen from Table 1, the lone-pair halogen bonds with urea (ca. −7 kcal mol^{-1}) are stronger than those with formaldehyde (ca. −4 kcal mol^{-1}), as expected from the better electron-donating properties of the former carbonyl oxygen. Note also the very good absolute agreement with experimental binding energies for ureas and amides ($\Delta H°$ ca. −5 kcal mol^{-1}).[57] However, although the torsional potential about the N−C=O···X is stabilizing over the entire range and not very sensitive to distortions of the O···X−X angle either, we were unable to identify perpendicular halogen bonds as energy minima for urea but only approximately planar ones. Nevertheless, the perpendicular halogen-bonding geometries lie energetically very close; the same conclusion can be reached from the halogen-bonding potential maps recently published for an amide.[79] This accounts for the fact that geometrical confinement as well as subtle steric hindrance effects, as they occur in proteins from the peptide backbone or from orthogonal hydrogen bonds[24] and in cucurbiturils from the macrocyclic inclusion itself, may readily favor a perpendicular approach of the halogen. In fact, as revealed by ab initio calculations, when both oxygen lone pairs in urea are "blocked" by hydrogen-bonded water molecules, the structure with perpendicularly bonded dihalogen now becomes a minimum with essentially the same stability (−6.84 kcal mol^{-1}; see Table 1 and Supporting Information).

Table 1. Calculated Energies (MP2/aug-cc-pVDZ-PP) of the Fully Geometry-Optimized Structures for the Interaction between I_2 and Br_2 with Urea, Formaldehyde, and Hydrogen-Bonded Urea

complex	H/N−C=O···X dihedral angle (deg)	E^a (kcal mol^{-1})
urea·I_2	10	−10.91 (−7.35)
urea·Br_2	10	−9.65 (−6.58)
$CH_2CO·I_2$	0	−6.55 (−4.59)
$CH_2CO·Br_2$	0	−6.07 (−4.25)
$(H_2O)_2$·urea·I_2^{b}	87	−11.46 (−6.84)

[a] Values in parentheses are with counterpoise (CP) correction for basis set superposition errors. [b] See Supporting Information for the structure.

Most importantly, the perpendicular interaction between the carbonyl oxygen and the dihalogens is stabilizing even for a nonlinear arrangement of the dihalogen (Figure 5); in particular, when the interactions were calculated as a function of the O···X−X "polar" angle (other angles and distances were kept the same as in the crystal structures), sizable stabilization energies resulted near 140° (the experimentally observed angle) even without further geometry optimization. The calculated stabilization energies with and without counterpoise correction converged at expanded basis sets (see Supporting Information)

