Supporting Information

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SI Text

In Table S1, the computational estimates are obtained as follows. The reactant and product molecular configurations are first relaxed separately at the Perdew–Burke–Ernzerhof + van der Waals (PBE+vdW) level of theory (1), using the all-electron program package FHI-aims program package (2). We used tight settings for the numeric atom-centered orbital basis sets and integration grids, as explained elsewhere (2). Following relaxation, the complex geometries are subjected to a single point calculation using the hybrid PBE0 (3, 4) +vdW functional, which yields their electronic energies, E. The Gibbs free energy of each complex is then estimated using the ideal gas thermodynamic relationship, $G = F + k_B T$, where k_B is the Boltzmann constant, $T = 298$ K, and F is the Helmholtz free energy. Assuming that the coupling between translational, vibrational, and rotational degrees of freedom can be neglected, F is estimated as a sum of their independent contributions (5); that is, $F = F_{trans} + F_{vib} + F_{rot}$, where

$$F_{trans} = -k_B T \left[\ln \left(\frac{mk_B T}{2\pi\hbar^2} \right)^{3/2} + \ln \frac{k_B T}{P} + 1 \right],$$

$$F_{vib} = E + \sum_{i}^{3N-6} \left[\frac{\hbar\omega_i}{2} + k_B T \ln \left(1 - \exp^{-\frac{\hbar\omega_i}{k_B T}} \right) \right],$$

and

$$F_{rot} = -\frac{3}{2} k_B T \ln \left[\frac{2k_B T}{\hbar^2} (I_A I_B I_C)^{1/3} \pi^{1/3} \right].$$

In the expressions above, N is the number of atoms in the molecule; I_A, I_B, and I_C are the molecular moments of inertia; $P = 1$ atmosphere; m is the molecular mass; and ω_i are the harmonic vibrational frequencies obtained from a Hessian analysis of the PBE+vdW energy surface. The reaction free energy changes, ΔG, are then obtained by subtracting the free energies of reactant complexes from the product complexes; that is, $\Delta G = \sum n_p G_p - \sum n_r G_r$, where n_p and n_r are the stoichiometries of the products and reactants. We find that computed values agree with experiments. The inclusion of dispersion vdW interactions is crucial, as shown by the amount of dispersion energy, $\Delta E_{vdW} = \Delta E_{PBE0+vdW} - \Delta E_{PBE0}$, in each computed reaction free energy change in Table S1.

