Decomplexation and complexation of alkali metal cations by a crown-ether-type podand in dichloromethane: a steered molecular dynamics study

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Abstract The decomposition of three complexes involving the alkali metal cations Li^+, Na^+ and K^+ and a potentially octadentate polyethylene-glycol-type podand(1,2-bis-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-benzene, hereafter *b33*) in dichloromethane was studied by steered molecular dynamics (SMD). This technique proved applicable to the problem. Analysis of the resulting trajectories allowed phenomenological descriptions of the decomposition processes. Use of the Jarzynski identity allowed the estimation of the corresponding free energies, which in turn allowed the estimation of the complex formation free energies in dichloromethane. These are very similar to the experimental values determined by liquid-liquid extraction, as long as a strong reduction of the podand denticity is considered, possibly due to the presence of competing water molecules. To the best of our knowledge, the present study is the first to use SMD to address the problem of determination of the free energies involved in the complexation of alkali cations by an extraction agent (here a podand), in a bulk solvent (here dichloromethane).

Keywords Steered molecular dynamics · Alkali cation extraction · Polyethylene-glycol-type podands · Liquid-liquid extraction

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1 Introduction

Since their discovery by Pedersen [1], crown-ethers (the simplest of coronands) have been well known for their ability to complex alkaline metal cations and act as extraction agents towards them, promoting their transference from aqueous to organic phases. They are nowadays widely used in synthesis, and in analytical chemistry to give but two examples.

The characteristics of the structurally similar but synthetically less demanding polyethylene-glycol-type podands are not nearly so well known but may prove interesting. This led us to our ongoing experimental [2] and theoretical [3–5] study towards the characterization of these molecules as extraction agents towards alkaline metal cations.

It is widely recognized that there are numerous factors affecting the cation selectivity shown by crown-ethers towards cations. It is usually considered that one of the most important factors is the size match between the dimensions of the cation and of the central cavity of the coronand. In what concerns polyethylene-glycol-type podands, it has been found experimentally that independently of the size of the pseudo-cavity they are able to selectively extract K^+ (against Na^+ and Li^+) from water to dichloromethane (DCM), a very common solvent in liquid-liquid extraction [2]. In fact, the cation selectivity found for these systems is linked to the number of cation-oxygen interactions permitted by the size of the cation [2]. This rationale is supported by quantum calculations [5].

Our choice of solvent in the present work stems from the fact that a previous work [3] provided evidence supporting the hypothesis that the complexation step occurs in the organic (DCM) phase, thus assessment of the free energies of complex formation and decomposition will provide

valuable insight into the understanding of the experimentally found selectivity [2].

The theoretical assessment of the free energy of complexation in bulk dichloromethane (where the complexation is thought to occur [3, 6]) may provide valuable insight into the full understanding of the selectivity pattern found experimentally.

As the interactions between alkali metal cations and oxygen atoms are mainly non-covalent in nature, it is possible to use molecular dynamics to study the bonding between those cations and polyethylene-glycol-type podands. It is currently recognized that as long as some care is taken [7], molecular dynamics (MD) shows good phenomenological validity, in particular in systems where no heavy electronic rearrangements (e.g. due to covalent bond breaking or bond forming) happen. Consequently, it is currently the method of choice to model systems as ours, not only because it allows the explicit inclusion of hundreds of solvent molecules (comprising thousands of atoms), but also because they are extremely fluxional and, as such, not adequate to a high-level quantum calculation. It is noteworthy that alkali metal cation complexation by crown-ethers was one of the first problems to be studied by MD [8, 9], and most published work in this area has been on them [8–14], on spherands [15–21] or on cryptands [14, 21–26], with only a few studies involving podands [3, 4, 27–29].

These complexes are quite stable in dichloromethane, and decomplexation is a rare event, at least on the nanosecond time scale [3]. Steered molecular dynamics (SMD) has been known to allow the study of such rare events in a reasonable time span by application of a time-dependent external force that pulls the system through a chosen reaction coordinate. An average of the work (W) done through this process (over a set of decomplexation trajectories) may be related to the free energy difference between the final (free) and initial (complexed) states (ΔG) by what is known as the Jarzynski identity [30],

$$\langle \exp[-W/k_\mathrm{B}T] \rangle = \exp[-\Delta G/k_\mathrm{B}T] \qquad (1)$$

SMD has been used to get insights into processes such as the mechanical stability of proteins [31–38], the unfolding and the binding or unbinding of biomolecules [39–46], the transport across membranes [47–51], conformational studies [52] or even the development of new materials [53] or the clarification of enzymatic pathways [54]. In this paper, we report the use of SMD to assess the free energy of decomplexation of the Li$^+$, Na$^+$ and K$^+$ cations from their complexes with the polyethylene-glycol-type podand $b33$ (Fig. 1), in bulk DCM.

