Non-Covalent Interactions of Organic Halogen Compounds with Aromatic Systems – Analyses of Crystal Structure Data

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The Cambridge Structural Database showed in mid 2002 about 20.000 structures containing halogen atoms and aryl rests with distances *d* between the aryl center and the halogen atom, which would allow both hydrogen bonds with the aromatic hydrogens and/or van der Waalsinteractions with the π-cloud. The latter are characterized by short distances *d* and by small angles *α* between the vector along the aryl centroid–halogen line and the perpendicular vector originating in the aryl center (the plane normal). The cases with $d <$ 3.0 Å for F; and $d < 3.5$ Å for Cl, Br or I (outliers neglected), and $\alpha \approx 10 \pm 5°$, indicating predominating van der Waals forces, amount to several hundreds. The majority of fragments exhibit larger *d* and *α* values, in line with avoidance of electrostatic repulsion between the negative partial charges of the halogens and the π-cloud center, and with an increasing electrostatic attraction with the aromatic hydrogen atoms. The corresponding hydrogen bonds are characterized by longer distances *d* and by angle values of $\alpha > 60°$ (about 40 % of the fragments), with only very few cases close to linear hydrogen bonds (then with $\alpha = 90°$). Compounds containing metal–halogen bonds were omitted in view of possible strong orientational interferences. The structures were screened with four different halogen binding modes, all of them containing the halogen attached to a carbon atom, but with different hybrizations at the connecting carbon centers. The results show only small differences in the distance distributions, with a slight preference for smaller *α* values for sp^2 frameworks.

Introduction and Aims

The van der Waals interactions[1] belong to the most often cited non-covalent forces, also in the solid state.[2] On the other hand they are the least well-characterized "non-bonded" interactions; furthermore they pose particular problems for theoretical evaluation in view of the need to include polarizability functions, requiring also with the DFT method immense calculation times.[3] A number of recent computational papers on the interactions of halide anions with electron-deficient arenes[4] have shown, as to be expected, dominating electrostatic attractions with the π-moieties, which can play only a small role in the few experimentally established complexations[5] with undisturbed aryl moieties.

For studies in aqueous solution it is difficult to separate the interactions from hydrophobic driving forces. The most common approach to identify on structural grounds van der Waals interactions is based on the occurrence of interatom or inter-group distances below the sum of van der Waals radii of non-interacting atoms. Evidently, such geometric features seen in the solid state are the consequence of interaction energies which as such can be investigated only by independent methods, such as by measurements of supramolecular complex equilibrium constants.

Recently, one of the present authors has on the basis of equilibrium measurements in aqueous solution developed a scale of free energy increments for pairwise dispersive interactions between common functions in organic compounds, which for the first time could be separated from the much weaker hydrophobic driving forces.[6] The association data, collected in aqueous medium, showed substantial dispersive binding contributions for complexes between halogen atoms and aryl derivatives, increasing as expected from fluorine to iodine. The aim of the present investigation is to evaluate, by a systematic analysis of crystal structures in the Cambridge Structural Database (CSD),[7] the frequency and the geometric arrangements of corresponding pairwise interactions in the solid state, with the hope to differentiate van der Waals interactions with the π-moiety from hydrogen bonds with the C–H bonds of aromatic entities.

In countless X-ray-based publications one finds the statement that structures are stabilized by van der Waals interactions; thus, a ISI data base search for this combination yielded alone from 1996 to september 2002 about 50 corresponding references.[8] There are, however, to the best of

