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# Liquid-Liquid Extraction of Alkali Cations by 18-Crown-6: Complexation and Interface Crossing Studied by MD and PMF Simulations

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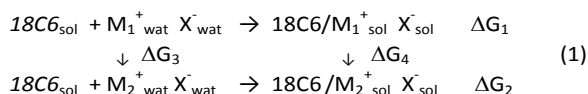
In order to get microscopic views of what happens at the water/chloroform interface upon selective extraction of alkali cations ( $M^+ = Na^+, K^+, Cs^+$ ) by the 18-crown-6 macrocycle "18C6", we studied by MD and potential of mean force "PMF" simulations their complexation in the source phase (water) and at the interface, and the interface crossing by the different species. The binding free energies in water calculated without polarization (NO-POL) or with polarization (POL) are in good accord with experiment. At the interface, the  $K^+$  and  $Cs^+$  complexes are found to be stronger than in water, while the  $Na^+$  complex is weaker. The free energy profiles for interface crossing by 18C6 and the 18C6/ $M^+ Pic^-$  complexes ( $Pic^-$  is the trinitrophenolate anion), calculated with different models, reveal a deep minimum at the interface, indicating that they are surface active, in spite of their centrosymmetrical structure. These results hint for a complexation process occurring "right at the nano-interface", a feature further supported by a POL simulation where 18C6 rapidly ( $< 5$  ns) captures  $K^+$  at the interface along the dynamics. Regarding the extraction selectivity, we show that the  $K^+$  complex is the most stable one at the interface, and that it is most easily transferred to the receiving phase. The complexation and extraction selectivity for  $K^+$  obtained from the PMF route is also evidenced by "alchemical mutations". These simulations point to the importance of the aqueous "nano-interface" for complexation, recognition and chemical reactivity in confined aqueous media.

## Introduction.

Selective  $M^{n+}$  cation extraction from an aqueous to an "oil" phase is an important separative technique for analytical and industrial purposes.<sup>[1, 2]</sup> It has also, from a more fundamental point of view, bearing for our understanding of processes like ion transport through biological membranes, ion sensing, phase transfer catalysis and molecular recognition in chemistry and biology. The case of macro(poly)cyclic extracting ligands like crown ethers, cryptands, calixarenes and their derivatives, and their complexes is at the core of supramolecular chemistry.<sup>[3-11]</sup> In this paper, we focus on 18-crown-6 "18C6" that, in spite of its "simplicity",<sup>[12]</sup> displays key recognition features of ion extractants and carriers. Like its more lipophilic dicyclohexyl- or dibenzo- derivatives (noted DCH18C6 and DB18C6, respectively), 18C6 extracts alkali picrate  $M^+ Pic^-$  salts (where  $Pic^-$  is the picrate, trinitrophenolate anion), from an aqueous to an oil phase (chloroform), with a marked selectivity for  $K^+$ , i.e. the cation that best fits inside the cavity.<sup>[13, 14]</sup> Extraction is generally based on the vigorous shaking or stirring of the aqueous solution containing the salts and of the oil solution where the extractant is dissolved, and involves metastable heterogeneous mixtures that finally separate. The efficiency of the process thus depends not only on the "stability" of the 18C6/ $M^+$  complex, but also on differential

solvation and medium effects, on the nature of  $X^-$  counterion, of the oil phase, of the hydrophobicity and partitioning of the extractant.<sup>[14, 15]</sup> In order to understand (and hopefully predict) the net effect of the related multiple competing forces, it is crucial to analyse the structural and energetic features of the free ligand and of its complexes in solution(s). What happens at the water/oil interface is also stressed to be of capital importance in solvent extraction,<sup>[1, 16]</sup> but is hardly characterized at the molecular level by experiments alone.

In this paper, we use molecular dynamics "MD" and free energy perturbation simulations to "predict" the most important thermodynamic feature, namely the difference in free energies  $\Delta G$  between two states stepwise connected via small perturbations.<sup>[17-19]</sup> Critical facets of the extraction process are studied by potential of mean force "PMF" calculations, comparing  $Na^+$  to  $K^+$  and  $Cs^+$  cations: (i)  $M^+$  complexation in the source phase, (ii)  $M^+$  complexation at the interface, (iii) transfer across the interface of  $M^+ Pic^-$  alone, of 18C6 alone, and of the 18C6/ $M^+ Pic^-$  complexes. The binding selectivity between  $M_1^+$  versus  $M_2^+$  will be estimated via the PMF route (as  $\Delta\Delta G_c = \Delta G_1 - \Delta G_2$ ) and via the "alchemical mutations" of  $M_1^+$  to  $M_2^+$  uncomplexed ( $\Delta G_3$ ) or complexed ( $\Delta G_4$ ):  $\Delta\Delta G_c = \Delta G_3 - \Delta G_4$  (Scheme 1). Depending on the solvent "sol", the reactions correspond to the complexation in the source phase (sol = water) or to the assisted extraction (sol = chloroform).



Regarding 18C6, there are pioneering free energy studies of  $K^+$  or  $Cs^+$  complexation in water based on "PMF" simulations<sup>[20-22]</sup> or by an annihilating procedure,<sup>[23]</sup> while the  $Na^+ / K^+$

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Electronic Supplementary Information (ESI) available: Tables S1-S4 contain atomic charges and polarizabilities, tests on QM versus AMBER interaction energies in the gas phase, dissociations energies  $\Delta A_{diss}$  of complexes. Figures S1-S16 include snapshots along the PMF trajectories, and distances and energy analysis along the dynamics or the PMFs. See DOI: 10.1039/x0xx00000x

selectivity has been calculated by the "alchemical route" in water<sup>[24]</sup> and in methanol.<sup>[25]</sup> Note that these calculations used different  $M^+$  and 18C6 models (for instance  $q_0$  charges of 18C6 are -0.406 e in refs.<sup>[20, 21, 26]</sup>, -0.60 e in ref.<sup>[27]</sup> and -0.34 e in ref.<sup>[23]</sup>), different simulation protocols and solvent models, preventing us to consistently compare the two routes for the three cations. We thus first revisit the PMF of  $K^+$  complexation to define a consistent protocol to predict the binding energy of the three cations in water (as a reference), and at the interface. Insights into the binding selectivity will be obtained via the PMF routes and mutations. Following previous work,<sup>[27-35]</sup> we then investigate the free energy profiles for interface crossing by the different partners of the extraction process: the  $K^+$  Pic<sup>-</sup> salt, 18C6 uncomplexed, and the three 18C6/ $M^+$  Pic<sup>-</sup> complexes. Because of the availability of experimental thermodynamic data,<sup>[36, 37]</sup> the studied system is particularly interesting and challenging. Ion complexation and extraction are mainly driven by non-covalent electrostatic forces whose representation is stressed to be critical. We thus compare different force field models based on 1-6-12 pairwise additive potentials without polarization "NO-POL", and a force field with polarization "POL". How these influence the stability of the complexes and the partitioning of a neutral (18C6) or charged solute ( $M^+$  free or complexed) is also highly relevant for studying other assisted transfer or interfacial processes.

## Methods.

**MD Simulations of Solutions.** Molecular dynamics simulations were performed with the AMBER10 software<sup>[38]</sup> with the following representation of the potential energy  $U$ :

$$U = \sum_{bonds} k_l (l - l_0)^2 + \sum_{angles} k_\theta (\theta - \theta_0)^2 + \sum_{dihedrals} \sum_n V_n (1 - \cos(n\phi - \gamma)) + \sum_{i < j} \left[ \frac{q_i q_j}{R_{ij}} - 2\epsilon_{ij} \left( \frac{R_{ij}^6}{R_{ij}} \right) + \epsilon_{ij} \left( \frac{R_{ij}^{12}}{R_{ij}} \right) \right] \quad (2)$$

It accounts for the deformation of bonds, angles, dihedral angles, electrostatic and van der Waals interactions (assumed to be pairwise additive in this "NO-POL" 1-6-12 potential), using the Cornell *et al.* force field parameters.<sup>[39]</sup> The solvents were represented explicitly, using the Chang *et al.*'s model for  $CHCl_3$ <sup>[40]</sup> and TIP3P<sup>[41]</sup> or SPC/E<sup>[42]</sup> water. The  $Na^+$ ,  $K^+$  and  $Cs^+$  parameters (see Table S1) are from Dang *et al.*<sup>[43]</sup> The 1-4 van der Waals and Coulombic interactions were divided by 2.0 and 1.2, respectively. The atomic charges of Pic<sup>-</sup> are from ref.<sup>[44]</sup>. The choice of charges on 18C6 determines its conformation and its binding properties, and we started with the set (with  $q_0 = -0.406$  e) used by Dang *et al.* to "successfully" calculate the PMF for the  $K^+$ <sup>[20, 21]</sup> and  $Cs^+$  complexation<sup>[45]</sup> in SPC/E water. We found it, however, to underestimate the stability of the  $Na^+$ ,  $K^+$  and  $Cs^+$  complexes in the gas phase (by 30% to 17%, when compared to QM results; see Table S2) and in water (see below). This led us to test two other sets, with  $q_0$  charges of -

0.60 and -0.34 e, respectively. The 18C6(-0.6) charges are obtained by scaling the 18C6(-0.4) charges by a factor 1.5 to mimic the polarization of 18C6 by  $M^+$ <sup>[46]</sup> and to better account for 18C6... $M^+$  interactions in the gas phase (see Table S2). The 18C6(-0.34) charges stem from an ESP HF/6-31G(d,p) calculation on 18C6 D<sub>3d</sub>. They are given in Table S1, together with the corresponding dipole moment of Me<sub>2</sub>O, as a benchmark of "polarity". The corresponding complexation energies with 18C6 in the gas phase are given in Table S2, and compared to QM reference values. To investigate the effect of polarization, we additionally performed "POL" simulations where polarization is described in AMBER via atomic polarizabilities for the solvents (POL3 water,<sup>[47]</sup> polarizable chloroform<sup>[40]</sup>), for 18C6 ( $q_0 = -0.40$  e) and the ions (see parameters in Table S1). Non-bonded interactions were calculated with a 12 Å atom-based cut-off, correcting for the long-range electrostatics by using the Ewald summation method (PME approximation).<sup>[48]</sup> The solutions were simulated with 3D-periodic boundary conditions. Their characteristics are given in Table 1.

