

Halogen Bonding | Hot Paper |

Refined SMD Parameters for Bromine and Iodine Accurately Model Halogen-Bonding Interactions in Solution

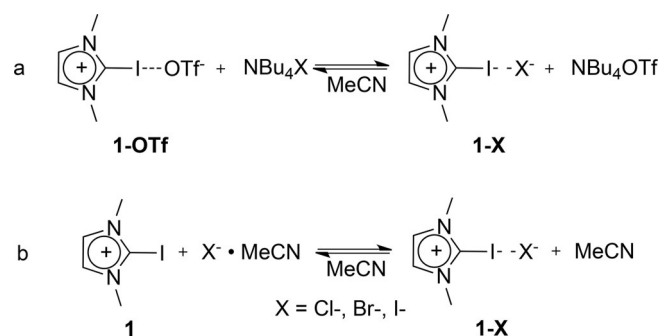
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Abstract: Motivated by the need to calculate liquid-phase free energies of species and equilibria involving halogen bonding, recent experimental data were used to optimize new Coulomb radii for Br and I for use in the SMD universal solvation model for calculating free energies of solvation. The use of the SMD model with these parameters for Br and I and the SMD values of all other parameters is called SMD18. After parametrization, the SMD18 model was tested for data not used in the parametrization. These data are standard-state free energies (equivalent to equilibrium constants) for 18 ionic equilibria involving Cl, Br, and I halogen bonding in acetonitrile, and the agreement of theory and experiment is satisfactory. The SMD18 model is then used to compare hydrogen bonding to halogen bonding and to reassess the interpretation of recent experiments.

Halogen bonding describes the noncovalent interaction between electrophilic halogen substituents and Lewis bases.^[1] Since the late 1990s, it has played a major interpretive role in understanding crystal structures^[2] and has recently also been employed for an increasing number of applications in solution,^[3] including its use in organocatalysis.^[4] In the latter case, one approach is to remove halides from S_N1-type equilibria by the formation of halogen-bonded complexes, often with cationic halogen bond donors (halogen-based Lewis acids). With increased focus on the relevance of this fundamental interaction, thermodynamic binding data have become available for various halogen-bonded complexes, obtained either by NMR analysis or by isothermal titration calorimetry (ITC).^[5]

Computational modeling has the potential to play a key role in the design of improved receptors and catalysts that involve halogen bonding. Considering such interactions in the gas phase, the M06-2X density functional^[6] has previously been documented to provide good agreement with converged quantum chemical benchmarks.^[7,8] In solution, however, differential solvation effects associated with complexes and separated species may well be of similar magnitude to halogen-bonding interactions themselves, and thus they may play a critical role in dictating association constants. The SMD solvation model has seen extensive use since its introduction in 2009,^[9] and its general accuracy for the prediction of solvation free energies for uncharged and ionic solutes in both aqueous and organic solvents is about ±1 and ±4 kcal mol⁻¹, respectively.^[9-11] In this work, we first report application of the SMD model to study halogen bonding interactions of halides with iodoimidazolium ions^[12] in acetonitrile. Then we use calorimetric data for a small training set to refine the SMD Coulomb radii for Br and I, and we show that the refined model exhibits excellent performance on a subsequent test set, suggesting that it should have general utility for future studies of halogen bonding in solution.

The test set employed is shown in Scheme 1(a) and comprises the binding free energies of chloride, bromide, and iodide,



Scheme 1. Halide complexation by iodoimidazolium salts.

all titrated into acetonitrile solution as their corresponding tetrabutylammonium salts, with *N,N'*-dimethyliodoimidazolium triflate. The relevant 298.15 K binding free energies have been measured from isothermal titration calorimetry^[5] as -21.4, -19.3, and -16.1 kJ mol⁻¹, respectively (see Supporting Information).