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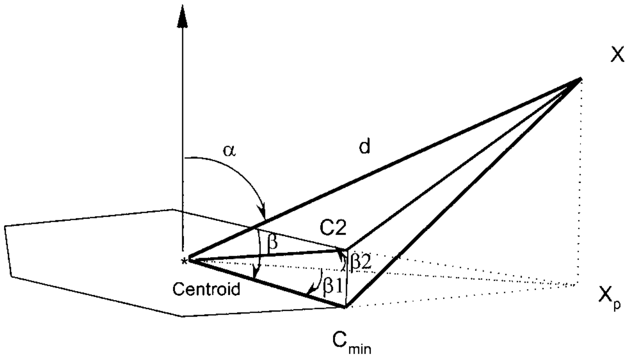
our knowledge few papers which address dispersive interactions in crystals with respect to forces between specific groups such as halogens and e. g. π-systems.[9] A number of investigations contain data on van der Waals distances for interactions also with halogens, but only few analyze in detail such interactions by comparison to other studies. Csöregh et al.[10] have found in substituted triptycene derivatives typically distances between d_{ar-X} = 3.33 and 3.75 Å between the phenyl ring centroid and chlorine, supported by an unpublished CSD statistical analysis (footnote 24 in ref.[10]). Interestingly, a complex of a phenyl-substituted calix[6]pyrrole and trichloroethanol shows aryl centroid−Cl distances between d_{ar-X} = 3.00 and 3.40 Å.[11] Similar stabilizing interactions were indicated in complexes of the same host with nitroderivatives by d_{ar-X} = 3.55 Å between sandwiched aromatic pyrrole and nitrogroup planes.[11]

Results and Discussion

The 5.23 version of CSD, (updated in May 2002 and July 2002), containing 269899 structures were screened with the program ConQuest[12] (version 1.4) for fragments containing halogen atoms bound either to aromatic or aliphatic carbon residues within a given distance *d* between the aryl centroid and the halogen X. The distance *d* was chosen long enough to include also linear and weak hydrogen bonds between the halogen and the aromatic H atoms in the plane of the aryl unit. Thus, we added up: 1.4 Å for the centroid−C distance, 1.0 Å for the C–H bond, 1.2 Å for the H van der Waals radius, and the halogen X van der Waals radius. In addition we added another 0.3 Å, allowing also for weak H···Hal hydrogen bonds. The *d* values thus chosen were for F 5.4 Å, for Cl 5.7 Å, for Br 5.8 Å, and for I 5.9 Å. Less reliable structures with *R* factors above 0.075 (using the ConQuest filter) and those with disorder, or with errors were excluded.

Fortunately, weak hydrogen bonds involving covalently bound halogens as acceptors were analyzed in detail in a recent excellent monograph;[13] structural evidence for aromatic C–H bond as donors, however, was presented only for C–F, and not for other halogen acceptors. Scatterplots show F···H distances between 2.3 and 3.0 Å, and F···H–C angles between 100 and 175°, with no correlation between those. It has been pointed out that for weak hydrogen bonds the usual restriction of A···H--D angles above at least 130° cannot be applied, with values even below 90° considered to be acceptable.[13,14] A more homogeneous data set from fluorobenzenes did show only a weak correlation, with similar F···H distances and F···H–C angles as before. These findings are important for the present analysis as they could provide a help to distinguish hydrogen bonding from dispersive contributions in halogen−aryl interactions.

As structural indicator for dispersive binding contributions between the halogen and the aryl units we use the angle *α* between the vector along the aryl centroid–X line, and the perpendicular vector originating in the aryl center (the plane normal; see Scheme 1). Increasing van der Waals interactions are expected to show up in smaller values of *α* and shorter distances *d*. In order to evaluate possible differences of the halogen atom placed in line, or above the aromatic C–H vector we also introduced the angle *β* between this vector and the arene centroid-X vector.



Scheme 1. Geometric model with distance *d* and angle α/β parameters.

The possible geometries for organic halogen derivatives C–Hal interacting with an aromatic moiety on the basis of model calculations for C–Cl with two commonly used force fields shows, as expected, one extreme position of the halogen atom directly above the arene center with *α* = 0.0°; then one expects for e. g. C–Cl as the shortest possible distance *d* = 3.5 to 4.0 Å. In this position the halogen could take a maximum advantage of dispersive interaction with highly polarizable π-moiety, but would suffer at the same time from rather extreme electrostatic repulsion between the partial negative charges at the halogen and the π-cloud. The other extreme, characterized by *α* = 90° and e. g. for Cl by the long distance *d* = 5.2 to 5.5 Å or more, is the location of the halogen within the aromatic plane; this allows maximum Coulomb attraction between the halogen and the positively charged H atoms attached to the arene ring, but no interaction with the π-system. In the position between these extremes, the C–Hal interaction with the aromatic moiety can take advantage of both a dispersive forces and hydrogen bond-like Hal···H–C interactions.

