



Electrostatics and polarization determine the strength of the halogen bond: a red card for charge transfer

Tore Brinck¹ · André Nyberg Borrfors¹

Received: 13 January 2019 / Accepted: 29 March 2019 / Published online: 24 April 2019
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Abstract

A series of 20 halogen bonded complexes of the types R–Br \cdots Br $^-$ (R is a substituted methyl group) and R’–C≡C–Br \cdots Br $^-$ are investigated at the M06-2X/6-311+G(d,p) level of theory. Computations using a point-charge (PC) model, in which Br $^-$ is represented by a point charge in the electronic Hamiltonian, show that the halogen bond energy within this set of complexes is completely described by the interaction energy (ΔE^{PC}) of the point charge. This is demonstrated by an excellent linear correlation between the quantum chemical interaction energy and ΔE^{PC} with a slope of 0.88, a zero intercept, and a correlation coefficient of $R^2 = 0.9995$. Rigorous separation of ΔE^{PC} into electrostatics and polarization shows the high importance of polarization for the strength of the halogen bond. Within the data set, the electrostatic interaction energy varies between 4 and $-18 \text{ kcal mol}^{-1}$, whereas the polarization energy varies between -4 and $-10 \text{ kcal mol}^{-1}$. The electrostatic interaction energy is correlated to the sum of the electron-withdrawing capacities of the substituents. The polarization energy generally decreases with increasing polarizability of the substituents, and polarization is mediated by the covalent bonds. The lower (more favorable) ΔE^{PC} of CBr₄–Br $^-$ compared to CF₃Br \cdots Br $^-$ is found to be determined by polarization as the electrostatic contribution is more favorable for CF₃Br \cdots Br $^-$. The results of this study demonstrate that the halogen bond can be described accurately by electrostatics and polarization without any need to consider charge transfer.

Keywords Halogen bonding · Electrostatic potential · Induction · Charge transfer · Energy decomposition · Sigma-hole

Halogen bonding and the σ -hole

According to the recent IUPAC definition: “A halogen bond occurs when there is evidence of a net attractive interaction between an electrophilic region associated with a halogen atom in a molecular entity and a nucleophilic region in another, or the same, molecular entity” [1]. Halogen bonding is a classical interaction in chemistry that has received considerable interest during the last decades due to a large increase of applications within wide areas of chemistry, medicine, and material science [2]. Although the denotation *halogen* bonding is relatively recent, the first literature reports of halogen bond

complexes can be traced to the nineteenth century [3]. Mulliken was a pioneer in the theoretical analysis of halogen bond complexes and interpreted these as donor–acceptor complexes based on spectral analysis [4]. An interpretation that remained the commonly accepted paradigm until the beginning of the twenty-first century. However, already in 1992, Brinck, Murray, and Politzer showed that the halogen bond donating capability of halogenated methanes can be explained by a region of positive surface electrostatic potential at the end (tip) of the halogen atom along the R–X axis [5].

In 2005 Clark, Murray, and Politzer, together with Hennemann, introduced the σ -hole concept to rationalize the positive surface electrostatic potential of the halogen; the σ -hole was originally viewed as an electron depletion at the halogen tip formed owing to the singly occupied valence p -orbital of the halogen in the direction of the R–X bond [6]. Clark, Murray, and Politzer have remained the main advocates of the σ -hole concept, continuously revising and developing the theoretical interpretation of the σ -hole and its importance for halogen bonding [7–12]. Whereas the σ -hole bonding originally was considered mainly electrostatic in nature,

This paper belongs to the Topical Collection Tim Clark 70th Birthday Festschrift

✉ Tore Brinck
tore@kth.se

¹ Applied Physical Chemistry, Department of Chemistry, CBH, KTH Royal Institute of Technology, SE-100 44 Stockholm, Sweden

Clark, Murray, and Politzer have in recent years emphasized the importance of polarization as a natural and inseparable companion to the electrostatic interaction [9–11]. Furthermore, dispersion is considered as polarization, following Feynman's interpretation [13] based on the Hellmann–Feynman theorem [10]. Charge transfer, on the other hand, is argued to lack physical significance for noncovalent interactions and to be the result of mathematical modeling, as there is no rigorous approach to separate intra-molecular and inter-molecular reorganization of the electron density [10].

Although the σ -hole interpretation has received considerable acceptance within the scientific community, it has also continuously been challenged by scientist arguing that charge-transfer and orbital interactions must be considered for a complete description of halogen bonding [14–18]. In a recent study, Head-Gordon and coworkers analyzed the potential energy surfaces for a series of complexes of the type $CX_3I^{***}Y^-$ ($X=F, Cl, Br$ and $Y=F, Cl, Br, I$) by absolutely localized molecular orbitals energy decomposition analysis (ALMO-EDA) [18]. The ALMO-EDA is designed to provide a lower bound to the charge-transfer energy. In this analysis, it was found that for any given Y^- the complexation energy of $CX_3I^{***}Y^-$ decreases in the order F, Cl, Br, I , whereas the sum of the Pauli repulsion, electrostatic, and polarization energies increases in the same order. The decrease in the complexation energy was consequently attributed to the charge transfer energy, which in ALMO-EDA is defined as the remaining part of the interaction energy when other energy contributions have been subtracted out.

In a recent article, Clark and Heßelmann responded to the work of Head-Gordon and coworkers by showing that the interaction energy of the entire set of complexes is linearly correlated to the surface electrostatic potential of the σ -hole, if the surface electrostatic potential is computed from the electron density of the halogen bond donor polarized by a unitary negative charge at the position of the negative halide ion [12]. The correlation coefficient is excellent, $R^2 = 0.994$, demonstrating that the variation in complexation energy is fully reproduced by the polarized surface potential.