All systems were first relaxed by 3000 steps of energy minimization and by a MD simulation of 0.5 ns at 300 K and a constant pressure of 1 atm to adjust the densities. Subsequent dynamics was performed at constant volume. The temperature was maintained at ca. 300 K by coupling the solution to a thermal bath using the Berendsen algorithm<sup>[49]</sup> with a relaxation time of 0.2 ps. The MD trajectories and velocities were calculated using the Verlet algorithm with a time step of 2 fs, in conjunction with SHAKE constraints on O-H and C-H bonds.

The trajectories were saved and analyzed every ps using our MDS software and VMD<sup>[50]</sup> for pictures. Interactions energies between selected groups were calculated using the Ewald summation.

**Table 1:** Characteristics of the simulations in water and at the water/chloroform interface.

	Solutes	Solvent $n_{CHCl_3}/n_{H_2O}$	Box size (Å <sup>3</sup> )	$C_i^a$	Time (ns) MD + PMF
Water	1 Na <sup>+</sup> 18C6 Cl <sup>-</sup>	0/869	30 <sup>2</sup> x30	0.06	2 + 7 to 42
	1 K <sup>+</sup> 18C6 Cl <sup>-</sup>	0/869	30 <sup>2</sup> x30	0.06	2 + 4 to 126
	1 Cs <sup>+</sup> 18C6 Cl <sup>-</sup>	0/869	30 <sup>2</sup> x30	0.06	2 + 7 to 42
Interface	1 K <sup>+</sup> Pic <sup>-</sup>	473/2087	40 <sup>2</sup> x(40+40)	0.03	2 + 120
	1 M <sup>+</sup> 18C6 Pic <sup>-</sup>	469/2096	40 <sup>2</sup> x(40+40)	0.03	2 + 120
	1 K <sup>+</sup> DCH18C6 Pic <sup>-</sup>	472/2103	40 <sup>2</sup> (40+40)	0.03	2 + 120
	1 K <sup>+</sup> 18C6 Pic <sup>-</sup>	801/3514	60 <sup>2</sup> x(30+30)	0.01	2 + 60
	30 K <sup>+</sup> 18C6 Pic <sup>-</sup>	301/1751	40 <sup>2</sup> x(40+40)	0.9	5

<sup>a</sup> Concentration (M) with respect to the water phase.

<sup>b</sup> Simulated time.

**Potential of Mean Force (PMF) calculations.** We calculated the Helmholtz free energy profiles  $\Delta A(d)$  for dissociation of the 18C6/ $M^+$  complex, or for transfer across the interface, using

the same protocol as in earlier work.<sup>[27]</sup> For the dissociation PMF of the complex, the distance  $d$  between  $M^+$  and the center-of-mass "CM" of 18C6 was increased from  $d_0$  in the complexed state ( $\lambda = 0$ ) to  $d_1$  in the decomplexed state ( $\lambda = 1$ ) via intermediate steps:  $d = (1-\lambda) d_0 + \lambda d_1$  Å, by increments  $\Delta d = \sim 0.2$  Å, i.e.  $\Delta\lambda = 0.025$ . For interface crossing by a solute  $S$  ( $S = K^+ \text{ Pic}^-$ , 18C6 alone, the 18C6/ $M^+ \text{ Pic}^-$  complexes), the reaction coordinate  $d$  was the distance between CM( $S$ ) and the CM(system) where the "system" is the whole simulation box, and we used  $\Delta d$  steps of  $\sim 0.5$  Å, as in related PMF studies.<sup>[27, 33, 51]</sup> From the resulting  $\Delta A(d)$  curve we calculated  $\Delta A(z)$  where the reference position of the "interface" (Gibbs dividing surface with  $z = 0$ ) is defined by the crossing between the water and chloroform density curves recalculated at every step.

$$\Delta A = \int_0^1 \left\langle \frac{\partial U}{\partial \lambda} \right\rangle d\lambda \quad (3)$$

The change in free energy at each step  $\lambda$  was calculated using the thermodynamic integration method (TI) based on equation (3).<sup>[17]</sup> At each  $\lambda$  step of the (de)complexation PMF, we typically performed 0.01 ns of equilibration plus 0.5 ns of data collection and averaging, requiring  $\sim 25$  ns to cover a separation distance of 10 Å. These PMFs are noted PMF<sub>0.01+0.5</sub> in short. Other sampling times were also tested (up to PMF<sub>0.01+3</sub>), comparing dissociation to association pathways to assess the hysteresis. Because of the imposed constraints and of the incomplete sampling of the angular orientations, the PMF curves do not exactly afford the free energy of association  $\Delta A_{\text{ass}}$  (or  $\Delta G_{\text{ass}}$ , at constant pressure, assumed to be similar for condensed phases), however.<sup>[23],[52-54]</sup> We thus estimated the association constant as:

$$K_{\text{ass}} = \int_0^\infty 4\pi d^2 \exp(-A(d)/RT) dd \quad (4)$$

and from there deduced the free energy of association  $\Delta G_{\text{ass}} = -RT \log K_{\text{ass}}$  or of dissociation  $\Delta G_{\text{diss}} = -\Delta G_{\text{ass}}$ . The resulting  $\Delta G_{\text{diss}}$  energy is generally smaller in magnitude than the free energy minimum along the PMF,<sup>[55]</sup> by  $\approx 3.5$  to 5 kcal/mol in the  $K^+ \dots 18C6$  complexation study of Dang and Kollman.<sup>[20, 21]</sup> Note that Equation (4) assumes an isotropic distribution of the interacting partners, which is not the case at short 18C6... $M^+$  distances (see for instance cumulated positions in Figure S1). Thus, absolute  $\Delta G_{\text{diss}}$  values estimated with this procedure should be considered with care. However, comparisons from one cation to the other, using a same protocol should be meaningful.

"Alchemical mutations" of  $M_1^+$  (initial state,  $\lambda = 0$ ) to  $M_2^+$  (final state,  $\lambda = 1$ ) in solution were achieved by the TI procedure

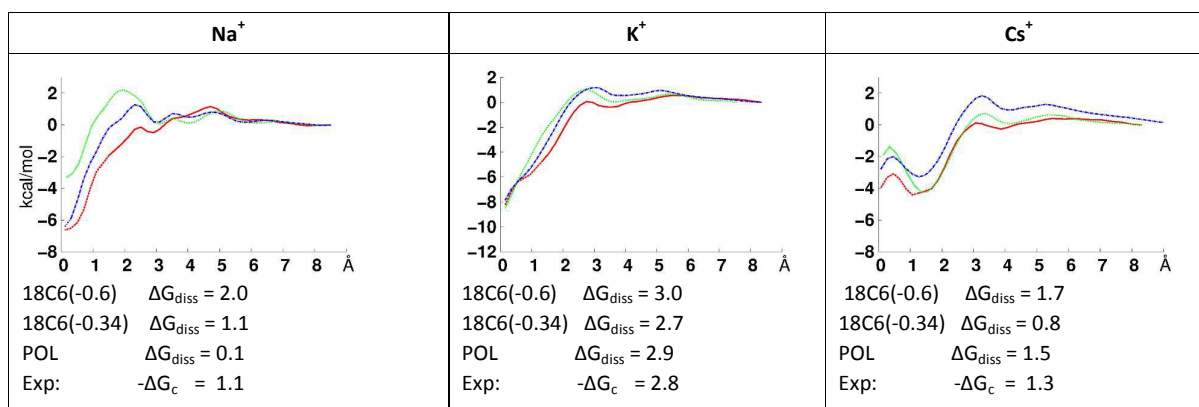
implemented in AMBER-12,<sup>[56]</sup> using an hybrid potential  $V(\lambda) = (1-\lambda)V_0 + \lambda V_1$  and a five-point quadrature to calculate  $\Delta A = \sum_i w_i \langle \partial V / \partial \lambda \rangle_i$ , using the tabulated  $\lambda$  values and  $w_i$  weights:  $\lambda = 0.04691, 0.23076, 0.5, 0.76923, 0.95308$  and  $w = 0.11846, 0.23931, 0.28444, 0.23931, 0.11846$ , respectively. At each  $\lambda$  state, we performed 0.25 ns of equilibration plus 0.25 ns of production (averaging). A test on  $\text{Cs}^+ / K^+$  mutation with 0.01+0.5, instead of 0.25+0.25 ns of sampling was found to yield identical  $\Delta G$ 's.

## Results.

### Complexation of $M^+ X^-$ by 18C6 in water and at the water/chloroform interface studied by PMF simulations.

This section starts with an analysis of PMF results on  $K^+ \text{ Cl}^-$  complexation by 18C6 in water, with the aim to assess a protocol (electrostatic representation and sampling procedure) that satisfactorily predicts the binding energy  $\Delta G_{\text{diss}}$ . We then consider the case of  $\text{Na}^+$  and  $\text{Cs}^+$  in water, and of the three cations at the interface.