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In order to model the binding event itself, we considered the reaction shown in Scheme 1(b). Moving from (a) to (b) is equivalent to considering the triflate and tetrabutylammonium ions to be fully separated from *any* counterions in acetonitrile solution, and further recognizes that modeling the monatomic halide ion as a supersolute complex including a single acetonitrile solvent molecule (when the former is *not* engaged in a halogen bond with **1**) is consistent with best practice for modeling the solvation of small, highly charged ions with the continuum solvation models.^[13] All substrates were fully optimized, including SMD continuum solvation, at three recommended^[7] levels of density functional theory for halogen bonding, namely, M06-2X,^[6] B97-1,^[14] and ω B97X-D.^[15,16]

In the first phase ((re)optimization of SMD radii), the def2-TZVPPD basis set was used for all atoms (including its associated effective core potential for I) when computing electronic energies.^[17] In the second phase (validation of SMD with optimized radii for other halogen-bonding complexes), the def2-TZVP basis set was used for all atoms except the halogens (which were treated with def2-TZVPD and its associated effective core potential for I) because convergence problems were encountered with the first-mentioned basis. Free energies in solution were computed by summing electronic energies, thermal contributions from gas-phase translation, rotation, and vibration, solvation free energies, and standard-state concentration corrections from the gas phase to 1 M for all solutes other than uncoordinated MeCN as the product of reaction b of Scheme 1 (a concentration of 18.8 M was used for MeCN as solvent). The particle-in-a-box, rigid-rotator, quantum-mechanical harmonic-oscillator (QMHO) partition functions were used to compute gas-phase thermal contributions, except that for frequencies below 100 cm⁻¹ the approach of Grimme^[18] was employed to correct for the known deficiency of the QMHO approximation for very low frequencies. In all cases, the temperature of the respective ITC measurements (298.15 or 303.15 K, see below) was used for the thermal corrections. The utility of gas-phase partition functions in combination with the SMD solvation model for computing free energies in solution has been previously demonstrated.^[19] All calculations were run with Gaussian 09.^[20]

In the SMD solvation model, each atom has a defined Coulomb radius, which is the radius defining a sphere that, when combined with analogous (usually overlapping) spheres for all other atoms in a given molecule, establishes the boundary between the quantum mechanical interior characterized by a dielectric constant of 1 and the surrounding continuum characterized by the dielectric constant of the bulk solvent. However, when originally parametrized in 2009,^[9] no molecules containing iodine were included, and the iodine Coulomb radius was set (as a placeholder) to its Bondi van der Waals radius of 1.98 Å.^[21] Exploratory calculations of the binding free energies in Scheme 1(b) immediately indicated that this radius was much too small, and we instead began by setting it to 2.74 Å, a value optimized for the SM1 solvation model which was parameterized for molecules containing iodine in 1991.^[22] With all other parameters set at default SMD values, we obtained the

results shown in Table 1 (rows 2–4) for the three halogen-bonding free energies in Scheme 1(b).

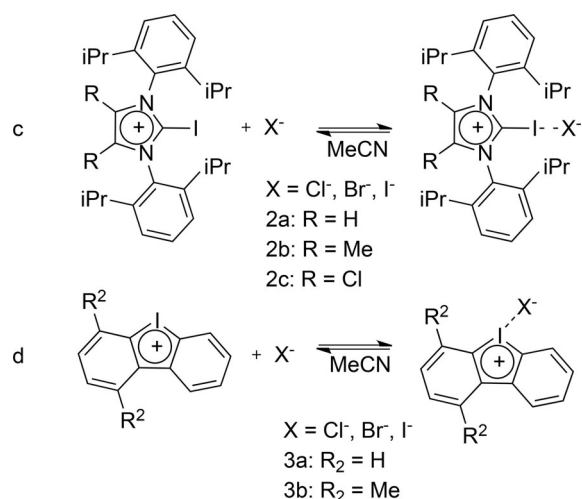
Table 1. Experimental and computed 298.15 K free energies (kJ mol⁻¹) for reactions in Scheme 1(b).^[a]

Coulomb radii	Method	X = Cl ⁻	X = Br ⁻	X = I ⁻
$r_{\text{Cl}}, r_{\text{Br}}, r_{\text{I}}$ [Å]	Experiment	-21.4	-19.4	-16.2
2.38, ^[b] 3.06, ^[b] 2.74 ^[c]	M06-2X	-22.3 (0.9) ^[b]	-31.9 (12.5)	-16.6 (0.4)
	B97-1	-26.8 (5.4)	-37.9 (18.5)	-21.5 (5.3)
	ω B97X-D	-20.1 (1.3)	-27.6 (8.2)	-5.3 (10.9)
2.38 ^[b] 2.60, 2.74, ^[c]	M06-2X	-22.3 (0.9) ^[d]	-19.6 (0.2) ^[d]	-16.6 (0.4) ^[d]

[a] Unsigned errors in parentheses. [b] Original (placeholder) SMD value. [c] Value taken from SM1 (ref. [22]). [d] This row corresponds to SMD18.