The objective of the current work has been to investigate the point charge (PC) approximation in more detail. The use of a PC-model is intriguing in its simplicity and it allows for the exclusion of charge-transfer effects, as there are no electrons that can be transferred. However, it remains to be determined whether such a model can provide consistent results upon larger variations in the chemical environment of the halogen atom, rather than just changing the halogen substituent in CX_3I . In addition, we evaluated the PC approximation within the classical theory of electrostatics and polarization, as this theory shows that the interaction energy depends upon the cost of polarizing the electron density and therefore cannot be expressed by the electrostatic potential of the polarized charge distribution alone. A further advantage is that the

classical theory allows for the interaction energy to be rigorously separated into contributions from electrostatics and polarization.

In this work, we studied a range of halogen bonded complexes of the types; $R-Br^{***}Br^-$ where R is a substituted methyl group, i.e., $R=CH_3, CH_2NH_2, CH_2F, CH_2Br, CH_2CHO, CH_2CN, CH_2NO_2, CF_2CN, CF_2NO_2, CF_3$, and CBr_3 ; and $R'-C\equiv C-Br^{***}Br^-$ where R is a substituent, i.e., $R'=H, NH_2, F, Br, CN, NO_2$, and the aromatic substituents $R'=C_6H_5, C_6F_5$, and $p-C_6H_4NO_2$. The selection of $R-Br^{***}Br^-$ complexes was inspired by the work of Rosokha et al. [15], as they argue that the halogen bond in these types of complexes has a significant contribution from charge transfer due to the interaction of the Br^- lone pair with the $C-Br$ σ^* -orbital. Complexes of the $R-Br^{***}Br^-$ type are expected to behave similarly to $R-I^{***}Br^-$ complexes, which were studied by Head-Gordon and coworkers, but the former type of complexes is easier to characterize theoretically; Br , in contrast to I , can be modeled without consideration of relativistic effects. We chose to include a group of alkyne halogen bond donors as previous studies have indicated that these generally form stronger complexes than alkyl halogen bond donors, and they exhibit larger substituent effects [19, 20]. Furthermore, the chosen substituents include both inductive and resonance acceptors, as we hypothesized that the latter type would promote charge transfer more effectively. Despite the efforts to maximize the potential for charge transfer, our results show that the halogen bond interactions of these complexes are governed by electrostatics and polarization and that charge transfer is of negligible importance.

Methods and procedure

The halogen bonded complexes have been analyzed by full structure optimization using Kohn–Sham density functional theory at the M06-2X/6-311+G(d,p) level. The M06-2X functional is highly accurate for main-group chemistry, including noncovalent interactions and it explicitly accounts for dispersion interactions [21]. It has been evaluated against the halogen bond benchmark data base (XB51) and been shown to provide excellent geometries and energies [22]. The RMSD of M06-2X for interaction energies is 0.43 kcal mol⁻¹, which is much lower than, e.g., MP2 extrapolated to infinite basis set (RMSD = 0.92 kcal mol⁻¹). The 6-311+G(d,p) basis set used herein is sufficiently flexible and diffuse to reduce the basis set superposition error to acceptable levels. Additional computations have been performed at the same level of theory using a point charge to represent the Br^- anion. These computations used the optimized geometries of the halogen bonded complexes, but a negative point charge (-1 au) was placed at the position of Br^- . In addition, the electrostatic potential was computed from the unperturbed density, and from the point

charge perturbed density, of the halogen bond donors in the geometries of the complexes. All computations were performed using the Gaussian 16 suite of software [23].

The classical interaction energy of a point charge (PC)

The electrostatic potential of an atom or a molecule is rigorously defined by

$$V(\mathbf{r}) = \sum_A \frac{Z_A}{|\mathbf{R}_A - \mathbf{r}|} - \int \frac{\rho(\mathbf{r}') d\mathbf{r}'}{|\mathbf{r}' - \mathbf{r}|} \quad (1)$$

where Z_A is the charge on nucleus A located at \mathbf{R}_A , and $\rho(\mathbf{r})$ is the electron density function. $V(\mathbf{r})$ is a real physical observable and can be determined from an experimentally obtained charge distribution obtained by, e.g., diffraction methods. More commonly, $V(\mathbf{r})$ is determined computationally by wavefunction theory or Kohn–Sham density functional theory. In this respect, it should be noted that $V(\mathbf{r})$ is a one-electron property and as such less sensitive to computational level and basis set than, e.g., the electronic energy. The electrostatic interaction energy with a point charge is defined by

$$\Delta E_{ES}^{PC} = qV(\mathbf{r}_q) \quad (2)$$

and corresponds to the energy of the Coulombic interaction between a point charge q located at \mathbf{r}_q and the static (unperturbed) charge distribution of the molecule. It equals the exact interaction energy in the limit of an infinitesimal point charge, as the polarization at this limit is negligible. It is also possible to compute $V(\mathbf{r})$ from a polarized electron density. If $V^{PC}(\mathbf{r})$ refers to the potential obtained from a density polarized by a point charge q located at \mathbf{r}_q then $qV^{PC}(\mathbf{r}_q)$ is the energy of the Coulombic interaction between q and the polarized charge distribution of the molecule or atom. It must be noted, however, that this is not the same as the total interaction energy, as there is a cost of polarizing, or deforming, the electron density. According to the classical description of polarization, which is based on a linear response to the electric field generated by the point charge, the total interaction energy is given by

$$\Delta E^{PC-Lin} = 1/2q[V(\mathbf{r}_q) + V^{PC}(\mathbf{r}_q)] \quad (3)$$

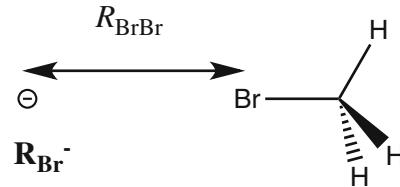
The polarization energy, i.e., the classical induction energy, is defined by

$$\Delta E_{Pol}^{PC-Lin} = \Delta E^{PC-Lin} - \Delta E_{ES}^{PC} = 1/2q[V^{PC}(\mathbf{r}_q) - V(\mathbf{r}_q)] \quad (4)$$

and the cost of polarizing the electron density is the difference between the total interaction energy and the Coulombic interaction energy of the polarized system

$$\begin{aligned} \Delta E_{\rho\text{-def}}^{PC-Lin} &= \Delta E^{PC-Lin} - qV^{PC}(\mathbf{r}_q) \\ &= -1/2q[V^{PC}(\mathbf{r}_q) - V(\mathbf{r}_q)] = -\Delta E_{Pol}^{PC-Lin} \end{aligned} \quad (5)$$