**$K^+$  complexation in water.** We reconsidered with present computer means the dissociation PMF study of 18C6(-0.4)/ $K^+$  reported by Dang and Kollman,<sup>[20, 21]</sup> using their  $K^+$  parameters, SPC/E water model, the same PMF<sub>0.01+0.08</sub> sampling, and obtained identical results ( $\Delta G_{\text{diss}} = 1.9$  kcal/mol; see Figure S2) with significant hysteresis, though (2.0 kcal/mol) when ones compares the dissociation to the association PMFs. Increasing the sampling (PMF<sub>0.01+0.16</sub>, PMF<sub>0.01+0.5</sub>, PMF<sub>0.01+1</sub>, or PMF<sub>0.01+2</sub> simulations) reduced the hysteresis, but also reduced the stability of the complex ( $\Delta G_{\text{diss}} = 1.2, 0.0, 0.4$  and  $0.7$  kcal/mol, respectively) that became too low, compared to the experiment ( $-\Delta G_{\text{exp}} = 2.8$  kcal/mol), which suggests that the  $K^+ \dots 18C6(-0.4)$  interactions are underestimated. In fact, with the 18C6(-0.6) model, the  $\Delta G_{\text{diss}}$  energy (3.0 kcal/mol; PMF<sub>0.01+0.5</sub>) is within 0.2 kcal/mol the same as the experimental one, and close to the value obtained from the association pathway ( $\Delta G_{\text{ass}} = -3.3$  kcal/mol, see Figure S3). Increasing further the sampling (PMF<sub>0.01+1</sub>, PMF<sub>0.01+2</sub> or PMF<sub>0.01+3</sub> simulations) yields  $\Delta G_{\text{diss}} = 1.5, 2.4$  and  $2.2$  kcal/mol, respectively (Table 2), also close to the experimental value. Note that these  $\Delta G_{\text{diss}}$  energies neither display a regular evolution with the sampling time nor systematic improvement, compared to the experiment. Thus, to avoid too prohibitive computer costs, we decided to use the PMF<sub>0.01+0.5</sub> procedure for the other systems (see free energy curves in Figure 1). With the POL model (18C6(-0.4) charges), this yields  $\Delta G_{\text{diss}} = 2.9$



**Figure 1:** Dissociation PMF<sub>0.01+0.5</sub> of 18C6/ M<sup>+</sup> Cl<sup>-</sup> complexes in water. Free energy curves ( $\Delta A$  in kcal/mol, as a function of the distance  $d$  in Å) with three models: 18C6(-0.6) (red), 18C6(-0.34) (blue) and POL (green) Snapshots at different "POL" positions are shown in Figure S6. PMF curves with other sampling and charges are given in Figures S2 and S3 (for K<sup>+</sup>) and S4 to S6 (for Na<sup>+</sup>, K<sup>+</sup>, Cs<sup>+</sup>).

and 2.7 kcal/mol, respectively, for the dissociation and association pathways, in excellent agreement with experiment. A nice agreement is also found with the 18C6(-0.34) charge set (NO-POL):  $\Delta G_{\text{diss}}$  energy 2.7 kcal/mol. In summary, while the 18C6(-0.4) (NO-POL) charge set underestimates the stability of the K<sup>+</sup> complex, the 18C6(-0.6) and 18C6(-0.34) sets are quite satisfactory. The binding energy of K<sup>+</sup> thus does not merely increase with the magnitude of the  $q_0$  charges of the binding sites, owing to longer range interactions with the alkyl groups and to their representation.

**Table 2:** Dissociation free energies ( $\Delta G_{\text{diss}}$  in kcal/mol) of the 18C6/K<sup>+</sup> Cl<sup>-</sup> complex in water. Comparison of different electrostatic models and PMF<sub>0.01+t</sub> sampling times t.<sup>a</sup>

Water model	$q_0(18C6)$ (e)	Time t (ns)	$\Delta G_{\text{diss}}$ Diss / Ass <sup>b</sup>	$\langle \Delta G_{\text{diss}} \rangle^c$
SPC/E	-0.4	0.08	1.9 / -0.1	1.0±1.0
		0.16	1.2 / 1.2	1.2±0.0
		0.5	0.0 / 0.2	0.1±0.1
		1.0	0.4 / 0.0	0.2±0.2
		2.0	0.7 / 0.1	0.4±0.3
	-0.6	0.5	3.0 / 3.3	3.1±0.1
		1.0	1.5 / 1.8	1.6±0.2
		2.0	2.4 / 2.8	2.6±0.2
		3.0	2.2 /	
	-0.34	0.5	2.7 / 1.9	2.3±0.4
		1.0	2.2 /	
		3.0	2.2 / 1.7	1.9±0.3
POL3	-0.40+POL	0.5	2.9 / 2.7	2.8±0.1
	-0.34+POL	0.5	5.0 / 4.6	4.8±0.2

a: Experiment :  $-\Delta G_{\text{exp}} = 2.8$  kcal/mol.<sup>[11]</sup>

b: PMF starting either from K<sup>+</sup> complexed (Dissociation PMF) / or uncomplexed (Association PMF).

c: Average between Dissociation and Association pathways

**Na<sup>+</sup> and Cs<sup>+</sup> complexation in water.** We now turn to the Na<sup>+</sup> and Cs<sup>+</sup> complexation, simulated with the PMF<sub>0.01+0.5</sub> sampling, first without polarization. With the 18C6(-0.4) charges, the stability of the Na<sup>+</sup> and Cs<sup>+</sup> complexes is found to be too low (by  $\Delta\Delta G \approx 1.1$  and 0.8 kcal/mol, respectively; see Table 3), while with the 18C6(-0.6) charges, it is too high (by  $\Delta\Delta G = 0.9$  and 0.4 kcal/mol, respectively; see Figure 1 and S5). As expected, an intermediate 18C6(-0.5) set yields a good compromise for Na<sup>+</sup>, K<sup>+</sup> and Cs<sup>+</sup> complexes ( $\Delta\Delta G = 0.0$ , 0.6 and 0.0 kcal/mol, respectively). The 18C6(-0.34) model is also quite satisfactory ( $\Delta\Delta G = 0.0$ , 0.1 and -0.5 kcal/mol, respectively). Note that with the different models, the K<sup>+</sup> complex is the most stable one, while the Na<sup>+</sup> and Cs<sup>+</sup> ones have similar stabilities: with either 18C6(-0.5) or 18C6(-0.34) charges,  $\Delta\Delta G_{\text{diss}} \approx 0.2$  kcal/mol (as experimentally), while with 18C6(-0.6) charges,  $\Delta\Delta G_{\text{diss}} \approx -0.3$  kcal/mol. With the POL model, PMF<sub>0.01+0.5</sub> simulations also predict that Na<sup>+</sup> and Cs<sup>+</sup> complexes are less stable than the K<sup>+</sup> one. When compared to the experiment, the "POL"  $\Delta G_{\text{diss}}$  energy is in excellent agreement for Cs<sup>+</sup> ( $\Delta\Delta G = 0.2$  kcal/mol), but it is weaker for Na<sup>+</sup> (by  $\Delta\Delta G = 1.0$  kcal/mol).

The free energy profiles ( $\Delta A(d)$  in Figure 1) display similar features for the three cations. As M<sup>+</sup> approaches from  $\approx 9$  to 4 Å, they are rather flat, reflecting the lack of effective attractions between 18C6 and M<sup>+</sup> that retains its hydration shell. At  $\approx 3$  Å appears a small energy barrier ( $\approx 1$  to 2 kcal/mol) corresponding to water stripping from M<sup>+</sup>, followed by a free energy decrease of  $\approx 3$  to 8 kcal/mol when the final complex forms. For the Na<sup>+</sup> and K<sup>+</sup> complexation, there is a single free energy minimum at  $\approx 0$  Å, when M<sup>+</sup> sits near the center of the crown ("nested" position). In the Cs<sup>+</sup> case, however, one finds a second minimum, at  $\approx 1.8$  Å ("perched" position, on top of the ring), of similar energy with the two NO-POL models, but more stable with the POL one.

**Na<sup>+</sup>, K<sup>+</sup> and Cs<sup>+</sup> complexation at the interface.** Since the 18C6(-0.34) model accounts well for the stability of the complexes in water at moderate computer cost, we used it to simulate them for



**Table 3:** Dissociation free energies ( $\Delta G_{\text{diss}}$  in kcal/mol) of the 18C6/ $M^+ X^-$  complexes in water and at the interface, obtained by PMF<sub>0.01+t</sub> calculations. Selectivities  $\Delta\Delta G$  obtained from the PMF route and from "alchemical mutations" ("*Mut*" in *italics*). The corresponding  $\Delta A$  energies are given in Table S3. The mutation energies of  $M^+$  uncomplexed ( $\Delta G_3$ ) and complexed ( $\Delta G_4$ ; see Scheme 1) are given in Table 5.