The CSD contains a surprisingly large number of fragments involved in non-covalent interactions of aryl components with halogens, providing a statistically meaningful basis (Figure 1 and Figure 2). The often used absolute number of structures (hits) meeting a special structural requirement depends inter alia on the general, or even commercial interest for a particular compound class (this is obvious e. g. in the large number of fluorine derivatives). Therefore we characterize the statistical significance of a observed population by comparison to the **total** number of pertinent structures, including the large number of those which do not meet the search criterion of a minimum distance *d*. Noticeably, we find for all fragments 9 % to 34 % with halogen and aromatic units within the critical distance *d* (Table 1 and Table 2). Thus, 10502 of all 72738 chlorine and arene containing structures indicate non-covalent interactions with aromatic moieties. For the analysis of the interactions we dissected the halogen derivatives into four different binding modes, which could take into account possible dif-

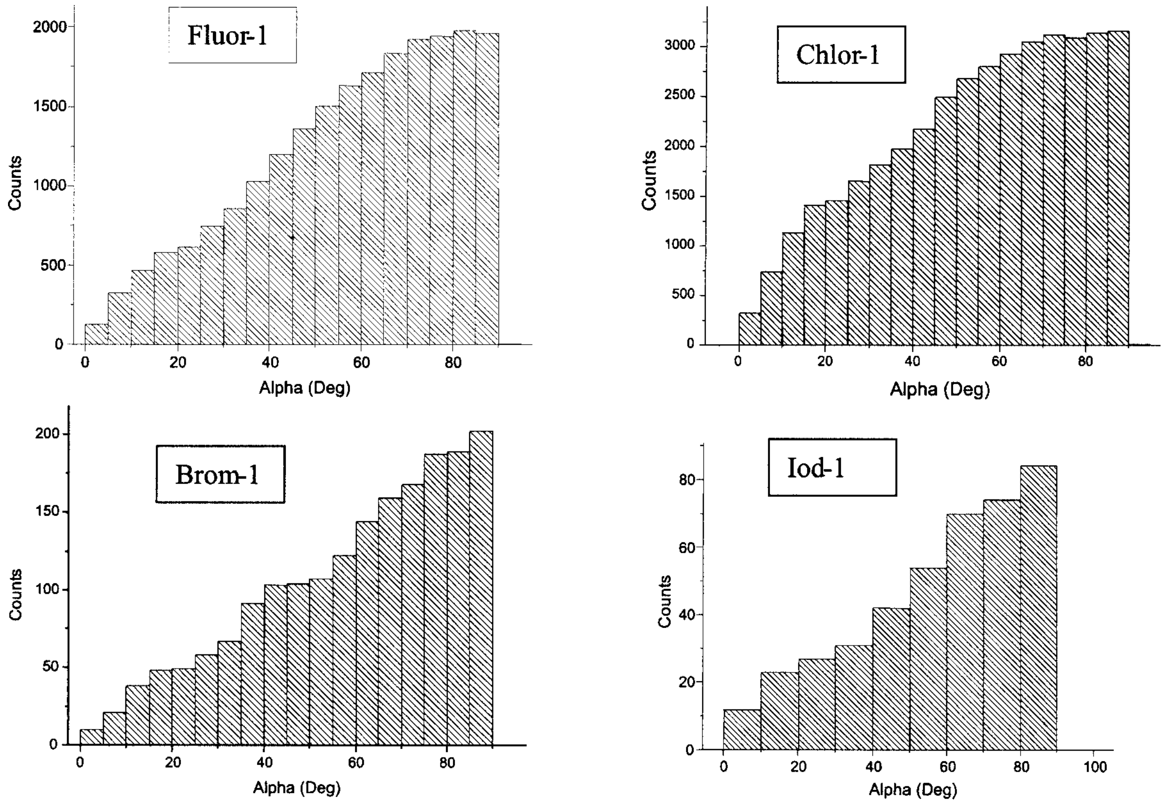


Figure 1. Frequency as function of angle *a*, for RHal type 1.