The quantum chemical PC-model of the halogen bond complexes



The scheme above shows the point charge model for the interaction of Br^- with a halogen bond donor of the type R–Br. The nuclear geometry of R–Br is taken from the full geometry optimization of the complex, and the point charge ($q_{\text{Br}^-} = -1$) is placed at the position (\mathbf{R}_{Br^-}) of the Br nucleus in the complex. The total interaction energy (ΔE^{PC}) between the point charge and R–Br is obtained as the difference in the Born–Oppenheimer energy with and without the point charge included in the electronic Hamiltonian. It should be noted that the relaxed geometry of R–Br in the complex is used for both calculations. The ΔE^{PC} can be divided into an electrostatic interaction energy and a polarization (induction) energy

$$\Delta E^{PC} = \Delta E_{ES}^{PC} + \Delta E_{Pol}^{PC} \quad (6)$$

where the electrostatic contribution can be computed directly from the electrostatic potential at \mathbf{R}_{Br^-} ,

$$\Delta E_{ES}^{PC} = q_{\text{Br}^-} V(\mathbf{r}_q) = -V(\mathbf{R}_{\text{Br}^-}) \quad (7)$$

and the polarization energy is given by

$$\Delta E_{Pol}^{PC} = \Delta E^{PC} - \Delta E_{ES}^{PC} = \Delta E^{PC} + V(\mathbf{R}_{\text{Br}^-}) \quad (8)$$

The energy cost of polarizing the electron density is analogous to Eq. 5 described by

$$\Delta E_{\rho\text{-def}}^{PC} = \Delta E^{PC} + V^{PC}(\mathbf{R}_{\text{Br}^-}) \quad (9)$$

Furthermore, the polarization is expected to approximatively follow linear response, and thus

$$\Delta E^{PC} \approx -1/2[V(\mathbf{R}_{\text{Br}^-}) + V^{PC}(\mathbf{R}_{\text{Br}^-})] \quad (10)$$

and

$$\Delta E_{\rho\text{-def}}^{PC} \approx -\Delta E_{Pol}^{PC} \quad (11)$$

In fact, how well these relationships are fulfilled provides an indication to what extent the system behaves according to classical polarization theory.

Finally, there is an energy cost of deforming the nuclear geometry of RBr into its geometry in the complex. This term, $\Delta E_{\text{Nuc-def}}$, is simply computed as the difference in the quantum chemical energy (Born–Oppenheimer energy) of RBr at the two geometries. It should be remembered that the driving force for the deformation is to lower the total interaction energy of the complex.

PC approximation and the PES of $\text{CF}_3\text{Br}\cdots\text{Br}^-$ and CBr_4-Br^-

We will first analyze the PC approximation with respect to the potential energy surfaces (PES) of the $\text{CF}_3\text{Br}\cdots\text{Br}^-$ and CBr_4-Br^- complexes along the Br–Br[−] distance (R) as shown in Fig. 1. The relevant energy components at the equilibrium geometry of the complexes are presented in Table 1. Starting with $\text{CF}_3\text{Br}\cdots\text{Br}^-$ we note that the PC interaction energy (ΔE^{PC}) is very similar to the full quantum chemical interaction energy (ΔE_{Int}) at long R , i.e., distances beyond 5 Å. It can be further be noted that at distances longer than twice the equilibrium distance ($R > 2 R_{\text{eq}}$) the electrostatic interaction energy ($\Delta E_{\text{ES}}^{\text{PC}}$) is only marginally higher than ΔE^{PC} , e.g., 0.37 kcal mol^{−1} at $R = 6.5$ Å. However, the difference between ΔE^{PC} and $\Delta E_{\text{ES}}^{\text{PC}}$, i.e., the polarization/induction energy ($\Delta E_{\text{Pol}}^{\text{PC}}$), increases in magnitude as R decreases. At the equilibrium geometry of the complex ($R_{\text{eq}} = 3.13$ Å), $\Delta E_{\text{ES}}^{\text{PC}} = -9.61$ kcal mol^{−1} and $\Delta E_{\text{Pol}}^{\text{PC}} = -5.43$ kcal mol^{−1}, and thus $\Delta E_{\text{Pol}}^{\text{PC}}$ constitutes 36% of ΔE^{PC} .

Returning to the comparison between ΔE^{PC} and ΔE_{Int} , there is a small but significant difference between the two in the region $3.5 < R < 5$ Å, with ΔE_{Int} being lower by at the most 1.5 kcal mol^{−1} ($R = 3.8$ Å). This difference can be attributed to contributions from polarization of Br[−] and dispersion

interactions, contributions that are short ranged in nature and that are not accounted for by the PC-model. However, at shorter R , ΔE_{Int} is beginning to level off, and at $R = 3.2$ Å, ΔE^{PC} becomes lower than ΔE_{Int} . This is partly an effect of charge penetration; the nuclei of CF_3Br , in particular Br, penetrate inside the electron density distribution of Br[−], resulting in a reduced shielding of the nucleus of Br[−] and higher Coulombic interaction energy [24, 25]. In addition, there is a repulsive contribution to ΔE_{Int} due to the Pauli antisymmetry requirement. Neither the charge penetration of Br[−] nor the Pauli repulsion are accounted for by the PC approximation, and hence the lower ΔE^{PC} compared to ΔE_{Int} at small R . In addition, there is the cost of deforming the structure of CF_3Br to its geometry in the complex, i.e., $\Delta E_{\text{Nuc-def}}$, which amounts to 1.1 kcal mol^{−1} and is missing from ΔE^{PC} . At the equilibrium geometry, ΔE^{PC} and ΔE_{Int} differ by 2.1 kcal mol^{−1}, and the values are −15.0 and −12.9 kcal mol^{−1}, respectively.