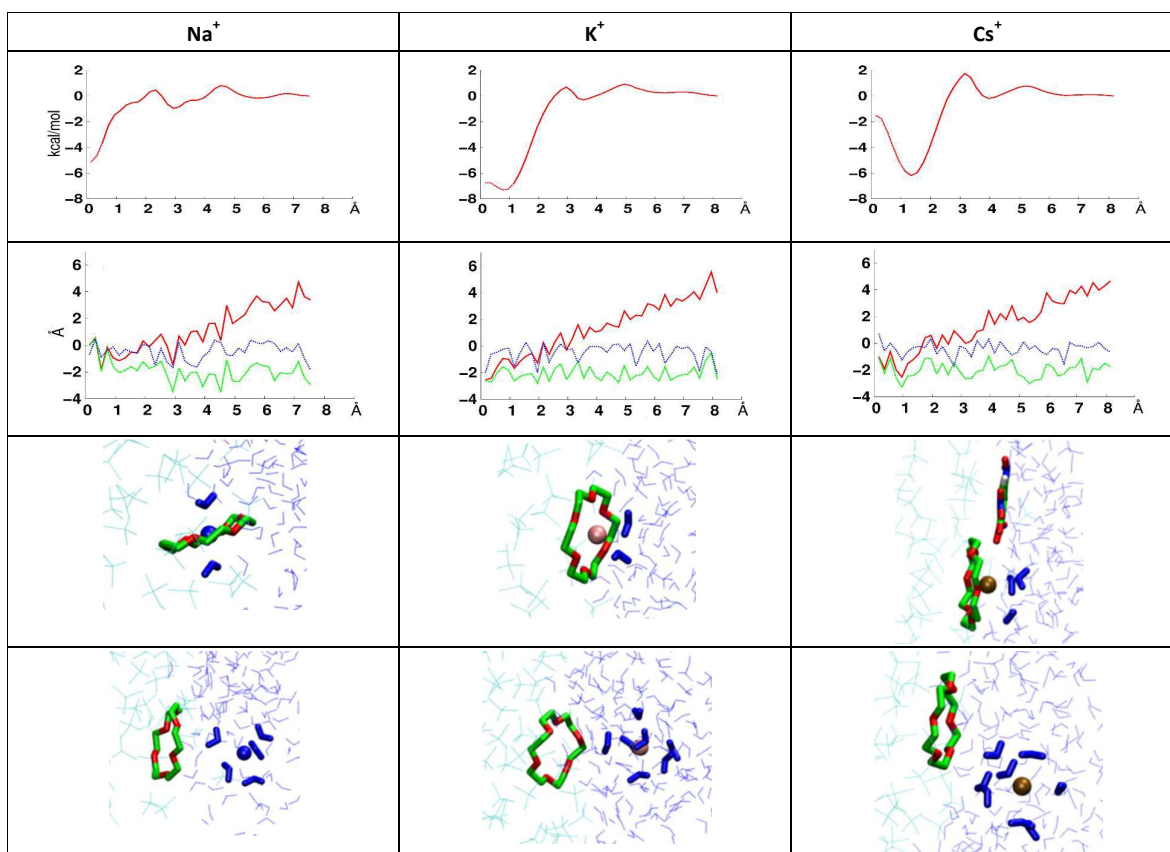
		$q_0$	$t$	$\Delta G_{\text{diss}}$			Selectivity $\Delta\Delta G$			Order
				$\text{Na}^+$	$\text{K}^+$	$\text{Cs}^+$	K/Na	Cs/K	Na/Cs	
In water $\text{M}^+ \text{Cl}^-$										
	SPC/E	-0.4	0.16	0.9	1.2	-0.1	-0.3	+1.3	-1.0	$\text{K} \approx \text{Na} > \text{Cs}$
			0.5	0.04/-0.2 <sup>a</sup>	0.03/0.2 <sup>a</sup>	0.5/-0.03 <sup>a</sup>	+0.01	-0.5	+0.5	$\text{Cs} \approx \text{Na} \approx \text{K}$
			Mut.				-2.8	+1.9	+0.9	$\text{K} > \text{Cs} > \text{Na}$
		-0.5	0.16	0.8	2.8	2.2	-2.0	+0.6	+1.4	$\text{K} > \text{Cs} > \text{Na}$
			0.5	1.1	3.4	1.3	-2.3	+2.1	+0.2	$\text{K} > \text{Cs} \approx \text{Na}$
			Mut.				-2.5	+2.2	+0.3	$\text{K} > \text{Cs} \approx \text{Na}$
		-0.6	0.16	3.2	3.5	2.2	-0.3	+1.3	-1.0	$\text{K} > \text{Na} > \text{Cs}$
			0.5	2.0	3.0	1.7	-1.0	+1.3	-0.3	$\text{K} > \text{Na} \approx \text{Cs}$
			Mut.				-2.2	+1.8	+0.4	$\text{K} > \text{Cs} \approx \text{Na}$
		-0.6 Ch. <sup>b</sup>	Mut.				-3.1	+2.4	+0.7	$\text{K} > \text{Cs} \approx \text{Na}$
		-0.34 <sup>c</sup>	0.5	1.1 / 1.0 <sup>a</sup>	2.7 / 1.9 <sup>a</sup>	0.8 / 1.1 <sup>a</sup>	-1.6	+1.9	-0.3	$\text{K} > \text{Na} \approx \text{Cs}$
			3.0	0.8 / 0.5 <sup>a</sup>	2.2 / 1.7 <sup>a</sup>	0.9 / 1.0 <sup>a</sup>	-1.4	+1.3	+0.1	$\text{K} > \text{Cs} \approx \text{Na}$
	Mut.					-2.8	+2.1	+0.1	$\text{K} > \text{Cs} \approx \text{Na}$	
	TIP3P	-0.4 +POL	0.5	0.1	2.9	1.5	-2.8	+1.4	+1.4	$\text{K} > \text{Cs} > \text{Na}$
			Mut.				-3.3	+2.3	+1.0	
		-0.6	0.5	2.5	5.6/1.3 <sup>a</sup>	2.0	-3.1	+3.6	-0.5	$\text{K} > \text{Na} \approx \text{Cs}$
			Mut.				-3.8	+0.1	+3.7	$\text{K} \approx \text{Cs} > \text{Na}$
		-0.6 Ch. <sup>b</sup>	0.5	1.4	5.1	4.6	-3.7	+0.5	+3.2	$\text{K} > \text{Cs} > \text{Na}$
			Mut.				-3.8	+0.9	+2.9	$\text{K} > \text{Cs} > \text{Na}$
			Exp. <sup>c</sup>		1.1	2.8	1.3	-1.7	+1.5	+0.2
At the interface $\text{M}^+ \text{Pic}^-$										
	$\text{CHCl}_3 / \text{SPC/E}$	-0.34 <sup>c</sup>	0.5	0.4	3.9	3.2	-3.5	+0.7	+2.8	$\text{K} > \text{Cs} > \text{Na}$
			Mut.				-2.9	+1.2	+1.7	$\text{K} > \text{Cs} > \text{Na}$

a: Dissociation / Association pathways. b: Cheatham's  $M^+$  parameters.<sup>[71]</sup> c: Experimental energy of (de)complexation..<sup>[11]</sup>

2 ns at the interface (with  $Pic^-$  as counterion) and to calculate their PMF<sub>0.01+0.5</sub> of dissociation. One first observes that along the dynamics, the  $Na^+$ ,  $K^+$  and  $Cs^+$  complexes remain at the interface and do not dissociate. Their structural characteristics (Table 4 and Figure S10) are similar to those found in pure water, regarding the  $M^+ \dots O$  distances, the hydration number of  $M^+$  (2 to 3  $H_2O$  molecules are coordinated to  $M^+$ ), and the shape of the crown that remains  $D_{3d}$  on the average. The OC-CO dihedrals can exchange between  $g^+$  ( $\approx +60^\circ$ ) and  $g^-$  ( $\approx -60^\circ$ ) values along the dynamics, and the number  $n_{g^\pm}$  of  $g^+ \leftrightarrow g^-$  conversions depends on the cation size and on the solvent environment. In bulk water,  $n_{g^\pm} = 61$  (for  $Na^+$ ), 9 (for  $K^+$ ) and 0 (for  $Cs^+$ ). At the interface,  $n_{g^\pm} = 26$ , 0 and 0, respectively. We note that the complexes are more rigid (there are less conversions) at the interface, presumably because  $M^+$  is hydrated in an asymmetrical manner (especially for  $K^+$  and  $Cs^+$ ), namely at the face of the crown that turns towards water. The other face is less hydrated and turns towards chloroform, yielding an "amphiphilic solvation" (Figure 2). Another distinguishing feature concerns the  $Pic^-$  counterion that forms transient tight contacts with the complex (especially with  $Na^+$  and  $Cs^+$ ) at the interface, but is always dissociated in bulk water. An energy component analysis (Table 4) indicates that, at the interface,  $M^+$  interacts with 18C6 and with

water nearly as much as in bulk water, while the 18C6 moiety is no more attracted by water. At the interface, like in water or in the gas phase, the attraction energy of  $M^+$  with 18C6 follow the order  $Na^+ > K^+ > Cs^+$ .

The free energy profiles for dissociating the 18C6/ $M^+$  complexes at the interface (see Figure 2) are similar to those in water. As decomplexation proceeds,  $M^+$  progressively moves into the "bulk" water phase (up to  $\approx 5$  Å from the interface), while 18C6 and  $Pic^-$  stay there: at  $z \approx -2$  and 0 Å (somewhat on the oil side), respectively. Regarding the  $Cs^+$  complex, an interesting difference, compared to bulk water is observed: the "perched" structure (at  $d \approx 1.2$  Å) is now clearly preferred over the "nested" one (by  $\approx 4$  kcal/mol), presumably because the former is more "amphiphilic" and better solvated at the interface than in pure water (see Figure 2). Quantitatively, the free energies of binding of  $K^+$  and  $Cs^+$  ions are higher at the interface ( $\Delta G_{\text{diss}} = 3.9$  and 3.2 kcal/mol, respectively) than in pure water (2.7 and 0.8 kcal/mol, respectively), especially for  $Cs^+$ . This feature is consistent with the "amphiphilic" stabilization of 18C6/ $Cs^+$  by the two solvent components at the interface. The  $Na^+$  complex behaves differently, as it becomes less stable at the interface than in water ( $\Delta G_{\text{diss}} = -0.4$  and -1.1 kcal/mol, respectively), presumably owing to antagonistic solvation



**Figure 2:** Dissociation PMF<sub>0.01+0.5</sub> of the 18C6(-0.34)/M<sup>+</sup> Pic<sup>-</sup> complexes at the interface. From top to bottom: (i) free energy curves ( $\Delta A$  in kcal/mol, as a function of the  $d$  distance in Å); (ii) distance between the interface and M<sup>+</sup> (red), Pic<sup>-</sup> (blue) and 18C6 (green) as a function of the  $d$  separation (in Å); (iii) and (iv): snapshots of associated and dissociated states.

contributions: Na<sup>+</sup> is strongly attracted by water and coordinates water on the two faces of the crown, while 18C6 is attracted by the oil side of the interface. Regarding the binding selectivity at the interface, it is again in favor of K<sup>+</sup>.

#### Migration of 18C6, the K<sup>+</sup> Pic<sup>-</sup> salt and of the 18C6/M<sup>+</sup> Pic<sup>-</sup> complexes across the chloroform / water interface.

In this section, we investigate the free energy profiles  $\Delta A(z)$  for interface crossing by the K<sup>+</sup> Pic<sup>-</sup> salt alone, 18C6 alone and the three 18C6/M<sup>+</sup> Pic<sup>-</sup> complexes, from water to a chloroform phase, using the PMF<sub>0.5+1</sub> sampling as in previous work<sup>[27]</sup> unless otherwise indicated. In order to be consistent with that work, we selected here the TIP3P water model for simulations without polarization.

**Transfer of the uncomplexed K<sup>+</sup> Pic<sup>-</sup> salt.** The PMF for transferring the K<sup>+</sup> Pic<sup>-</sup> salt has been calculated as a function of the distance  $d$  between the interface and the CM(K<sup>+</sup> Pic<sup>-</sup>), starting at  $d = 2$  Å, when both ions sit near the interface ( $z = 0$ ), at  $\approx 8$  Å from each other. When the CM was pulled to the water side, both ions moved to water to form a solvent separated ion pair. On the other hand, when the CM was pulled to the oil phase, only the Pic<sup>-</sup> anion moved there, while K<sup>+</sup> cation always remained in bulk water. The

reluctance of the salt alone to solubilize in the oil phase is consistent with experiment, while the free energy minimum of  $\Delta A(d)$  (Figures 3 and S11) confirms the surface activity of the Pic<sup>-</sup> anion, dissociated from K<sup>+</sup>. Regarding the ion extraction mechanism, it is thus clear that complexation cannot take place in the oil phase.