Table 1 shows that the results for Cl⁻ obtained using its default SMD radius of 2.38 Å, together with the chosen radius for iodine of 2.74 Å, are in quite good agreement with experiment for all three functionals. In the case of I⁻, good agreement is also observed for M06-2X and B97-1 using the 2.74 Å radius, but it appears that ω B97X-D does less well for the *gas-phase* component of this binding free energy (as the various solvation free energies computed at this level of theory are essentially identical to those from the other two functionals). For Br⁻, by contrast, all 3 functionals showed considerably larger errors, all of which would be consistent with the predicted solvation free energy of Br⁻·MeCN being underestimated. Considering that the default SMD radius for Br was 3.06 Å—larger than that for I—we considered alternative radii from 2.38 to 2.85 Å (the values previously employed in SM1^[22] and SM8^[23]). We found that a value of 2.60 Å minimized the error for the binding free energy with M06-2X, which we chose to take as our optimal functional based on its superior performance for the Cl and I cases. We also surveyed small variations in the radius for I, but found that the original choice of 2.74 Å was (fortuitously) optimal. As shown in the final row of Table 1, using the refined radii with M06-2X reduces the mean unsigned error of the three binding free energies to 0.6 kJ mol⁻¹, which is startlingly good agreement with experiment, even though the test set is small. The use of the SMD model with these new Coulomb radii for Br and I and the original values for all other parameters will be called SMD18.

In order to assess the utility of the refined Br and I radii further, we computed the binding free energies for 15 other halogen-bonding equilibria in acetonitrile (Scheme 2) with M06-2X as the density functional. Nine of these cases still involve an iodoimidazolium ion (**2a–c**) as one partner in the equilibria, albeit with different substituents than in **1**, while for the remaining six cases the cation is a hypervalent dibenziodolium ion (**3a,b**). The computed binding free energies are compared to experiment in Table 2.^[24] The mean unsigned error over this test set is 3.7 kJ mol⁻¹ and the maximum error is 8.1 kJ mol⁻¹, which we consider to be quite good performance, especially considering that the mean unsigned error in computed SMD ionic solvation free energies themselves in polar solvents is on the order of 17 kJ mol⁻¹.^[9]



Scheme 2. Additional halogen-bonded complexes used as test cases for SMD18 (experiment involved **2a–c** as BARF salts and **3a,b** as triflate salts).

With a validated model in hand, we are in a position to consider a question that can arise in the study of halogen bonding: what are the relative strengths of halogen bonding to halide ions as compared to hydrogen bonding to hydrogen atoms of the same Lewis acid? We have examined this for the particular cases of **1**, **2a**, and **2b**, where the relevant hydrogen atoms are found at the “back” of the heterocycle. For **1** and **2b**, we have also examined the energetics associated with anion– π interactions with the halides. The relevant optimized geometries are shown in Figure 1.

The computed binding free energies for hydrogen bonding for **1**, **2a**, and **2b** are 5.1, 7.8, and 10.6 kJ mol^{−1} (see Supporting Information). These are all positive values, indicating that at standard-state concentrations of 1 M, the complex would be disfavored relative to the separated reactants, although a local minimum exists on the potential-of-mean-force surface.^[25] This is clearly in stark contrast to the negative binding free energies associated with the alternative halogen bonding (Table 1), and inconsistent with prior results from MD simulations using classical force fields.^[24a] The computed binding free energies for anion– π bonding for **1** and **3b** are 0.2 and −0.7 mol^{−1} (see SI), and no stable minimum featuring this interaction could be found for other substrates. This agrees with the same earlier MD study^[24a] which concluded that anion– π interactions can be ruled out.