When comparing the PES of CBr_4-Br^- and $\text{CF}_3\text{Br}\cdots\text{Br}^-$, there are similarities but also significant differences in the behavior of the different energy terms. First of all, we note that the former interaction is significantly weaker at long R . This is due to a smaller electrostatic contribution to the interaction, i.e., higher $\Delta E_{\text{ES}}^{\text{PC}}$. However, $\Delta E_{\text{Pol}}^{\text{PC}}$ is consistently lower than for $\text{CF}_3\text{Br}\cdots\text{Br}^-$, resulting in CBr_4-Br^- having lower ΔE^{PC} (and ΔE_{Int}) than $\text{CF}_3\text{Br}\cdots\text{Br}^-$ at shorter distances. Comparing ΔE^{PC} and ΔE_{Int} of CBr_4-Br^- , these are again very similar at long R , but diverge in the intermediate region ($3.5 < R < 5$ Å). Compared to $\text{CF}_3\text{Br}\cdots\text{Br}^-$, the difference between the two energies in this region is larger, which can be attributed to larger contributions to ΔE_{Int} from polarization/induction of Br[−] and dispersion. Both effects can be attributed to the higher polarizability of CBr_4 compared to CF_3Br , which results in a stronger

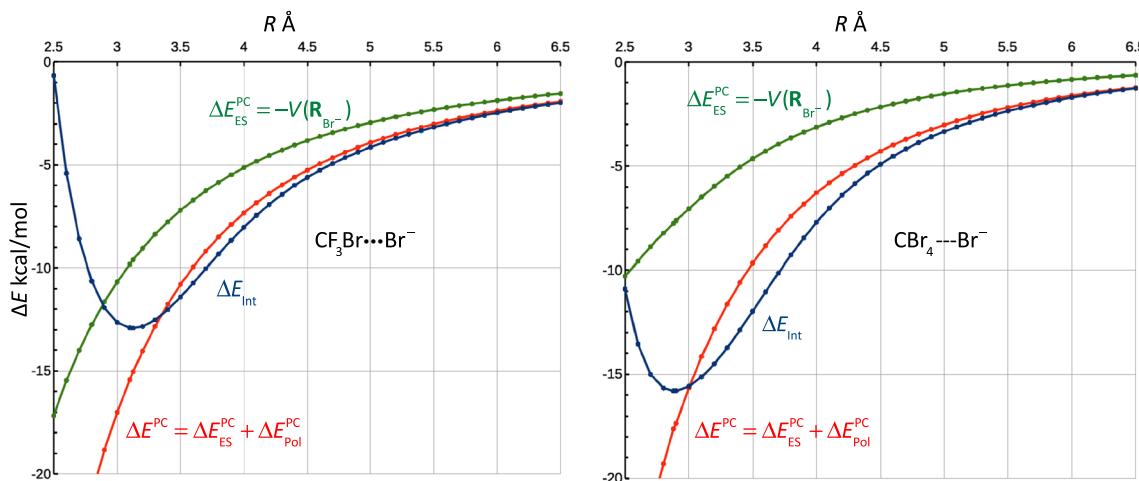


Fig. 1 The full quantum chemical interaction energy (ΔE_{Int}), together with the interaction energy of a point charge (ΔE^{PC}) located at the position of Br[−] and its electrostatic component ($\Delta E_{\text{ES}}^{\text{PC}}$), plotted as a

function of the Br–Br[−] distance (R) for the $\text{CF}_3\text{Br}\cdots\text{Br}^-$ and CBr_4-Br^- complexes. Note the much larger contribution from polarization, as defined by the difference $\Delta E_{\text{Pol}}^{\text{PC}} = \Delta E^{\text{PC}} - \Delta E_{\text{ES}}^{\text{PC}}$, in the latter complex

Table 1 Equilibrium Br–Br[−] distance (in Å) and different energy components^a (in kcal mol^{−1}) of the point charge interaction energy (ΔE^{PC}) and the quantum chemical interaction energy (ΔE_{Int}) for the halogen bond complexes

Complex	R_{BrBr}	$\Delta E_{\text{ES}}^{\text{PC}}$	$\Delta E_{\text{Pol}}^{\text{PC}}$	$\Delta E_{\rho-\text{def}}^{\text{PC}}$	ΔE^{PC}	$\Delta E_{\text{Nuc-def}}$	ΔE_{Int}
R–Br, R =							
CH ₂ NH ₂	3.45	4.2	−4.6	4.4	−0.5	1.0	0.0
CH ₃	3.40	3.5	−4.0	3.9	−0.5	0.1	−0.9
CH ₂ F	3.33	−0.7	−4.4	4.3	−5.1	0.3	−4.7
CH ₂ Br	3.23	−1.7	−5.6	5.4	−7.3	0.4	−6.6
CH ₂ CHO	3.22	−2.1	−5.6	5.4	−7.7	0.4	−7.3
CH ₂ CN	3.12	−4.6	−6.2	6.0	−10.8	0.5	−10.2
CH ₂ NO ₂	3.19	−6.1	−5.5	5.3	−11.6	0.6	−10.3
CF ₃	3.13	−9.6	−5.4	5.2	−15.0	1.1	−12.9
CBr ₃	2.88	−7.8	−9.9	9.5	−17.7	1.3	−15.8
CF ₂ CN	2.97	−12.1	−6.9	6.6	−18.9	1.0	−16.8
CF ₂ NO ₂	2.97	−14.6	−7.2	6.9	−21.8	1.3	−19.0
R′–C≡C–Br, R′ =							
NH ₂	3.24	−3.1	−5.5	5.4	−8.6	0.4	−7.3
H	3.20	−6.8	−5.4	5.3	−12.2	0.2	−10.8
ar-C ₆ H ₅	3.18	−5.6	−7.0	6.8	−12.6	0.2	−11.0
F	3.16	−8.1	−5.5	5.4	−13.6	0.5	−11.9
Br	3.15	−8.0	−6.4	6.2	−14.4	0.3	−12.6
ar-C ₆ F ₅	3.10	−10.8	−7.5	7.4	−18.4	0.4	−16.0
p-C ₆ H ₄ NO ₂	3.11	−11.0	−7.7	7.6	−18.7	0.4	−16.4
CN	3.05	−16.0	−7.2	7.0	−23.2	0.4	−20.5
NO ₂	3.02	−17.6	−7.2	7.1	−24.8	0.8	−21.7