**Transfer of 18C6 uncomplexed.** Experimentally, 18C6 mainly partitions in chloroform, but a significant amount (about 15%) solubilizes in water.<sup>[57]</sup> Its weak extraction constant ( $k = 6.1$  at 25°C),<sup>[37]</sup> corresponds to a free energy of transfer  $\Delta G_t$  of only  $\approx 1.1$  kcal/mol. Furthermore, we note that its extraction is driven by a positive entropy ( $T\Delta S_t \approx 5.2$  kcal/mol), but disfavored by the enthalpy ( $\Delta H_t \approx 4.1$  kcal/mol).<sup>[37]</sup> Predicting its partitioning is thus quite challenging. We recently compared three models of 18C6, and found that the result markedly depends on its "polarity": without polarization (NO-POL), 18C6(-0.6) prefers water, 18C6(-0.4) prefers chloroform, while with the POL model (polarizable 18C6(-0.4) and solvents), 18C6 has no preference for either phase (see Figure S12).<sup>[27]</sup> Beyond the "simple" case studied here, it is important to correctly predict at moderate computer cost the partitioning of species like drugs,<sup>[58]</sup> extractants, or phase transfer catalysts. We thus decided to calculate a new PMF using the 18C6(-0.34) model.

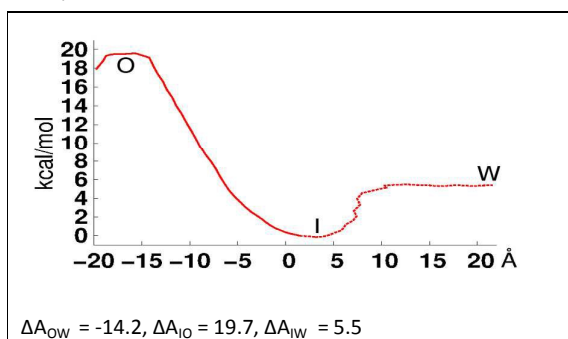
**Table 4:** Analysis of 18C6(-0.34)/  $M^+$  complexes in water and at the interface:  $M^+ \dots O(18C6)$  and  $M^+ \dots X^-$  distances (in Å), hydration number of  $M^+$ ,  $n_{+/-}$ , number of  $g^+ \leftrightarrow g^-$  interconversions of OC-CO dihedrals, and interaction energies ( $E$  in kcal/mol) between 18C6,  $M^+$  and Water. Averages during 2 ns. See also Figures S7 to S9. Results with other models are given in Table S4.

	$Na^+$	$K^+$	$Cs^+$
<i>In Water</i>			
$d_{M-O(18C6)}$	2.8 (x6)	3.0 (x6)	3.2 (x6)
$d_{M-Cl}$	16 ± 3	15 ± 3	15 ± 3
$N_{Water}(M^+)$	2.0 ± 0.1	2.7 ± 0.5	3.5 ± 0.7
$n_{+/-}$	61	9	0
$E_{18C6/M}$	-67 ± 3	-53 ± 3	-47 ± 3
$E_{18C6/Wat}$	-16 ± 5	-21 ± 5	-27 ± 6
$E_{M/Wat}$	-74 ± 10	-63 ± 9	-53 ± 9
<i>At the interface</i>			
$d_{M-O(18C6)}$	2.8 (x6)	3.0 (x6)	3.2 (x6)
$d_{M-Pic}$	7 ± 1	20 ± 11	13 ± 5
$N_{Water}(M^+)$	2.1 ± 0.3	2.1 ± 0.7	3.0 ± 0.8
$n_{+/-}$	26	0	0
$E_{18C6/M}$	-67 ± 4	-57 ± 3	-47 ± 3
$E_{18C6/Wat}$	0 ± 5	-2 ± 4	-2 ± 3
$E_{M/Pic}$	-44 ± 4	-23 ± 17	-30 ± 11
$E_{M/Wat}$	-60 ± 10	-61 ± 20	-54 ± 14

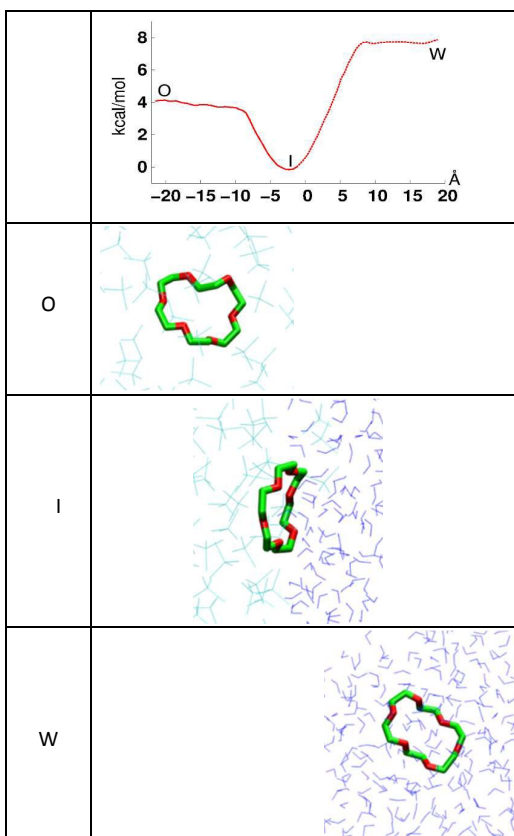
The resulting free energy curve (Figure 4) again displays a deep minimum at the interface ( $\Delta A_{Wi} \approx 8$  kcal/mol,  $\Delta A_{Oi} \approx 4$  kcal/mol) but the  $\Delta A_{Wo}$  energy difference ( $\approx 4$  kcal/mol) is now correctly in favor of the chloroform phase, somewhat too high, though. In summary, the predicted partitioning results from a subtle balance between the electrostatic representation of the two solvents and of the solute.<sup>[59]</sup> All models however confirm the surface activity of 18C6, in spite of its centrosymmetrical structure. This is a key feature, regarding the extraction mechanism.

#### Transfer of the 18C6/ $M^+$ Pic<sup>-</sup> complexes ( $M^+ = Na^+, K^+, Cs^+$ ).

Although the free energy profiles for interface crossing by the complexes are unknown, it is clear from extraction and



**Figure 3.** "Transfer" PMF<sub>0.5±1.0</sub> of  $K^+ Pic^-$  across the interface. Free energy curve ( $\Delta A$  in kcal/mol, as a function of the  $d$  distance in Å). Snapshots are given in Figure S11.



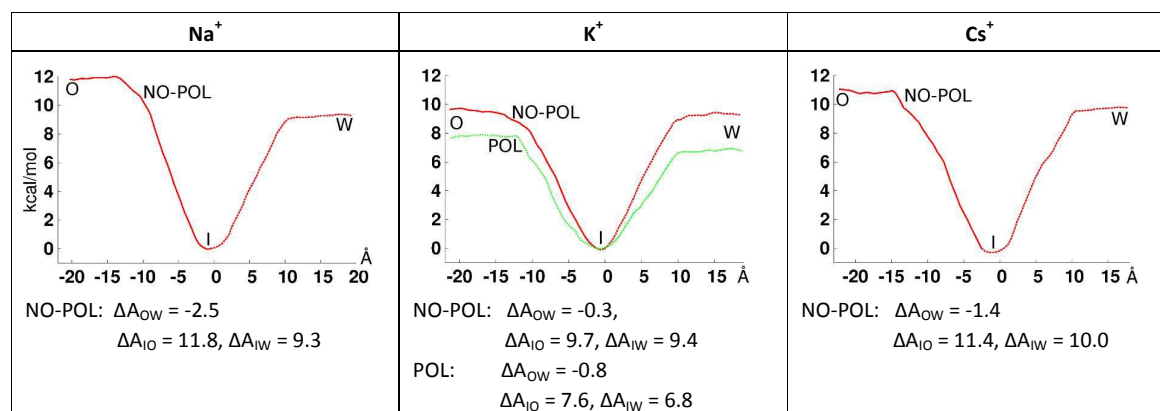
**Figure 4.** Transfer PMF<sub>0.5±1.0</sub> of 18C6(-0.34) across the interface.

Free energy curves ( $\Delta A$  in kcal/mol, as a function of the  $d$  distance in Å) and snapshots at the O, I and W positions. PMFs with the other models are shown in Figure S12.

thermodynamic experiments that the complexes prefer the oil phase. Experimentally, their free energies of transfer from water to chloroform are negative, more than for 18C6 uncomplexed:  $\Delta G_t \approx -4.7$ ,  $-6.5$  and  $-6.0$  kcal/mol, respectively for the  $Na^+$ ,  $K^+$  and  $Cs^+$  complexes.<sup>[37]</sup> Furthermore, in contrast to the case of 18C6 alone, their transfer is driven by a negative enthalpy ( $\Delta H_t \approx -4.4$ ,  $-7.9$  and  $-10.3$  kcal/mol, respectively), while the entropy is close to zero or unfavorable ( $T\Delta S_t \approx 0.2$ ,  $-1.4$  and  $-4.3$  kcal/mol, respectively).<sup>[37]</sup> As seen below, computationally "predicting" the partitioning of the three complexes is highly sensitive to their electrostatic representations.