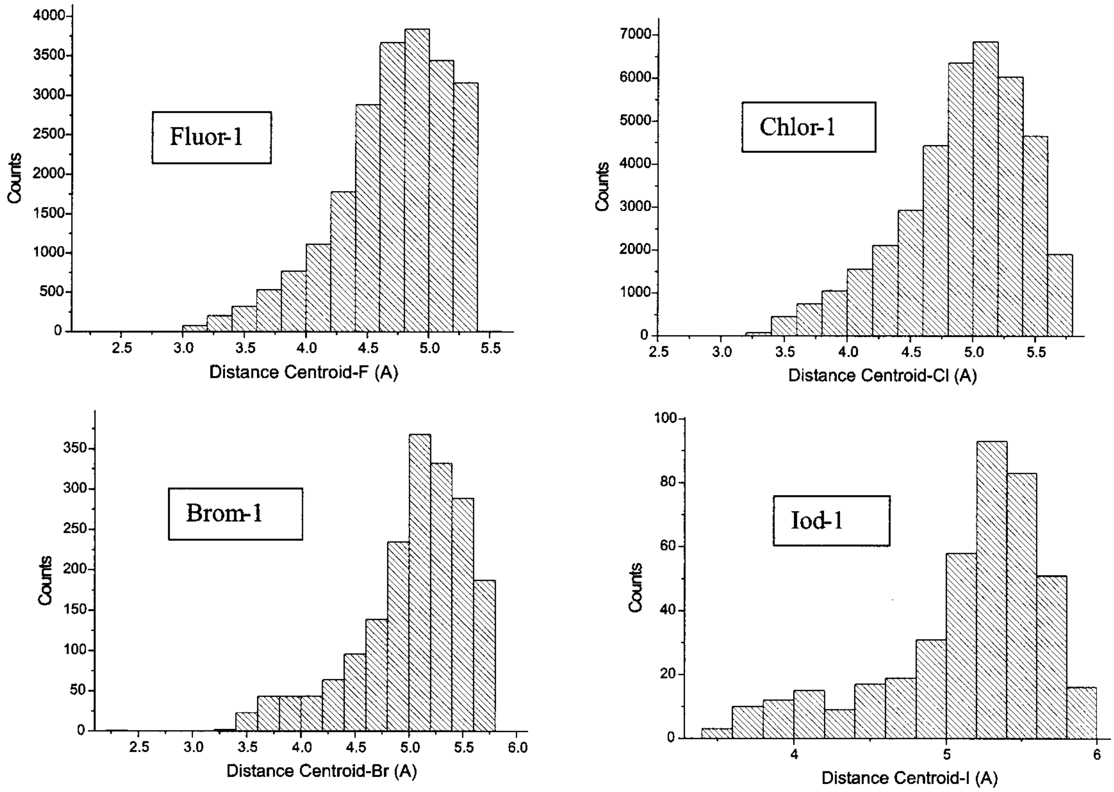


Figure 2. Frequency as function of distance *d* for RHal type 1.

Table 1. Fragments for angle α populations between 0–30°, 30–60° and 60–90°. Superscript ^{1}: the first d value is and outlier, the second (in parentheses) is realistic; superscript ^{2}: the first and second d values are outliers, the third (in parentheses) is realistic.