^a The different energy components are defined in the main text. Energies are here reported with only one decimal place to increase the readability, but energies with two decimal places are used for plots and linear regressions

dispersion interaction and a higher (induced) dipole moment of CBr₄; the induction energy resulting from polarization of Br[−] is quadratically dependent on the effective dipole moment of the halogen bond donor. The dipole moment of the PC polarized halogen bond donor at the equilibrium geometry of the complex is 3.06 and 3.56 Debye for CF₃Br and CBr₄, respectively. Potentially, one could also envision a larger charge-transfer contribution to the CBr₄–Br[−] complex, but, as we will discuss later, we find no indication for such a term to be significant in these types of complexes.

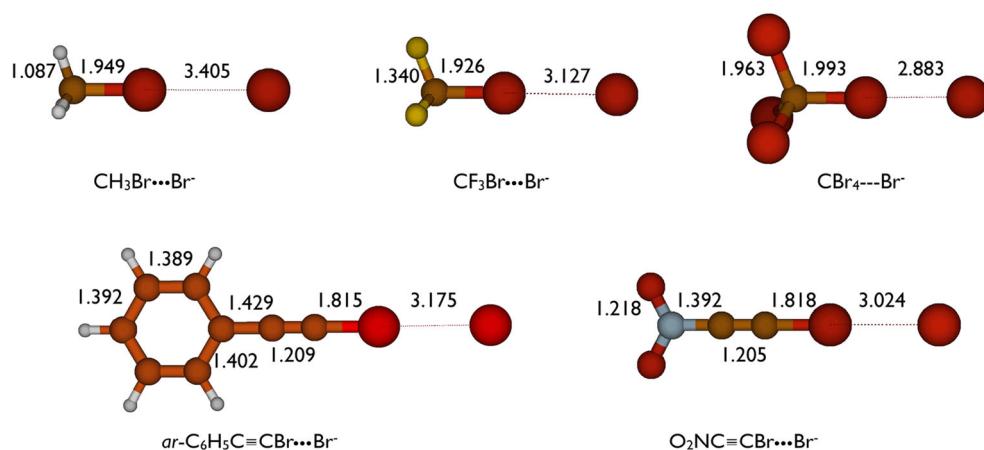
At the equilibrium geometry ($R = 2.88 \text{ \AA}$) of CBr₄–Br[−], ΔE^{PC} is 1.9 kcal mol^{−1} lower than ΔE_{Int} . This energy difference is very similar to the corresponding difference (2.1 kcal mol^{−1}) for CF₃Br••Br[−]. Thus, despite that the PC-model is approximate and only considers electrostatics and polarization, it reproduces the quantum chemical energy difference between the complexes; ΔE^{PC} and ΔE_{Int} of CBr₄–Br[−] are 17.6 and 15.8 kcal mol^{−1}, respectively, whereas the corresponding energies of CF₃Br••Br[−] are −15.0 and −12.9 kcal mol^{−1}. The results of the PC-model show that the lower complexation energy of CBr₄–Br[−] is entirely due to polarization ($\Delta E_{\text{Pol}}^{\text{PC}} = −9.9 \text{ kcal mol}^{-1}$), as

the electrostatic interaction ($\Delta E_{\text{ES}}^{\text{PC}} = −7.7 \text{ kcal mol}^{-1}$) is less favorable than for CF₃Br••Br[−] ($\Delta E_{\text{ES}}^{\text{PC}} = −9.61$). In the case of CBr₄–Br[−], $\Delta E_{\text{Pol}}^{\text{PC}}$ comprises 56% of ΔE^{PC} , which is much higher than the 36% contribution in CF₃Br••Br[−]. These results can be compared to the EDA results of Head-Gordon and co-workers for the analogous CF₃I••Br[−] and CBr₃I••Br[−] complexes [17]. They also found that the substitution of CF₃ by CBr₃ leads to a significant decrease in ΔE_{Int} . However, whereas Head-Gordon and coworkers attributed this result to charge transfer, our computations unambiguously show that the lower ΔE_{Int} of the brominated compound is a polarization effect.

Electrostatics and polarization determine the halogen bond energy

In Table 1 we list the different energy components of the PC-model together with the full quantum chemical interaction energy (ΔE_{Int}) for the entire set of halogen bonded complexes. Optimized geometries of selected complexes are presented in Fig. 2. We first note that the PC-model interaction energy generally is similar, albeit slightly larger, in magnitude to the

Fig. 2 Geometries of some representative complexes computed at the M06-2X/6-311+G(d,p) level of theory. Relevant interatomic distances are given in Angstrom