The first series of simulations used the 18C6(-0.6) charge set with the hope to prevent dissociation of the complex when its center of mass "CM" is moved from away from the interface. In the case of 18C6/ $Na^+$ , however, this was not sufficient and we thus added a weak harmonic constraint (with a force constant  $k$  of 20 kcal/mol.Å<sup>2</sup>) on the  $M^+ \dots O_{18C6}$  distances smaller than 2 Å or longer than 4 Å, in order to keep the integrity of the complexes. Furthermore, we observed that when the CM(complex) is pulled towards water, the Pic<sup>-</sup> anion does not accompany the 18C6/ $M^+$  moiety, but stays at the interface. An harmonic constraint ( $k = 20$  kcal/mol.Å<sup>2</sup>) was thus also imposed to keep  $M^+ \dots Pic^-$  distances in the 3-10 Å range to maintain the phases neutrality along the ion





**Figure 5.** Transfer PMF<sub>0.5+1.0</sub> of the 18C6/ $\text{M}^+$  Pic<sup>-</sup> complexes across the interface. Free energy curves ( $\Delta A(z)$  in kcal / mol) obtained with the 18C6(-0.6) NO-POL (red) and POL models (in green), with +1 charged  $\text{M}^+$  ion. Snapshots at typical positions are shown in Figure S13.

transfer. The PMF results are presented in Figures 5 and S13. With the three cations, a deep energy minimum (of about 10 kcal/mol with respect to the bulk phases) is observed at the interface, where the crown oscillates between different orientations. The transfer to the oil phase is found to be energetically similar for the  $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{Cs}^+$  complexes, but less favorable than the transfer to the aqueous phase ( $\Delta A_{WO} \approx 2.5$ , 0.3 and 1.4 kcal/mol, respectively). Increasing the sampling from PMF<sub>0.5+1.0</sub> to PMF<sub>0.01+1.5</sub> yields for the  $\text{K}^+$  complex a similar  $\Delta A_{WO}$  energy (-0.7 kcal/mol) and thus no preference for the oil phase, which remains inconsistent with the experiments. This led us to test three other electrostatic variants. The first one includes polarization effects, known to decrease the polarity of the solvents near the interface, and to increase the surface activity of ions.<sup>[60-66]</sup> We thus recalculated the PMF<sub>0.5+1</sub> of 18C6(-0.6)/ $\text{K}^+$ , using the POL parameters. The resulting free energy profile (Figure 5) is similar to the "NO-POL" one, with a deep minimum (of 6 to 8 kcal/mol) at the interface, and a tiny preference for the aqueous over the oil phase ( $\Delta A_{WO} \approx 0.8$  kcal/mol). It thus looks as if these simulated complexes are too well hydrated and still not hydrophobic enough.

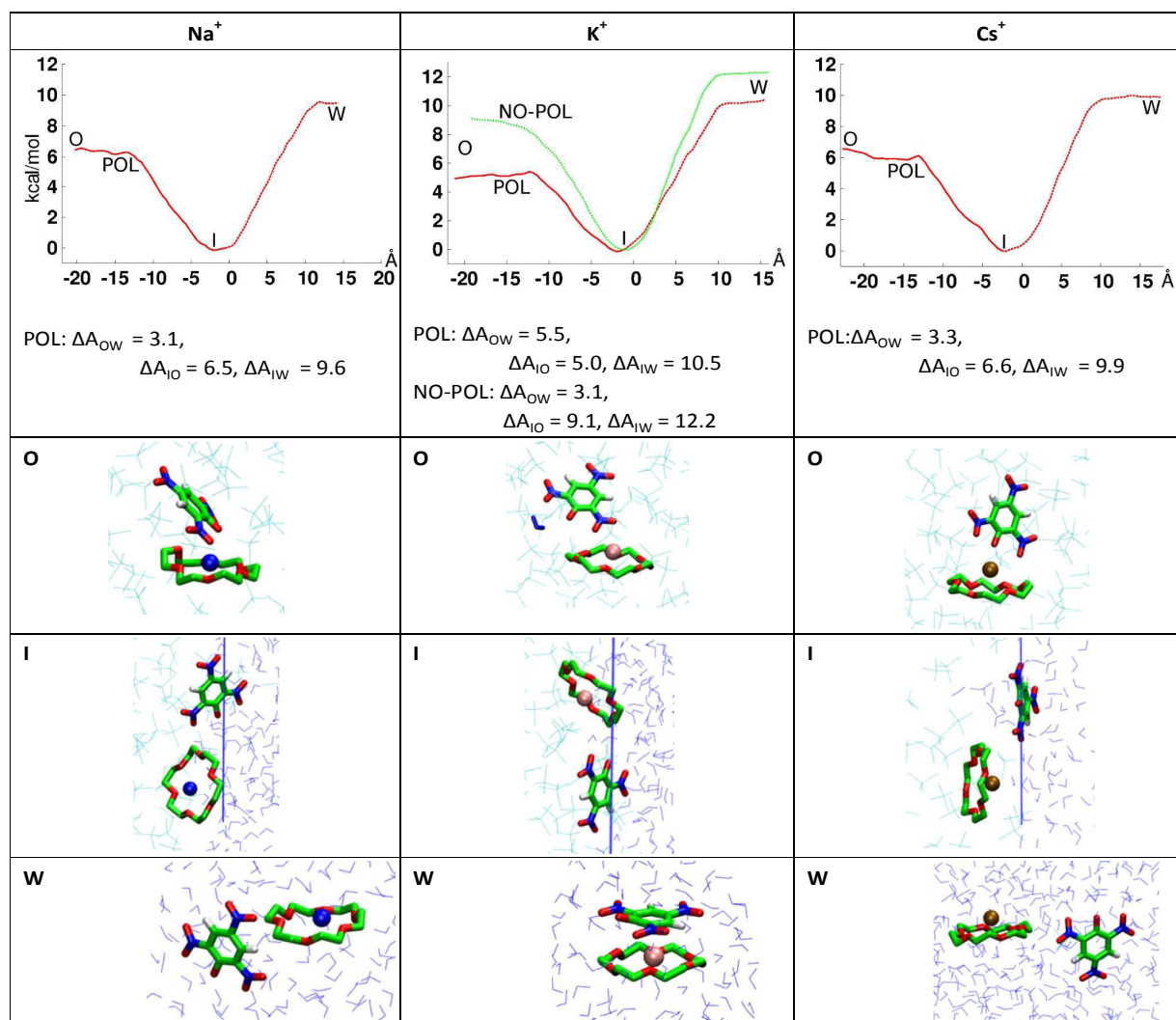
The two other variants deal with the charge distribution within the complexes, without or with polarization. Indeed the complexes were modelled so far, like in related simulations,<sup>[28, 30, 31, 35, 67]</sup> with an integer charge (+1) on the cation, thereby neglecting electron reorganization effects (ligand to cation charge transfer plus some internal polarization) upon complexation. However, mimicking the latter by ESP charges on the complex has been shown to markedly determine, for instance, the partitioning of uranyl or trivalent lanthanide cation complexes of TBP or amide ligands.<sup>[33, 51, 68]</sup> We thus decided to calculate ESP charges on the whole 18C6/ $\text{K}^+$  complex (6-31G(d,p) DFT level), yielding 18C6(+0.4)/ $\text{K}^+$ (+0.6) instead of 18C6(0)/ $\text{K}^+$ (+1) charges on 18C6 and the cation. With this set, we recalculated the PMF<sub>0.5+1</sub> with both NO-POL and POL models, keeping the same internal constraints as above. As seen in Figures 6 and S14, the resulting  $\Delta A_{WO}$  energies (-3.1 and -5.5 kcal/mol, respectively) are now in favor of the oil phase and the POL  $\Delta A_{WO}$  energy matches nicely (within 1 kcal/mol) the experimental energy of transfer  $\Delta G_t$  of the complex.<sup>[37]</sup> Furthermore, the two models confirm the high affinity of the complex for the interface ( $\Delta A_{IO} = 9.1$

and 5.0 kcal/mol, respectively). Repeating the PMF for the  $\text{Na}^+$  and  $\text{Cs}^+$  complexes with polarization and 18C6(+0.4)/ $\text{M}^+$ (+0.6) ESP charges also predicts a partitioning to the organic phase ( $\Delta A_{WO} = -3.1$  and -3.3 kcal/mol, respectively) and a deep minimum at the interface. Interestingly, among the three complexes, the  $\text{K}^+$  one is found to be most easily transferred, as seen above in the NO-POL simulations with 18C6(0)/ $\text{M}^+$ (+1) charges, and as observed experimentally.<sup>[37]</sup> The preferred  $\text{K}^+$  transfer likely stems from the "nested" position of this cation that does not co-extract water, while  $\text{Na}^+$  attracts more water (it co-extracts 1  $\text{H}_2\text{O}$  molecule to the oil phase), and  $\text{Cs}^+$  is perched over the ring, less shielded than  $\text{K}^+$  from the solvent.

**Transfer of the DCH18C6/ $\text{K}^+$  Pic<sup>-</sup> complex.** The affinity of the complex for the oil phase can thus be increased computationally by taking into account electronic reorganization, but also chemically via suitable substituents, as illustrated here with the DCH18C6 ligand. The latter still displays appreciable aqueous solubility (0.036 M at 26°C), but affords more hydrophobic complexes than 18C6 and better extracts alkali halides<sup>[14]</sup> or picrates<sup>[69]</sup> to organic phases. The PMF<sub>0.5+1</sub> free energy curve (Figure 7) for the DCH18C6/ $\text{K}^+$  Pic<sup>-</sup> complex (where the ligand is the *trans-syn-trans* isomer of maximum  $\text{C}_{2h}$  symmetry, and using DCH18C6(0)/ $\text{K}^+$ (+1) charges) now predicts a clear partitioning in chloroform ( $\Delta A_{WO} \approx -5.3$  kcal/mol) with a deep potential well at the interface ( $\Delta A_{IW} = 14.5$ ;  $\Delta A_{IO} = 9.2$  kcal/mol). A fortiori, taking into account electron redistribution effects within the complex will further enhance its partitioning in the chloroform phase.