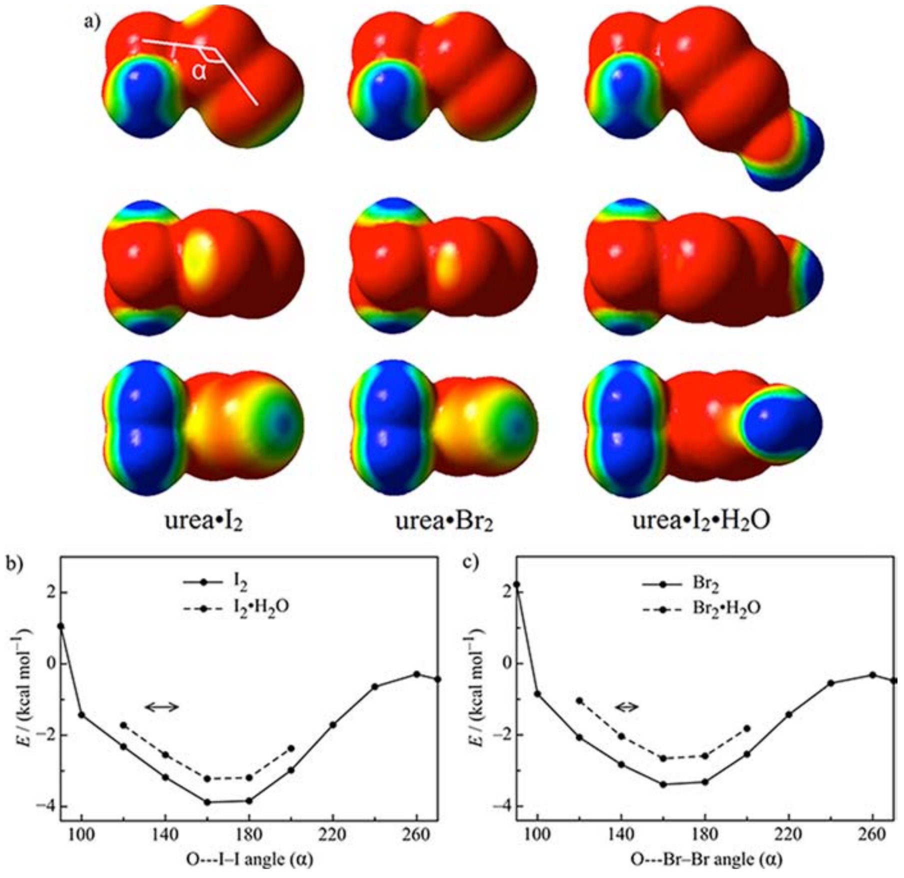

Figure 5. (a) Side, top, and bottom views of the electrostatic potential maps (HF/aug-cc-pVDZ-PP, the red to blue color range spans −5.0 to +25.0 kcal mol^{-1}) for the perpendicular complexes between urea·I_2, urea·Br_2, and urea·I_2·H_2O at an O···X−X angle of 140°. Plots of the interaction energies (MP2/aug-cc-pVDZ-PP with counterpoise correction) for (b) the urea·I_2 and (c) the urea·Br_2 complexes against the O···X−X angle (*α*, defined on top). See Tables S2 and S3 in the Supporting Information for data. The double arrows mark the range of O···X−X angles encountered in the crystal structures.

and were only slightly lowered when a water molecule was bonded to the other halogen (as in the crystal structures)[76] (cf. Figure 5). When a "urea trimer" is used as *multivalent* donor, which mimics the situation encountered in the CB6 structure (Figure 2), the interaction energy of diiodine increases by a factor of 2.5, reaching a substantial value of −7.88 kcal mol^{-1} (see Supporting Information). The combined structural and computational results furnish evidence that there is a net attractive interaction between the electropositive region on the halogens and the electron-donating carbonyl oxygens:[80] The interactions are halogen-bonding by nature.[32] While halogen-bonding interactions are known to be highly directional,[3−10] our results also reveal that they remain significantly stabilizing over a large range of $N{-}C{=}O\cdots X$, $O\cdots X{-}X$, and $C{=}O\cdots X$ angles, as they may be imposed by confinement.

■ CONCLUSION

Whereas perpendicular halogen bonds to carbonyl groups have recently emerged as an important—and apparently exclusive—structural motif in biomacromolecules,[19−21,24,47,64,65] contributing, among others, to thyroxin−thyroid hormone recognition,[81−83] our present investigation has revealed two examples of structurally comparable contacts in simple host−guest complexes. The combined experimental, statistical, and computational results suggest that perpendicular halogen bonding can become competitive when the π-electron system of carbonyl groups is enriched by electron-donating groups, which is the case for ureas, carbamides, amides, and esters. In these cases, macromolecular confinement and steric hindrance arising from orthogonal hydrogen bonds, whether inside biological structures or organic macrocycles, may readily favor this nonconventional supramolecular interaction. While perpendicular halogen bonds as well as orthogonal halogen and hydrogen bonds (*hX* bonds) have until now remained elusive for ketones and aldehydes, they become viable for amides, independent of whether biological or synthetic "small-molecule" systems are being investigated.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental section, X-ray crystallographic data, details of crystal packing, computational details and tabulated data, and database search results. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

w.nau@jacobs-university.de

Notes

The authors declare no competing financial interest.

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(32) The assignment of halogen bonds in this paper adheres to the recent IUPAC Provisional Recommendation: "A halogen bond $R{-}X\cdots Y{-}Z$ occurs when there is evidence of a net attractive interaction between an electrophilic region on a halogen atom X belonging to a molecule or a molecular fragment R−X (where R can be another atom, including X, or a group of atoms) and a nucleophilic region of a molecule, or molecular fragment, Y−Z.": Desiraju, G. R.; Ho, P. S.; Kloo, L.; Legon, A. C.; Marquardt, R.; Metrangolo, P.; Politzer, P. A.; Resnati, G.; Rissanen, K. Definition of the Halogen Bond. See http://www.iupac.org/fileadmin/user_upload/publications/recommendations/metrangolo_prs.pdf.

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