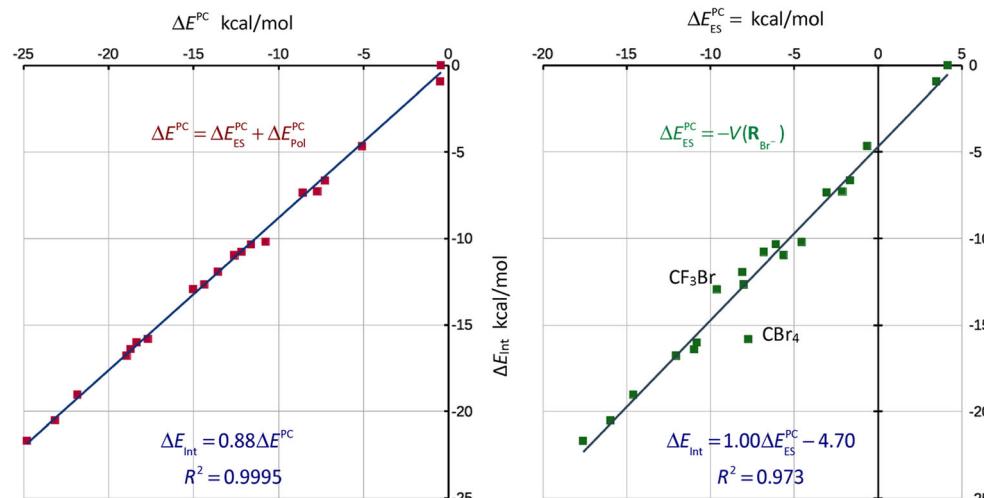
quantum chemical interaction energy (ΔE_{Int}) over the entire data set. There is an excellent linear relationship $\Delta E_{\text{Int}} = 0.88\Delta E^{\text{PC}}$ with a correlation coefficient of $R^2 = 0.9995$ and standard error in predicted ΔE_{Int} of 0.29 kcal mol⁻¹, as shown in Fig. 3. It should be remembered that ΔE^{PC} does not consider the cost of deforming the halogen bond donor to its geometry in the complex, and if $\Delta E_{\text{Nuc-def}}$ is added to ΔE^{PC} , the proportionality constant increases to 0.92 and R^2 decreases only marginally to $R^2 = 0.9990$.

The almost perfect correlation together with the slope being close to unity and the zero intercept show that the PC-model is able to reproduce the halogen bond interaction energy surprisingly well. The high quality of the correlation is remarkable considering that there are large variations in the chemical environment of the halogen bond donating Br. As indicated in the discussion of the PES of $\text{CF}_3\text{Br}\cdots\text{Br}^-$ above, there are energy contributions to ΔE_{Int} that are missing from ΔE^{PC} due to the PC approximation of Br^- . However, the correlation equation indicates that the sum of these contributions is a positive energy contribution that varies proportionality to ΔE_{Int} and typically amounts to around 8% of ΔE_{Int} . Thus, our results show that electrostatics and polarization are

sufficient to describe the variation in the halogen bond energy, and that charge transfer only has a marginal influence, at most, on the strength of the halogen bond.

Table 1 also lists the electrostatic interaction energy ($\Delta E_{\text{ES}}^{\text{PC}}$) and the polarization/induction energy ($\Delta E_{\text{Pol}}^{\text{PC}}$) for the entire data set, where the former is computed from the electrostatic potential at the position of Br^- and the latter using Eq. (7). Interestingly, the two components are on average of similar size; however, whereas $\Delta E_{\text{ES}}^{\text{PC}}$ varies between 4 and -18 kcal mol⁻¹, $\Delta E_{\text{Pol}}^{\text{PC}}$ varies less, and lies with the exception of $\text{CBr}_4\cdots\text{Br}^-$ (-9.9 kcal mol⁻¹) in the range of -4 to -8 kcal mol⁻¹. Figure 3 shows that there is a good linear correlation between ΔE_{Int} and $\Delta E_{\text{ES}}^{\text{PC}}$ ($\Delta E_{\text{Int}} = 1.00\Delta E_{\text{ES}}^{\text{PC}} - 4.7$) with an $R^2 = 0.973$. On the basis of this relationship, solely, one could easily make the interpretation that the interaction energy is dominated by electrostatics and has a nearly constant contribution from polarization of around -5 kcal mol⁻¹. However, the rationale for the correlation is not that the polarization contribution is nearly constant, as is obvious from Table 1, but that there is, when CBr_4 is excluded, a (weak) linear

Fig. 3 The graph to the left shows the excellent correlation between ΔE_{Int} and ΔE^{PC} for the entire data set of complexes of the types $\text{R}-\text{Br}\cdots\text{Br}^-$ and $\text{R}'-\text{C}\equiv\text{C}-\text{Br}\cdots\text{Br}^-$. The graph to the right shows the corresponding correlation between ΔE_{Int} and $\Delta E_{\text{ES}}^{\text{PC}}$, where $\Delta E_{\text{ES}}^{\text{PC}}$ is computed from the electrostatic potential at the position of the Br^- . The $\text{CF}_3\text{Br}-\text{Br}^-$ and CBr_4-Br^- complexes deviate the most from the correlation and their positions are indicated



correlation between $\Delta E_{\text{Pol}}^{\text{PC}}$ and $\Delta E_{\text{ES}}^{\text{PC}}$ with an $R^2 = 0.68$. This correlation can partly be explained by that a stronger interaction leads to a shorter Br \cdots Br distance, which lowers $\Delta E_{\text{Pol}}^{\text{PC}}$ due to the strong distance dependence of the polarization term. As an example, the weakest complex ($\text{NH}_2\text{CH}_2\text{Br}\cdots\text{Br}^-$) has a Br–Br distance of 3.45 Å and the strongest ($\text{NO}_2\text{—C}\equiv\text{C}\text{—Br}\cdots\text{Br}^-$) a distance of 3.02 Å. However, it should also be recognized that polarization reduces the electron density on the interacting Br and allows for a closer approach of the Br^- ; an example of this effect is the very short Br \cdots Br distance (2.88 Å) in $\text{CBr}_4\text{—Br}^-$, which also is the complex that has the lowest $\Delta E_{\text{Pol}}^{\text{PC}}$ of $-9.9 \text{ kcal mol}^{-1}$.