## Discussion

We have studied by MD and PMF simulations interfacial features of the liquid-liquid extraction of  $\text{M}^+$  alkali cations by 18C6, consistently comparing  $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{Cs}^+$  cations with different electrostatic models. As a prerequisite, complexation in the source phase has been thoroughly examined. This extends previous work on  $\text{RNH}_3^+$  complexation and extraction,<sup>[27]</sup> raising here the issue of binding strength and molecular recognition (selectivity) when the three cations are compared. In the following, we first discuss the selectivity



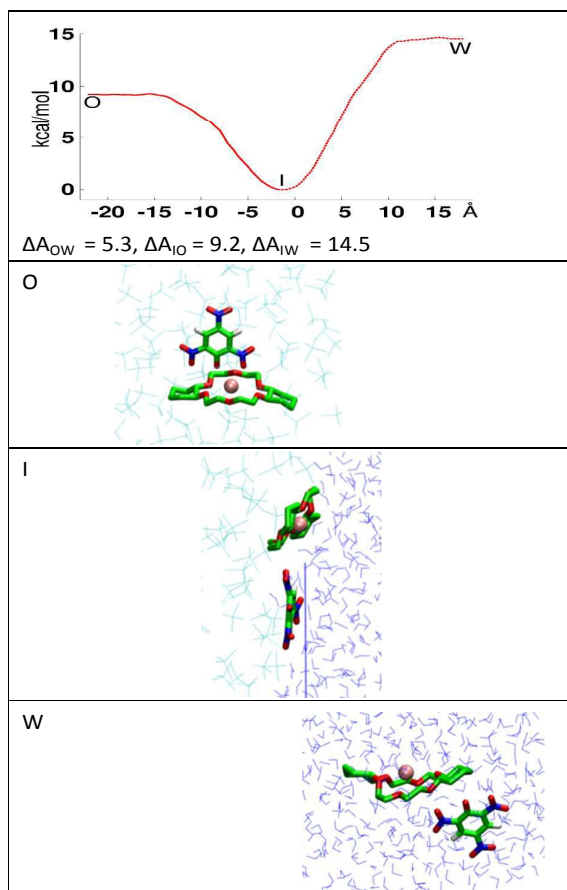
**Figure 6:** Transfer PMF<sub>0,0+1</sub> of 18C6/ $\text{M}^+$  Pic<sup>-</sup> complexes (depicted with 18C6(+0.4)/K(+0.6) ESP charges) across the interface. Free energy curves ( $\Delta A$  in kcal / mol) and snapshots at the O, I and W positions.

upon complexation in water and upon extraction. Then, we address the question of "what happens at the interface" upon cation extraction by 18C6, with implications regarding the extraction mechanism.

**Binding selectivities in water from the alchemical and the PMF routes.** Experimentally, the free energy  $\Delta G_c$  of  $\text{Na}^+$ ,  $\text{K}^+$  or  $\text{Cs}^+$  binding in water is driven by a negative enthalpic term ( $\Delta H_c = -2.2$ ,  $-6.2$  and  $-3.8$  kcal/mol, respectively), antagonistic to the entropic one ( $T\Delta S_c = -1.1$ ,  $-3.4$  and  $-2.4$  kcal/mol, respectively), both contributing to the selectivity, measured by  $\Delta\Delta G_c$ .<sup>[11]</sup> On the computational side,  $\Delta\Delta G_c$  may be obtained by the PMF route ("physical" complexation pathway) or via alchemical mutations. The latter should be more accurate, because they neither require to sample intermediate complexation steps along the PMF, nor to convert the  $\Delta A(d)$  into  $\Delta G_{\text{diss}}$  energies. The  $\text{K}^+/\text{Na}^+$ ,  $\text{Cs}^+/\text{K}^+$  and  $\text{Na}^+/\text{Cs}^+$  selectivities obtained for the

PMF and mutation routes ( $\Delta\Delta G_{\text{PMF}}$  and  $\Delta\Delta G_{\text{Mut}}$ , respectively) are reported in Table 3.

Mutations with the different models correctly predict the binding sequence:  $\text{K}^+ > \text{Cs}^+ > \text{Na}^+$ . The NO-POL  $\Delta\Delta G_{\text{Mut}}(\text{K}^+/\text{Na}^+)$  energies are  $\Delta\Delta G_{\text{Mut}} = 2.8$ ,  $2.2$ ,  $2.5$  and  $2.8$  kcal/mol, when  $q_0 = -0.34$ ,  $-0.6$ ,  $-0.5$  and  $-0.4$  e, respectively ( $\Delta\Delta G_{\text{exp}} = 1.7$  kcal/mol). For  $\text{K}^+/\text{Cs}^+$ ,  $\Delta\Delta G_{\text{Mut}} = 2.1$ ,  $1.8$ ,  $2.2$  and  $1.9$  kcal/mol, respectively ( $\Delta\Delta G_{\text{exp}} = 1.5$  kcal/mol). Note the rather weak dependence of  $\Delta\Delta G_{\text{Mut}}$  on 18C6 charges. The POL model somewhat overestimates the  $\text{K}^+/\text{Na}^+$ ,  $\text{Cs}^+/\text{K}^+$  and  $\text{Na}^+/\text{Cs}^+$  selectivities, by 0.6 to 1.1 kcal/mol, compared to experiment. The small preference for  $\text{Cs}^+$  over  $\text{Na}^+$  ( $\Delta\Delta G_{\text{exp}} = -0.2$  kcal/mol) is qualitatively reproduced with the different NO-POL and POL mutations, but somewhat too high, especially with the latter ( $\Delta\Delta G_{\text{Mut}} = -1.0$  kcal/mol). Comparing now the  $\Delta\Delta G_{\text{Mut}}$  to the  $\Delta\Delta G_{\text{PMF}}$  energies, they are found to agree with each other within  $\approx 1$  kcal/mol or less with both NO-POL and POL models.



**Figure 7.** Transfer PMF<sub>0.5±1.0</sub> of DCH18C6/  $K^+$  Pic<sup>-</sup> across the interface. Free energy curve ( $\Delta A$  in kcal / mol) and snapshots at the O, I and W positions.

Arguably, the calculated binding energies and selectivities are not only sensitive to the choice of 18C6 charges but also on the solvent and cation models (see for instance ref. [70]), as illustrated by the comparison of SPC/E to TIP3P water, and of  $M^+$  Dang's parameters used throughout the study to the Cheatham's ones [71] (Table 3). For the studied combinations, however, the  $\Delta G_{\text{diss}}$  and  $\Delta \Delta G_{\text{Mut}}$  energies generally differ by less than 1 kcal/mol, and the preference for  $K^+$  is found to be unchanged.

**Ion extraction selectivity.** The PMF simulations consistently indicate that  $K^+$  is best extracted because (i) it forms the most stable complex in the aqueous phase and at the interface, and (ii) its complex has the most negative free energy of transfer to the oil phase. Alternatively, the difference  $\Delta \Delta G_{\text{ext}}$  in free energies of extraction of  $M_1^+$  versus  $M_2^+$  ions can be estimated via the thermodynamic cycle (1), where the "solv" solvent is "oil" (chloroform):  $\Delta \Delta G_{\text{ext}} = \Delta G_{1-\text{ext}} - \Delta G_{2-\text{ext}} = \Delta G_{3-\text{aq}} - \Delta G_{4-\text{oil}}$ . The results obtained without polarization (18C6(-0.6) or 18C6(-0.34) charges; SPC/E water) and with the POL model are reported in Table 5, together with the experimental values.<sup>[37]</sup> With the three models, the calculated extraction order agrees

**Table 5:** Calculated differences in free energies of complexation and of extraction of  $M^+$  Pic<sup>-</sup> (in kcal/mol). See Scheme 1 for definitions, where "solv" is either water or "oil" (chloroform).

		$\Delta G_{3-\text{aq}}$	$\Delta G_{4-\text{aq}}$	$\Delta G_{4-\text{oil}}$	$\Delta \Delta G_{\text{c-aq}}$	$\Delta \Delta G_{\text{ext}}$
$\text{Na}^+ \rightarrow \text{K}^+$	(-0.6) <sup>a,b</sup>	17.2	15.0	11.3	2.2	5.9
	(-0.34) <sup>a,b</sup>	17.2	14.4	10.9	2.8	6.3
	POL(-0.4)	20.0	16.7	12.1	3.3	7.9
	Exp	16.7 <sup>c</sup>			1.7	3.6 <sup>d</sup>
$\text{K}^+ \rightarrow \text{Cs}^+$	(-0.6) <sup>a,b</sup>	9.5	11.3	12.1	-1.8	-2.6
	(-0.34) <sup>a,b</sup>	9.5	11.6	11.9	-2.1	-2.4
	POL(-0.4)	12.4	14.7	13.6	-2.3	-1.2
	Exp	11.0 <sup>c</sup>			-1.5	-2.0 <sup>d</sup>

a) SPC/E water. b) NO-POL model. c) Marcus, Y. *Ion Solvation*; Wiley: Chichester, 1985.

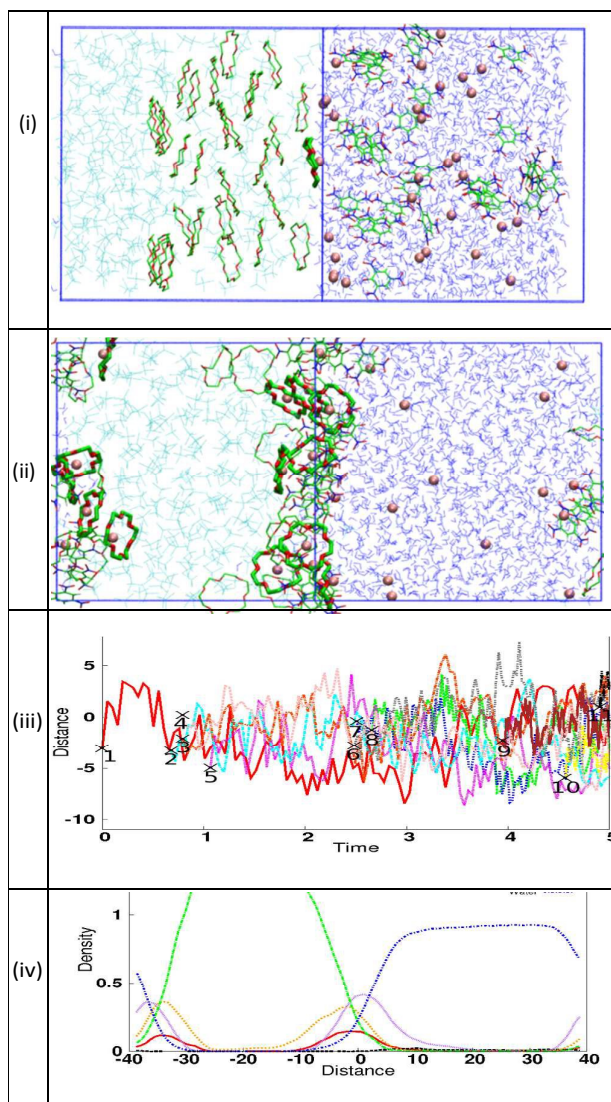
d) Takeda, Y.; Tanaka, A.; *Bull. Chem. Soc. Jpn.*, **1986**, 59, 733.