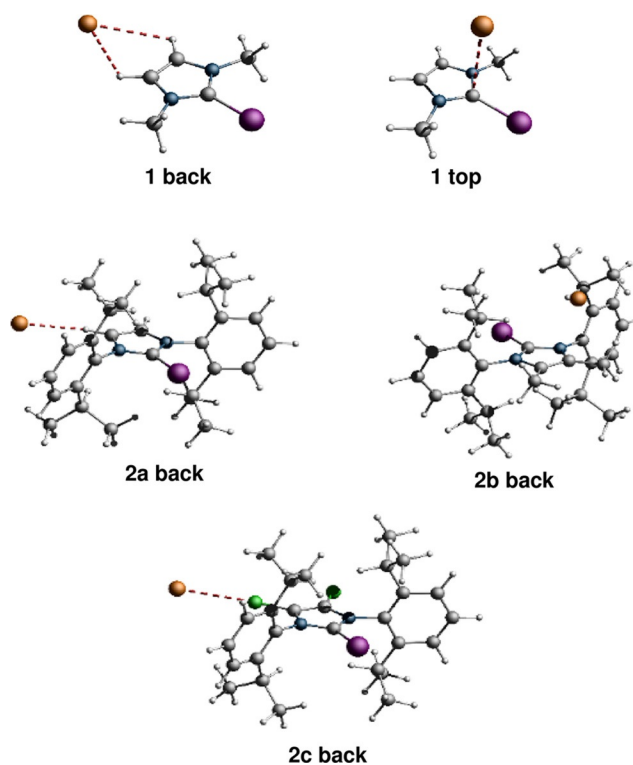


Figure 1. M06-2X/SMD18 optimized geometries for various binding modes of Br[−] to **1**, **2a–c**. Atom colors are light gray (H), dark gray (C), steel blue (N), green (Cl), gold (Br), and violet (I).

A closer inspection of the results provided in Table 2 reveals that theory predicts **3a** to bind chloride more strongly than bromide (or iodide), which is in agreement with the trend seen for all other substrates (see for example, the halide complexes of **2a–2c**). The experiment for **3a**, by contrast, shows a stronger binding for bromide compared to chloride. This casts some doubt on the experimental value, and indeed, it was noted in the original publication^[24b] (page S9 of the corresponding Supporting Information) that the fit of the isotherm “...deviates somewhat from the experimental values for molar ratios > 1 for unknown reasons. This behavior occurred reproducibly with multiple runs, and no better fit could be obtained...” (Figure 2). This provides a useful example, then, of how the computational model can be used in conjunction with experiment to assess the confidence with which specific measurements should be interpreted.

Table 2. Experimental and computed binding free energies (kJ mol^{−1}) for the equilibria in Scheme 2.^[a]

Halide	Method	1b	2a	2b	2c	3a	3b
Cl [−]	expt	−21.4	−26.1	−23.9	−30.2	−36.0	−32.2
	theor	−22.5 (1.1) ^[d]	−18.8 (7.3)	−19.2 (4.7)	−32.1 (1.9)	−41.1 (5.1)	−39.7 (7.5)
Br [−]	expt	−19.4	−23.3	−21.7	−28.2	−36.8	−31.0
	theor	−20.5 (1.1)	−18.2 (5.1)	−18.1 (3.6)	−31.0 (2.8)	−36.6 (0.2)	−35.0 (4.0)
I [−]	expt	−16.2	−20.9	−19.1	−24.9	−29.7	−25.9
	theor	−16.2 (0.0)	−12.8 (8.1)		−24.6 (0.3)	−29.1 (0.6)	−26.6 (0.7)

[a] Experiment at 303.15 K unless otherwise specified. Theory by M06-2X/def2-TZVPD/SMD18 with gas-phase components computed at $T=303.15$ K unless otherwise specified. [b] $T=298.15$ K. [c] Values in parentheses are unsigned errors.

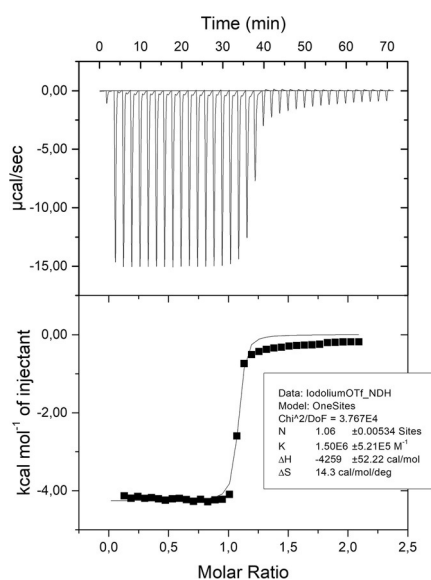


Figure 2. ITC results for **3a** as given in ref. [24b].