When we analyze the data for the substituted methyl bromide (R–Br) donors, there seems to be a general trend that $\Delta E_{\text{ES}}^{\text{PC}}$ is determined by the sum of the electron-withdrawing capacities of the substituents, i.e., substituents like F, CN, and NO_2 reduce $\Delta E_{\text{ES}}^{\text{PC}}$ in that order. The $\Delta E_{\text{ES}}^{\text{PC}}$ of the monosubstituted systems follows the same order as the Hammett σ_p constant. On the other hand, $\Delta E_{\text{Pol}}^{\text{PC}}$ decreases with increasing polarizability of the substituents, i.e., in the order $\text{H} \approx \text{F} < \text{NH}_2 < \text{CN} < \text{NO}_2 < \text{Br}$. Although, it may seem trivial that $\Delta E_{\text{Pol}}^{\text{PC}}$ should follow the polarizability of the substituents, the effect is much larger than would be expected from a through-space interaction, and this large substituent effect is a consequence of the polarization being mediated by the covalent bonds. In the case of $\text{CBr}_4\text{—Br}^-$, the substituent effect on $\Delta E_{\text{Pol}}^{\text{PC}}$ is larger than anticipated based on an additive contribution from the Br substituents. This can be attributed to the anomeric effect, which is present when several halogens of the same type are bonded to a carbon, and has been described by Clark and coworkers [12, 26].

We now turn to the data of the acetylenic Br donors, i.e., the complexes of the type R $'\text{—C}\equiv\text{C}\text{—Br}$. It can first be noted that the electrostatic interaction in general is more favored ($\Delta E_{\text{ES}}^{\text{PC}}$ is much lower) in comparison with the R–Br donors. This shows that the $\text{—C}\equiv\text{C}\text{—}$ functionality in itself has a strong electron withdrawing effect. This effect is further augmented by the substituent due to resonance interactions. Resonance electron acceptors generally have a similar quantitative effect on the $\Delta E_{\text{ES}}^{\text{PC}}$ as the same substituent on the R–Br donors, e.g., a NO_2 group lowers $\Delta E_{\text{ES}}^{\text{PC}}$ by around 10 kcal mol $^{-1}$ in both systems. Another example of the importance of resonance is the lower $\Delta E_{\text{ES}}^{\text{PC}}$ of the $p\text{-C}_6\text{H}_4\text{NO}_2$ substituent compared to a plain phenyl (C_6H_5) group. However, the effect of the NO_2 is only 5 kcal mol $^{-1}$ and thus half of the effect of an NO_2 attached directly to $\text{—C}\equiv\text{C}\text{—Br}$. In general, the $\Delta E_{\text{Pol}}^{\text{PC}}$ values are lower compared to the corresponding values for the R–Br donors. This can mainly be attributed to the R $'\text{—C}\equiv\text{C}\text{—Br}$ complexes being more stable and having shorter Br–Br distances due to the stronger electrostatic interaction. However, the substituent effects on $\Delta E_{\text{Pol}}^{\text{PC}}$ are similar in the

two types of complexes, with $\Delta E_{\text{Pol}}^{\text{PC}}$ decreasing with increasing polarizability of the substituent. Also here, we find that the substituent effect on $\Delta E_{\text{Pol}}^{\text{PC}}$ is mediated via the covalent bonds, and for the R $'\text{—C}\equiv\text{C}\text{—Br}$ complexes the bond-mediation is enhanced because of the conjugation.

In Table 1, we also list the density deformation energies, $\Delta E_{\rho\text{-def}}^{\text{PC}}$, and the values follow linear response closely, i.e., $\Delta E_{\rho\text{-def}}^{\text{PC}} \approx -\Delta E_{\text{Pol}}^{\text{PC}}$. This supports the interpretation that these interactions are governed by classical electrostatics and polarization. In general, the $\Delta E_{\rho\text{-def}}^{\text{PC}}$ values are around 0.2 kcal mol $^{-1}$ lower than the values that would correspond to an exact linear response behavior. This may seem surprising, as nonlinear contributions to the polarization are expected to lead to $\Delta E_{\rho\text{-def}}^{\text{PC}} > -\Delta E_{\text{Pol}}^{\text{PC}}$. However, there is also an energy cost ($\Delta E_{\text{Nuc-def}}$) for deforming the geometry of halogen bond donor to its geometry in the complex, and it can be expected that this deformation facilitates the polarization of the halogen bond donor and lowers $\Delta E_{\text{Pol}}^{\text{PC}}$.

Finally, we turn to the nuclear deformation energy ($\Delta E_{\text{Nuc-def}}$) of the complexes, which varies between 0.1 and 1.3 kcal mol $^{-1}$. Although, it is difficult to fully rationalize the variation of this quantity, some trends can be observed. First of all, we note, following the discussion of $\Delta E_{\rho\text{-def}}^{\text{PC}}$ from above, that those complexes which have the largest $\Delta E_{\text{Nuc-def}}$ also deviate the most from $\Delta E_{\rho\text{-def}}^{\text{PC}} = -\Delta E_{\text{Pol}}^{\text{PC}}$. Thus, this supports the hypothesis that a significant driving force for the nuclear deformation is to facilitate polarization and thereby maximize the Coulombic interaction between Br^- and the halogen bond donor. Secondly, some substituents, e.g., halogens, NH_2 , and NO_2 , generate larger $\Delta E_{\text{Nuc-def}}$ values than others, e.g., aromatic substituents and H. Thirdly, the R–Br \cdots Br $^-$ complexes generally have higher values than the corresponding R $'\text{—C}\equiv\text{C}\text{—Br}\cdots\text{Br}^-$ complexes. However, even though the variation in $\Delta E_{\text{Nuc-def}}$ is significant, the magnitude of $\Delta E_{\text{Nuc-def}}$ is generally small compared to the total interaction energy. This can be seen as a confirmation of the noncovalent character of these complexes, as it can be expected that a significant covalent contribution to the interactions would be accompanied with a larger $\Delta E_{\text{Nuc-def}}$.