Hal–1	F	Cl	Br	I
Total fragments	21820	39170	1867	417
α 0–30°	2862	6710	224	62
in % of all fragments d	13	17	12	14
for these (from-to)	2.291(2.956)^1−5.399	2.625(3.259)^1−5.698	3.395–5.789	3.5–5.609
α 30–60°	7591	13952	594	127
in % of all fragments d	35	36	32	30
for these (from-to)	2.521–5.4	3.195–5.699	3.781–5.797	3.857(4.166)^1−5.891
α 60–90°	11367	18508	1049	228
in % of all fragments d	52	47	56	55
for these (from-to)	3.981–5.4	3.563–5.699	2.266(4.249)^2−5.799	4.873–5.887
Hal–2	F	Cl	Br	I
Total fragments	354	2206	1235	232
α 0–30°	37	297	138	32
in % of all fragments d	10	13	11	14
for these (from-to)	2.956–5.368	3.354–5.695	3.395–5.714	3.5–5.609
α 30–60°	128	725	375	72
in % of all fragments d	36	33	30	31
for these (from-to)	3.448–5.387	3.804–5.696	3.953–5.794	3.857(4.166)^1−5.891
α 60–90	189	1184	722	128
in % of all fragments d	53	54	58	55
for these (from-to)	4.194–5.398	3.604(4.47)^1−5.697	4.562–5.799	4.873–5.887
Hal–3	F	Cl	Br	I
Total fragments	31344	20966	7689	1278
α 0–30°	4661	3045	1123	210
in % of all fragments d	15	15	15	16
for these (from-to)	2.39(2.838)^1−5.399	3.171–5.693	3.338–5.789	3.457(3.514)^1−5.883
α 30–60°	14924	9973	3482	551
in % of all fragments d	48	48	45	43
for these (from-to)	3.177–5.4	3.181(3.671)^1−5.699	3.685–5.798	3.926(4.062)^1−5.9
α 60–90°	11759	7948	3084	517
in % of all fragments d	38	38	40	40
for these (from-to)	3.198(3.439)^1−5.4	3.915–5.699	3.032(4.22)^1−5.8	4.677(4.829)^1−5.899
Hal–4	F	Cl	Br	I
Total fragments	2583	10396	5307	503
α 0–30°	383	1430	749	80
in % of all fragments d	15	14	14	16
for these (from-to)	3.026–5.389	3.171–5.689	3.403–5.789	3.514–5.833
α 30–60°	985	4487	2288	191
in % of all fragments d	38	43	43	38
for these (from-to)	3.177(3.403)^1−5.399	3.677–5.699	3.819–5.798	3.926(4.314)^1−5.9
α 60–90°	1215	4479	2270	232
in % of all fragments d	47	43	43	46
for these (from-to)	4.18–5.399	4.412–5.699	3.032(4.22)^1−5.8	4.829–5.892

ferences in charge density and polarizibility of the halogen atoms, depending on their binding to sp^3 or sp^2 carbon networks (see Scheme 2).

The populations found in the CSD are shown for selected types in Figure 1 and Figure 2, for all types in the Supporting Information (for Supporting Information see also the footnote on the first page of this article), Figures Ia−d and IIa–d; for a better overview they are grouped in categories in Table 1 with α angles of 0–30°, 30–60°, and 60–90°. It is known that a maximum in alpha histograms does not necessarily reflect a energy minimum, also due to the necessary angular (or "cone") correction.[15] The program Vista, which could take care of this, could not be used as the number of data in many cases was too large (over 10000) for its application. In absence of a clear-cut distinction from (pseudo-) hydrogen bonds with the aryl C–H bonds one can try to define all fragments with e. g. $\alpha < 60°$ as fragments where thevan der Waals interaction with the π-system dominates, and those with $\alpha > 60°$ feeling significant electrostatic with the positively charged aromatic H atoms. In most cases the populations show a similar pattern, with an increasing number of fragments towards relatively long aryl centroid–X distances d, with α values approaching $\alpha = 90°$. The sharp drop-off of fragments at these long distances is in line with the expected absence of (nearly) linear C–H···Hal hydrogen bonds.[13] Only very few fragments are found with aryl centroid–X distance d_{ar-X} below the sum of van der Waals radii, which is in line with the abovementioned repulsion between the negative partial charges in both the π-cloud and the halogen. A distinct minimum between two families around small or large α values is seen only for X = Cl, bound to sp^2 (see Supporting Information,

Table 2. Number of "hits" (structures) for each type.