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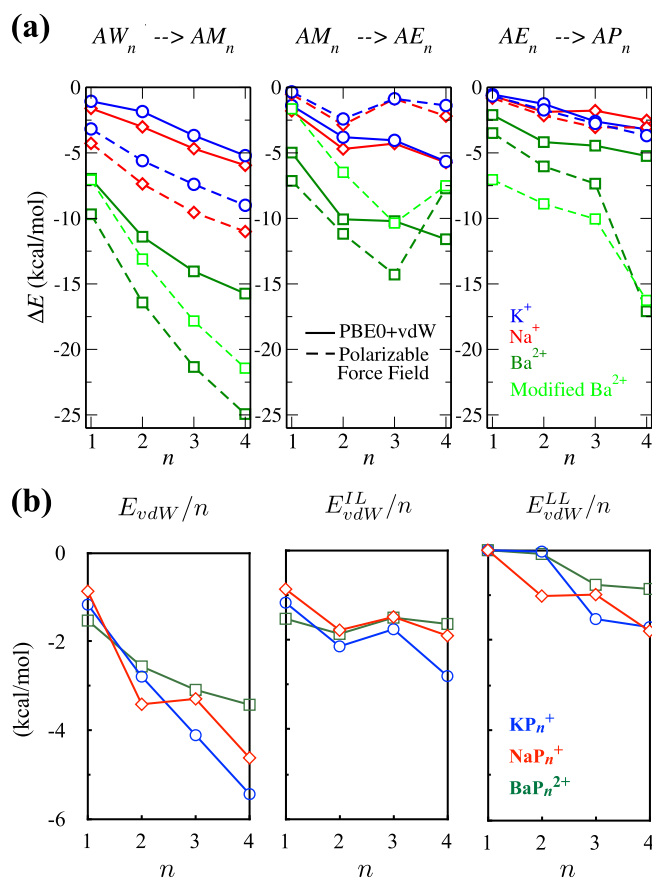
Fig. S1. (*A*) Comparison of substitution reaction energy change (Δ*E*) obtained from PBE+vdW (1) and a polarizable force field (2–4). The Δ*E* values are estimated for the substitution reactions studied in Fig. 2, and they are computed using geometries relaxed separately at the respective levels of theory. Geometry relaxations using PBE+vdW are carried out using the FHI-aims program (5) as described in *Materials and Methods*, and relaxations using the polarizable force field are carried out using the optimize algorithm of TINKER v6.2 (available at http://dasher.wustl.edu/ffe/) with an rms gradient cutoff of 0.001 kcal/mol/Å. Note that we use two separate parameter sets for Ba^{2+}, one taken from TINKER v4.3 (6) and the other (Ba^{2+} modified) in which we reduced the Ba^{2+} damping factor fivefold from 0.39 to 0.078, as suggested by Piquemal et al. (7) and Ponder et al. (8). We find that although a polarizable force field can reproduce the PBE0+vdW trends, the quantitative differences can be large. (*B*) To understand the origin of these differences, we examine one specific energetic contribution that is not modeled explicitly in the polarizable force field. The atomic C_6 dispersion coefficients are kept fixed in the polarizable force field. In contrast, the C_6 coefficients are variables in the PBE+vdW method that depend on self-consistent electron densities. For example in the ion–propanol complexes, we find that the C_6 coefficients of Na^+, K^+, and Ba^{2+} vary by factors of ∼8, ∼5, and ∼3, respectively. To understand the energetic consequences of such variations in C_6 coefficients in ion–propanol complexes, we divide the total dispersion energy (E_{vdW}) into intraligand (E_{vdW}^L), ligand–ligand (E_{vdW}^{LL}), and ion–ligand (E_{vdW}^{IL}) contributions. We define for a given geometry AP_n, $E_{vdW}(AP_n) = E_{PBE0+vdW}(AP_n) - E_{PBE0}(AP_n)$, $E_{vdW}^L(AP_n) = n \times (E_{PBE0+vdW}(P) - E_{PBE0}(P))$, $E_{vdW}^{LL}(AP_n) = E_{PBE0+vdW}(P_n) - E_{PBE0}(P_n) - E_{vdW}^L(AP_n)$, and $E_{vdW}^{IL}(AP_n) = E_{vdW}(AP_n) - E_{vdW}^{LL}(AP_n) - E_{vdW}^L(AP_n)$. We find that E_{vdW}^{IL} increases nonlinearly with the number of propanols in the complex and that, in fact, the E_{vdW}^{IL} values are correlated strongly with the ion C_6 coefficients (Pearson correlations >0.96). This suggests that the differences between PBE+vdW and the polarizable force field can emerge from the differences in the descriptions of dispersion interactions. The convergence with PBE+vdW may be improved by introducing C_6 coefficient variability in polarizable fields.

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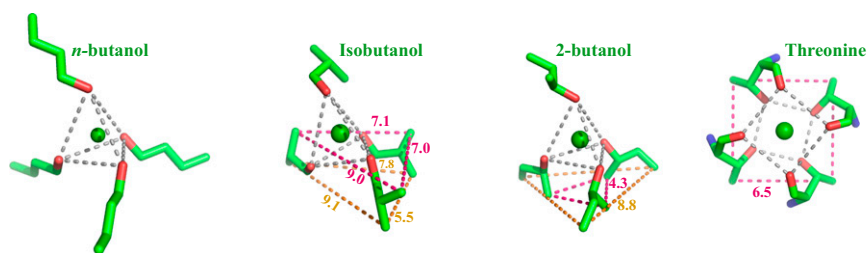
Fig. S2. Optimized configurations of representative fourfold butanol complexes compared with the S4 site. The central ion in each case is Ba^{2+}. The dashed lines serve as visual aids. The gray lines indicate the coordination geometry, and the magenta/orange lines indicate the distances between the branched methyl groups of adjacent ligands. All distances are in Å. We note that the packing of the branched methyl group of threonine in the S4 site of KcsA is intermediate between the packing of branched methyl groups in fourfold complexes composed of 2-butanols and isobutanols.
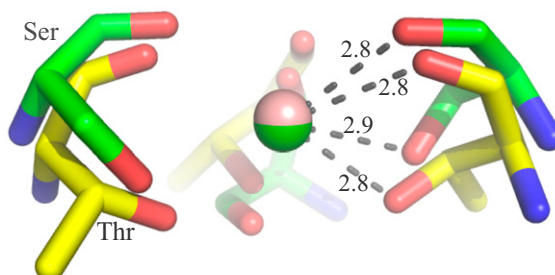
Fig. S3. Superimposed optimized configurations of the BaT₄ and BaS₄ complexes. Although the rmsd between the two optimized configurations is 1.01 Å, their coordination geometries are the same. Note that only three of the four bidentate ligands in the complexes are shown. The distances between the coordinating oxygen atoms and ions are in angstroms. Ser, serine; Thr, threonine.