Summary and concluding discussion

In this article, we found that the PC-model accurately describes the variations of the halogen bond interaction energy for a diverse group of halogen bond donors and their complexes with Br $^-$. The analysis of the PES of $\text{CBr}_4\text{—Br}^-$ and $\text{CF}_3\text{Br}\cdots\text{Br}^-$ shows that ΔE_{Int} and ΔE^{PC} are very similar at Br–Br $^-$ distances (R) larger than twice the equilibrium distance (R_{eq}). In the region $1.8 R_{\text{eq}} > R > 1.1 R_{\text{eq}}$, ΔE_{Int} is slightly lower than ΔE^{PC} due to energy contributions from polarization of Br $^-$ and

dispersion. At $R < 1.1 R_{\text{eq}}$, ΔE_{Int} begins to level off because of increasing charge penetration and Pauli repulsion. At R_{eq} , the sum of the four energy contributions is a positive energy contribution that typically amounts to around 8% of ΔE_{Int} . The remaining part of ΔE_{Int} is determined by ΔE^{PC} with the exception of a small contribution from $\Delta E_{\text{Nuc-def}}$. This is demonstrated by an excellent linear relationship ($R^2 = 0.999$) with a slope of 0.92, and a zero intercept, between ΔE_{Int} and $(\Delta E^{\text{PC}} + \Delta E_{\text{Nuc-def}})$ for the entire group of halogen bond donors. It should be remembered that charge transfer is completely absent from the PC-model, as there are no electrons than can be transferred to the halogen bond donor. Thus, the results of this study strongly indicate that charge transfer is of negligible importance for halogen bonding.

The analysis of halogen bonding interaction using the PC approximation has the added advantage that the interaction energy can be rigorously separated into electrostatics and polarization. Our results emphasize the important role of polarization in halogen bonding. Within the data set, $\Delta E_{\text{ES}}^{\text{PC}}$ varies between 4 and $-18 \text{ kcal mol}^{-1}$, whereas $\Delta E_{\text{Pol}}^{\text{PC}}$ varies between -4 and $-10 \text{ kcal mol}^{-1}$. In six out of 20 complexes, polarization contributes more strongly than electrostatics to the strength of the halogen bond, i.e., $\Delta E_{\text{Pol}}^{\text{PC}} < \Delta E_{\text{ES}}^{\text{PC}}$, and two of these would be unbound without polarization. The analysis further shows that the generally large polarization effect of the studied complexes cannot solely be attributed to the large polarizability of the Br atom, as the polarization is found to be bond-mediated and strongly dependent on the polarizability of the substituents; this effect is particularly pronounced for the $\text{R}'-\text{C}\equiv\text{C}-\text{Br}$ compounds where the bond-mediated polarization is found to be enhanced due to the conjugation. The very low $\Delta E_{\text{Pol}}^{\text{PC}}$ ($-9.9 \text{ kcal mol}^{-1}$) of CBr_4-Br^- is partly attributed to the anomeric effect that comes from having several Br bonded to the same C. However, despite the resonance enhanced substituent effects on $\Delta E_{\text{Pol}}^{\text{PC}}$, we found $\Delta E_{\text{Pol}}^{\text{PC}}$ to follow classical polarization with a linear response behavior with respect to the electric field.

We have shown that the difference in ΔE_{Int} between the $\text{CF}_3\text{Br}\cdots\text{Br}^-$ and CBr_4-Br^- complexes can be unambiguously rationalized in terms of the much lower $\Delta E_{\text{Pol}}^{\text{PC}}$ of the latter. This is in sharp contrast to the results of Head-Gordon and coworkers on the analogues $\text{CF}_3\text{I}\cdots\text{Br}^-$ and $\text{CBr}_3\text{I}\cdots\text{Br}^-$ complexes; they found the stronger interaction of the CF_3 substituted compound to be the result of a lower charge transfer energy [18]. We can only speculate on the reasons for the discrepancy between the results. It should be noted, however, that in the energy decomposition analysis (EDA) used by Head-Gordon the charge transfer energy is computed as the remaining part of the interaction energy when all other components have been subtracted out. Thus, in the hypothetical case that the EDA is not able to

completely describe the polarization effect, the missing part of the polarization energy will end up as a contribution to the charge transfer energy. Another reason for the discrepancy could potentially be that the $\text{CX}_3\text{I}\cdots\text{Br}^-$ complexes are very different in their behavior from the $\text{CX}_3\text{Br}\cdots\text{Br}^-$ complexes. However, a preliminary analysis using the PC-model confirms that the lower ΔE_{Int} of $\text{CBr}_3\text{I}\cdots\text{Br}^-$ compared to $\text{CF}_3\text{I}\cdots\text{Br}^-$ is an effect of the stronger polarization in the former complex.

We would also like to comment on the fact that Clark and Heßelmann in their study [12] were able to correlate ΔE_{Int} with the surface electrostatic potential maximum obtained from the polarized density alone, whereas Eq. 3 shows that the (unpolarized) electrostatic potential and the polarized potential contribute equally by a factor of 0.5 to the interaction energy. The reason for the successful correlation is probably the relatively small variation in the surface electrostatic potential maximum among the studied halogen bond donors in their study, and thus it is likely that the influence of the (average) electrostatic potential is accounted for by the intercept. It is indeed noteworthy that the slope of 0.43 in front of the polarized potential in the Clark and Heßelmann study is very similar to our proportionality constant of 0.88, from the ΔE_{Int} and ΔE^{PC} correlation, multiplied by the factor 0.5.

Finally, we would like to emphasize the advantage of using simple and at the same time physically relevant models when analyzing intermolecular interactions. In this study, charge transfer could be ruled out, as the PC-model accurately reproduces the halogen bond energy without having electrons that can be transferred. Furthermore, we were able to rigorously separate electrostatics from polarization and thereby demonstrate the high importance of polarization for the halogen bond. In an upcoming study we intend to use the same approach to investigate the character of the hydrogen bond to shed light upon the differences and similarities of halogen and hydrogen bonding.

Acknowledgments We would like to thank Tim Clark and his coauthors Jane Murray and Peter Politzer for continuously challenging our thinking and understanding of the halogen bond and intermolecular interactions. The original goal of this study was to demonstrate the importance of charge transfer for halogen bonding, but the results proved our hypothesis wrong. It feels appropriate to cite Newton, *if I have seen further it is by standing on the shoulders of Giants*.

Financial support of this study has been provided by the VR (Swedish Research Council), and computational time by the Swedish National Infrastructure for Computing (SNIC) at the National Supercomputer Centre in Linköping University as well as at the PDC Centre for High Performance Computing (PDC-HPC).

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