Halogen type	Hits meeting search criteria	Hits meeting search criteria [%]
Fluoro-1	2383	42
Fluoro-2	131	2
Fluoro-3	2202	39
Fluoro-4	472	8
all-Fluoro	4585	81
Chloro-1	4321	44
Chloro-2	552	6
Chloro-3	3547	36
Chloro-4	2082	21
all-Chloro	7868	80
Bromo-1	421	15
Bromo-2	318	11
Bromo-3	1683	59
Bromo-4	1245	43
all-Bromo	2104	73
Iodo-1	109	21
Iodo-2	73	14
Iodo-3	253	49
Iodo-4	108	21
all-Iodo	362	70

Figure I, type 3 and 4), and has been noted earlier.[10] For bromine compounds a similar, although weaker distribution is observed at least for the sp^2-bound types 3 and 4 (see Supporting Information, Figure I). In few cases one observes a population maximum between the extremes, e. g. for fluoro, type-1, around $\alpha = 50°$. A similar distribution is seen for iodo compounds for types the sp^2 types 3 and 4 (see Supporting Information, Figure I), although the statistical basis is smaller to the smaller number of available structures. There are no consistent differences between the different halides, which would be in line with the increase of non-covalent forces not only with respect to dispersive interactions with the π-cloud, but also with respect to hydrogen bonding in going from fluorine to iodine, independent of the halogen binding mode.

The distribution profiles as function of the distances *d* between the arene center and the halogen could be expected to follow that observed as function of the *α* angles. How-