Table S1. Comparison between experimental and computed reaction free energy changes ΔG involving Na^+, K^+ and Ba^{2+} ions forming complexes with water (W) and methanol (M) molecules

Gas phase reaction	Experiment ΔG	Theory $\Delta G^{\dagger}$	ΔE_{vdW}
$Na + W \rightleftharpoons NaW$	$-18.8^{\ddagger}$	-17.6	-0.3
$Na + 2W \rightleftharpoons NaW_2$	$-31.9^{\ddagger}$	-32.1	-0.8
$Na + 3W \rightleftharpoons NaW_3$	$-40.9^{\ddagger}$	-42.2	-1.7
$Na + 2M \rightleftharpoons NaM_2$	$-35.5^{\S}$	-35.6	-2.0
$Na + 3M \rightleftharpoons NaM_3$	$-44.7^{\S}$	-46.2	-4.8
$K + W \rightleftharpoons KW$	$-11.8^{\ddagger}$	-11.8	-0.7
$K + 2W \rightleftharpoons KW_2$	$-20.7^{\ddagger}$	-22.9	-1.4
$K + 3W \rightleftharpoons KW_3$	$-27.0^{\ddagger}$	-28.6	-2.1
$K + M \rightleftharpoons KM$	$-13.4^{\P}$	-13.7	-1.0
$K + 2M \rightleftharpoons KM_2$	$-23.1^{\parallel}$	-23.8	-3.3
$K + 3M \rightleftharpoons KM_3$	$-29.9^{\parallel}$	-29.3	-5.9
$BaW_4 + W \rightleftharpoons BaW_5$	-16.1^{**}	-14.6	-1.0
$BaW_5 + W \rightleftharpoons BaW_6$	-12.6^{**}	-14.0	-0.9

ΔE_{vdW} is the contribution of dispersion energy to the computed ΔG. All energies are in units of kcal/mol.

[†]Computed at temperature (T) = 298 K, except for the reaction $K + M \rightleftharpoons KM$, whose free energy was computed at T = 443 K.

[‡]Estimated at T = 298 K and taken from Tissandier et al. (1).

[§]Estimated by adding $NaW_n + nM \rightleftharpoons NaM_n + nW$ substitution reaction free energies obtained at T = 303 K (2) to corresponding NaW_n complexation energies obtained at T = 298 K (1).

[¶]Estimated by adding the $KW + M \rightleftharpoons KM + W$ reaction free energy obtained at T = 443 K to the KW complexation energy taken from ref. 2.

[∥]Estimated by adding $KW_n + nM \rightleftharpoons KM_n + nW$ substitution reaction free energies obtained at T = 302 K (2) to corresponding KW_n complexation energies obtained at T = 298 K (1).

[**]Estimated at T = 298 K and taken from ref. 3.

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Table S2. Effect of $T \rightarrow S$ substitutions on the structures of ion complexes

rmsd, Å	$A \equiv Na^+$	$A \equiv K^+$	$A \equiv Ba^{2+}$
Between AT_4 and AT_3S	0.13	0.46	0.85
Between AT_4 and AT_2S_2	0.13 (0.14)	0.69 (0.02)	0.84 (0.96)
Between AT_4 and AT_1S_3	0.14	0.64	0.96
Between AT_4 and AS_4	0.03	0.02	1.01

In the calculation of the rmsd between two ion complexes, only nonhydrogen atoms are considered. Note that two simultaneous $T \rightarrow S$ substitutions can be introduced in two different ways. In one case, the substitutions are made on adjacent threonine residues, and in the other case, the substitutions are made on nonadjacent threonine residues. The numbers in brackets correspond to substitutions made on adjacent threonine residues. We find that these substitutions result in only minor configurational changes. Although the configurational changes are generally higher in the case of Ba^{2+} complexes, they do not correspond to any changes in binding topology or geometry (Fig. S3).

Table S3. Changes in single point energy ΔE and free energy ΔG associated with the substitution reaction, $BaT_4 + 4S \rightleftharpoons BaS_4 + 4T$, estimated with and without vdW contributions

Substitution reaction energy	PBE0	PBE0+vdW	PBE0+mbd
$\Delta E = E_{BaS_4} + 4E_T - E_{BaT_4} - 4E_S$	3.1	5.2	4.9
$\Delta G = G_{BaS_4} + 4G_T - G_{BaT_4} - 4G_S$	2.5	6.9	—

The vdW contributions are evaluated in two different ways: (*i*) using a pairwise approximation (1), denoted by PBE0+vdw, and (*ii*) using a many-body correction scheme (2), denoted by PBE0+mbd. Free energies are evaluated at a temperature of 298 K and a pressure of 1 atm. All energies are in units of kcal/mol. We find that although the contributions of many-body vdW interaction terms to ΔE are small (0.3 kcal/mol), dispersion contributes significantly to the energy differences associated with the substitution reaction.

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