We anticipate that the SMD18 model, that is, SMD with new Coulomb radii for Br and I, will be useful for future modeling in systems designed to exploit halogen bonds with tuned strengths.^[26] Considering the impact of the new radii proposed here on bromine- and iodine-containing solutes in general, compared to the original SMD model, we emphasize that for iodine, there are no prior applications against which to compare, and the previous default radius was simply a placeholder. For bromine, the most sensitive case possible is the bromide anion. On going from the old to the new SMD radius, the solvation free energy of Br⁻ in MeCN changes from -225.8 to -257.5 kJ mol⁻¹, which actually reflects an improvement when compared to the experimental value of -248.1 kJ mol⁻¹.^[27] Considering neutral solutes containing bromine, they typically have electrostatic components of solvation free energies no more than 10% as large as the bromide anion, suggesting that variations in their solvation free energies would be expected to be at most 3 kJ mol⁻¹ (and likely less, as bonded bromine atoms are less solvent exposed than the isolated bromide anion). As an error of this magnitude is within the error of the SMD model in general for neutral solutes, we do not see a need for a full reoptimization of all other SMD18 parameters at this time, although if further refinements continue to be undertaken, such an effort may be worthwhile in the future.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: halogen bonding · halogens · intrinsic solvation model · nitrogen heterocycles · supramolecular chemistry

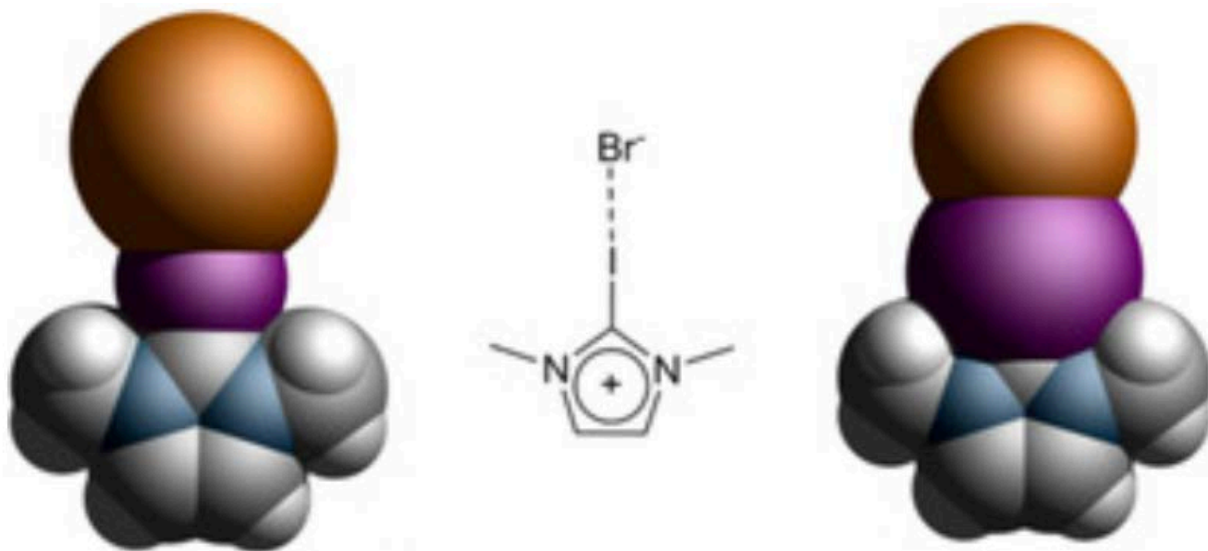
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Experimental data on halogen bonded complexes has been used to reoptimize the iodine and bromine radius in the SMD intrinsic solvation model. Subsequent testing of this new SMD18 model on several ionic equilibria provided very good agreement between experiment and theory.