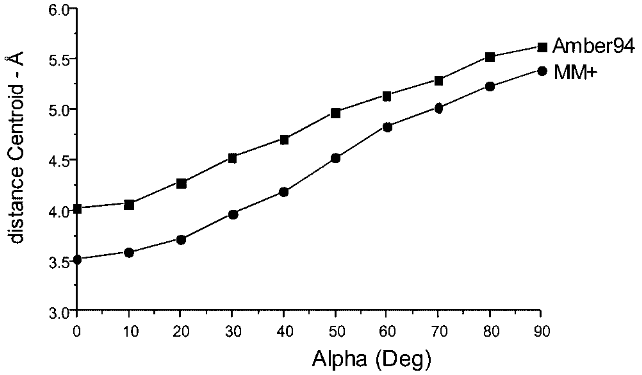
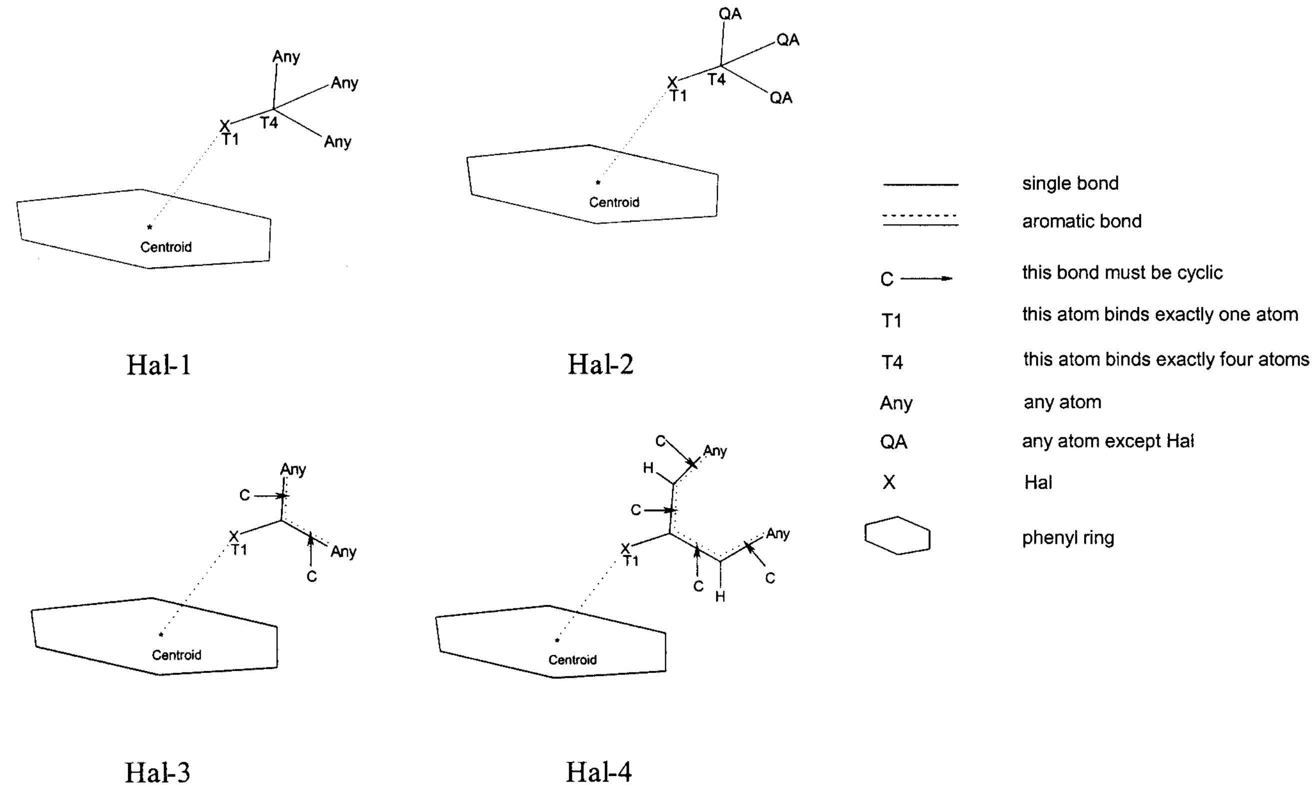


Figure 3. Expected function of distance *d* as function of the angle *α*; calculated for Me–Cl rolling over a benzene surface (from molecular mechanics calculations, see text).



Scheme 2. Structure queries: definitions used in the CSD search. As "X" the one, specific halogen was put in each search; e.g., Hal-1 describes four separated sets of data: Fluor-1, Chlor-1, Brom-1 and Iod-1; Hal-2: Fluor-2, Chlor-2, … etc.

ever, in contrast to the model force field calculations (Figure 3) comparison of the histograms show only in few cases a then very rough correlation between α and d (e. g. for bromo type 1). The observed scatter is not the result of variations in the angle β described by the vector component along the aryl centroid–X axis in the arene plane and the nearest centroid –C vector (see Scheme 1), as illustrated e. g. in scatter plots which show no preference for any particular β value (see Supporting Information, Figure III).

Conclusions

Generally, all histograms (Table 1, Supporting Information, Figures Ia–d, IIa–d) show an increasing population towards longer distances, but often maxima around α = 50 to 80°, indicating a support of the electrostatically favored hydrogen bonding by dispersive interactions with the π-moiety. For iodine derivatives there are in comparison to other halogens slightly more fragments with smaller distances, as expected with stronger dispersive forces due to the higher polarizability of iodine. The observed distributions indicate halogen positions, which take do advantage of sizeable van der Waalsinteractions with the π-moiety of aryl rings, in spite of the negative partial charges both at the π-cloud and the halogens.

Supporting Information: Figures Ia–d: Frequency as function of angle α, for RHal type 1 to 4, for fluoro; chloro, bromo, and iodo compounds. Figures IIa–d. Frequency as function of distance d, for RHal type 1 to 4; for fluoro; chloro, bromo, and iodo compounds. Figure III, chloro compounds: percentage of β1 in β1 + β2.

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