with the experimental one:  $K^+ > \text{Cs}^+ > \text{Na}^+$  ( $\Delta G_{\text{ext}} = -8.4$ ,  $-6.4$  and  $-4.8$  kcal/mol, respectively).<sup>[37]</sup> Thus,  $\text{Na}^+$  is the least well extracted cation, mainly because it has the highest dehydration energy;  $K^+$  interacts less well than  $\text{Na}^+$  with 18C6, but gets more easily dehydrated and thus complexed and transferred to the organic phase. The  $\text{Cs}^+$  case is intermediate between  $\text{Na}^+$  and  $K^+$ . Comparing now the selectivities of extraction ( $\Delta \Delta G_{\text{ext}}$ ) to those of complexation in water ( $\Delta \Delta G_{\text{c-aq}}$ ), the formers are higher (by a factor of  $\approx 2$  for  $\text{Na}^+ / \text{Cs}^+$ ), as observed experimentally. This stems from the fact that  $\Delta G_{4-\text{oil}}$  energies are lower than the  $\Delta G_{4-\text{aq}}$  ones, in keeping with the poorer solvation of the complexed cation in chloroform, compared to water.

**Interfacial activity and extraction mechanism.** The NO-POL and POL PMF simulations on interface crossing by 18C6 and by its 18C6/ $M^+$  Pic<sup>-</sup> complexes demonstrate the high surface activity of these species, in spite of their non-amphiphilic topologies. This feature is consistent with indirect data, like surface tension measurements at the air / water interface,<sup>[72]</sup> electrochemical<sup>[73-75]</sup> and kinetic studies on 18C6 derivatives.<sup>[76, 77]</sup> Regarding the extraction mechanism, our results strongly support a dominant interfacial process, as for amphiphilic extractants.<sup>[77, 78]</sup> Although 18C6 is somewhat soluble in water, it is more concentrated at the interface than in either bulk phase. On the water side, the Pic<sup>-</sup> anions adsorbed at the interface attract the  $M^+$  ions, facilitating their capture by 18C6. Generally speaking, the more lipophilic is the  $X^-$  anion, the higher is its surface activity (Hofmeister classification<sup>[79]</sup>) and the resulting attraction of  $M^+$  ions near the water surface.

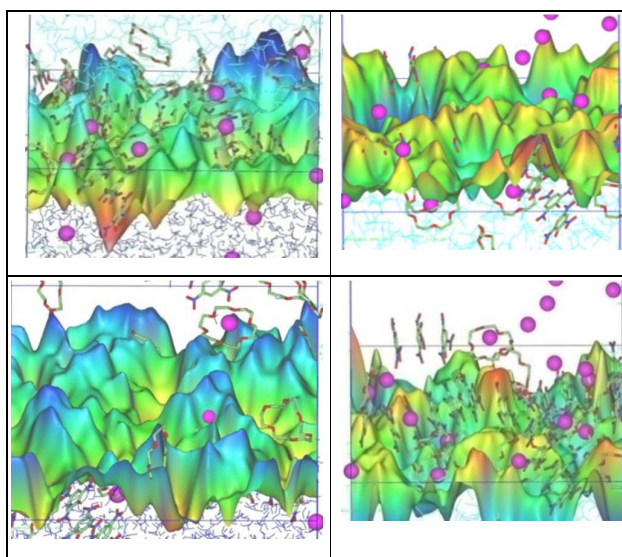
That complexation occurs "at the interface" is further nicely supported by the following MD experiment. We simulated a chloroform / water solution of 30 [ $K^+$  18C6 Pic<sup>-</sup>] species (18C6(-0.4); POL force field), involving a single 18C6/ $K^+$  complex depicted with 18C6(0)/K(+1) charges. Initially, the solutes were placed where they are most soluble, namely 18C6 in





**Figure 8:** 30  $K^+$  18C6  $Pic^-$  species at the interface (18C6(-0.4) POL model). From top to bottom: snapshot (i) at 0 ns and (ii) after 5 ns of dynamics; (iii)  $K^+$ -Interface distance (in Å) of the complexes as a function of time (in ns), from the time of their formation along the dynamics (excluding the complex preformed at 0 ns); (iv) density curves (average over the last ns; color codes: water *blue*, chloroform *green*, 18C6/M<sup>+</sup> complex *red*, 18C6 *yellow*,  $Pic^-$  *purple*,  $K^+$  *black*). A zoom on (ii) and (iii) is shown in Figure S15.

chloroform and the ions in water, while the complex was at the interface (see Figure 8(i)). During the dynamics, the system rearranged markedly: eleven additional complexes progressively formed near the two interfaces, and remained there until the end. Figures 8(iii) and S15(iii) plot their distance from the interface(s), starting from the time of their formation. After 5 ns, one finds four complexes at one interface, and eight on the other interface. All  $Pic^-$  ions and most uncomplexed



**Figure 9:** Views of the interfacial surface with 30  $K^+$  18C6  $Pic^-$  species (POL force field). The interface is shown "horizontally" with the water phase either below (left side) or on top (right side). Line 1: water surface; line 2: chloroform surface. The surface of a given liquid L is defined by the  $z_{max}$  positions of the L molecules that are not "isolated", but connected to the bulk L via other L molecules. A zoomed version of this Figure is given in Figure S16.

18C6 species have finally migrated to the interface(s). In the interfacial slab, some complexes oscillate up to 3 Å towards water and up to 7 Å towards the oil phase, without being fully extracted, though. Their migration to the bulk oil phase should be promoted by two main factors: physically, by saturation of the interface at higher concentrations<sup>[80]</sup> and, computationally, by taking into account the electron redistribution within the complex.

The picture of the "interface" emerging from the simulations (Figures 8 and 9) is, like for other biphasic water/oil systems,<sup>[81-83]</sup> a thin nano-region. The average water and oil density curves reach their bulk values  $\approx 1.5$  nm beyond the Gibbs surface ( $z = 0$ ). Instantaneously, the interface is very rough. The resulting "waves" have an amplitude of  $\approx 1.5$  nm and oscillate along the dynamics, favoring interactions between the reaction partners and thereby formation and diffusion of the complex. Such interfaces correspond to the "macroscopic" interface between the two liquids at rest, as well as those appearing at the surface of water-in-oil microdroplets that progressively form along the demixing process. Furthermore we note here interesting "aggregation" features of the  $Pic^-$  anions that form labile stacks, of up to twelve units at the interface, in spite of their coulombic repulsions. The resulting concentrated negative charge further attracts the cations and their complexes at the interface. Beyond ion extraction, aggregation phenomena near the interface may be viewed as a supramolecular organization process, involved for instance in the early steps of crystallization, or of formation of organized nano-structures, as

observed with highly charged polyoxometallate<sup>[84]</sup> or with dicarbolide anions.<sup>[85]</sup>

## Conclusions.

In order to get microscopic insights into a prototypical extraction system, MD and PMF simulations on the extraction of alkali picrate salts by 18C6 from an aqueous to an oil phase have been reported. As a prerequisite, we have considered the Na<sup>+</sup>, K<sup>+</sup> and Cs<sup>+</sup> complexation in the source phase (water), where PMFs with different charge models without or with polarization satisfactorily predict the binding energies of the three cations, and thus the "recognition" of K<sup>+</sup>. At the interface, the K<sup>+</sup> and Cs<sup>+</sup> complexes are found to be stronger than in bulk water, while the Na<sup>+</sup> one is weaker.

The calculated free energy profiles for interface crossing by 18C6 and its 18C6/M<sup>+</sup> Pic<sup>-</sup> complexes demonstrate their high surface activity and the preference for 18C6/K<sup>+</sup> over 18C6/Na<sup>+</sup> or 18C6/Cs<sup>+</sup> transfer to chloroform. The partitioning of 18C6 and of its complexes, experimentally driven by different thermodynamic "forces" (entropy and enthalpy, respectively), is computationally found to be quite sensitive to the electrostatic representation of the system. For the simulated complexes, explicit representation of polarization effects is found to be less important than electron reorganization upon complexation (as mimicked by atomic ESP charges). Regarding the extraction mechanism, we suggest that the ion capture by 18C6 mainly occurs "right at the nano- oil / water interface".

This work calls for methodological improvements regarding for instance the energy representation of the system and the free energy calculations (see for instance<sup>[23, 86, 87]</sup>) including time accelerating procedures and metadynamics with collective variables,<sup>[88]</sup> as well as for thermodynamic and structural characterization of liquid-liquid interfaces involved in assisted ion extraction.<sup>[89-91]</sup> Beyond extraction, the results contribute to our understanding of aqueous interfaces in areas like interfacial nanochemistry,<sup>[89]</sup> electrochemistry,<sup>[73]</sup> biphasic catalysis,<sup>[92]</sup> drug delivery and biological processes,<sup>[93]</sup> or enhanced reactivity in confined droplets.<sup>[94-96]</sup>

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## ARTICLE

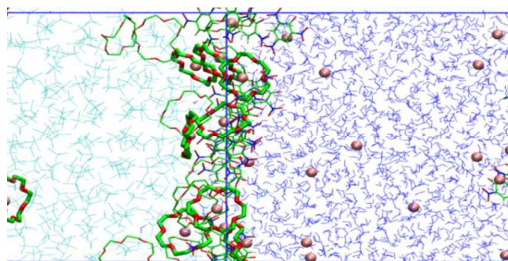
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**TOC Table of Content**

" Liquid-Liquid Extraction of Alkali Cations by 18-Crown-6: Complexation and Interface Crossing Studied by MD and PMF Simulations "

By Gael Benay and Georges Wipff \*



The 18C6/ $M^+$  Pic $^-$  complexes form and adsorb "right at the nano-interface" where 18C6 prefers the  $K^+$  guest.