A word about our choice of the picrate anion (the most frequently used anion in liquid-liquid extraction of alkali metal cations [55]) and its influence on the complex formation/decomposition processes seems appropriate here. In
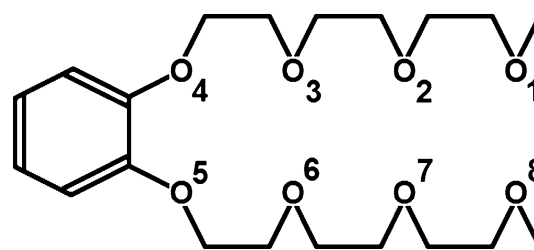
Fig. 1 *Schematic* representation of the $b33$ podand and the oxygen atom numbering scheme used in the text

a previous work [4], we showed that the presence of a picrate anion near the [K $b33$]$^+$ complex proved only slightly disrupting to its stability, reducing the average podand denticity from 8 to 7. In fact, the main effect seemed to be the stochastic formation of close ion-pairs involving the complex and this bulky anion. In what regards liquid-liquid extraction, the picrate ion is known to be soluble in organic and in aqueous media as well. By contrast, in a recent work on in liquid-liquid extraction by MD [56], the nitrate ion has been shown to be to hydrophilic to co-extract to the organic phase.

2 Methods

Steered molecular dynamics simulations were performed using the AMBER 9 [57] software package. The $b33$ podand molecule was parameterized as previously described [3, 4], in agreement with the typical premises followed in the general AMBER force field (GAFF) [58]. The van der Waals parameters used for the alkali cations were derived from the work of Åqvist [59], while dichloromethane was accounted for using the molecular mechanics parameters of Fox and Kollman [60].

The starting systems were prepared by immersing the solute (a [M $b33$]$^+$ molecule, where M stands for Li, Na or K) in the centre of boxes filled with DCM molecules to a minimum distance of 20 Å in every direction. The resulting boxes comprise a total of 825 DCM molecules. An initial ten thousand steps, minimization stage was performed on these boxes by applying the steepest descent method followed by an equal number of steps using the conjugate gradient method. This was followed by equilibration stages performed sequentially in two moments: first the systems were allowed to heat from 0 to 300 K in fifty thousand steps (with a time step of 1 fs), corresponding to 50 ps, using temperature control (Langevin dynamics with 1 ps^{-1} collision frequency), at constant volume (no pressure controls were applied). In the second equilibration moment, the systems were allowed to run for two hundred thousand steps (with the same time step), corresponding to 200 ps, at 300 K, using the same temperature control

conditions, at constant (isotropic) pressure, with a pressure relaxation time of 2 ps, in order to achieve a proper final density. During both equilibration steps, the solute movements were restrained by application of a force constant of 200 kcal mol^{-1} Å^{-2}. A 12 Å value for the cut-off was used throughout all minimization, equilibration and production steps.

Ten DCM carbon atoms (target atoms) involved in these SMD runs were chosen from each of the last equilibration frames (used as the starting frames in the production runs), among the ones that were distanced about 30 Å from the cations. During the 5-ns production runs, the movements of these target atoms were restrained by application of a force constant of 200 kcal mol^{-1} Å^{-2}. An equal restraining force constant was applied to the movements of a chosen carbon atom from the aromatic ring of the podand. In each of the simulations, the cations were pulled towards one of the chosen target atoms up to a distance of 3 Å, by a virtual spring (with a spring constant value of 50 kcal mol^{-1} Å^{-2} for Li$^+$ and Na$^+$, and 150 kcal mol^{-1} Å^{-2} for K$^+$), using the same general conditions as for the second equilibration runs.

The choice of the spring constant values was based on the need to maintain the system under the stiff-spring regime [36, 61, 62] and on the reduced work fluctuations experimentally observed [62]. As a velocity of 0.0033 Å ps^{-1} was used in a study [63] of water exchange in the K$^+$ and Na$^+$ hydration sphere in bulk water, and found adequate, and given that the solvent we used in our work is dichloromethane (a less viscous solvent than water), our choice of simulation time (corresponding to a mean pulling velocity of $v = 0.005$ Å ps^{-1}) was found long enough to minimize artificial friction effects with the solvent that would result in an increase in non-conservative work. In order to test our choice of spring constant and velocity values, several runs were performed at other values (5, 10, 50, 100 and 500 kcal mol^{-1} Å^{-2} and 0.250, 0.050, 0.025, 0.0010 and 0.005 Å ps^{-1}). These test runs showed that good stabilization was achieved with a velocity of 0.005 Å ps^{-1}, but similar total work values were achieved by use of velocities up to 0.025 Å ps^{-1}. As already noticed in other studies [62, 63], except for increased standard deviations, the mean total work was not found to be very sensitive to different force constant values within the chosen range tested.

3 Results and discussion

3.1 Phenomenological description of the decomplexation processes

In its initial structure (after the minimization and equilibration steps), the [M $b33$]$^+$ complexes show the central cation closely interacting simultaneously with a number of oxygen atoms present in the podand (five for Li$^+$, seven for Na$^+$ and eight for K$^+$). As the SMD simulations advance through the reaction coordinate, the number of close interactions gradually diminishes, starting from the central oxygen atoms (O$^{(4)}$ and O$^{(5)}$) and ending with one of the terminal oxygen atoms (O$^{(1)}$ or O$^{(8)}$) until the cation is eventually free from the podand.

As typical examples of the decomposition processes, we proceed with the analysis of the cation-oxygen distances as function of the simulation time, for each cation and for each podand oxygen atom based on three chosen SMD trajectories (Fig. 2), which are considered to be representative.
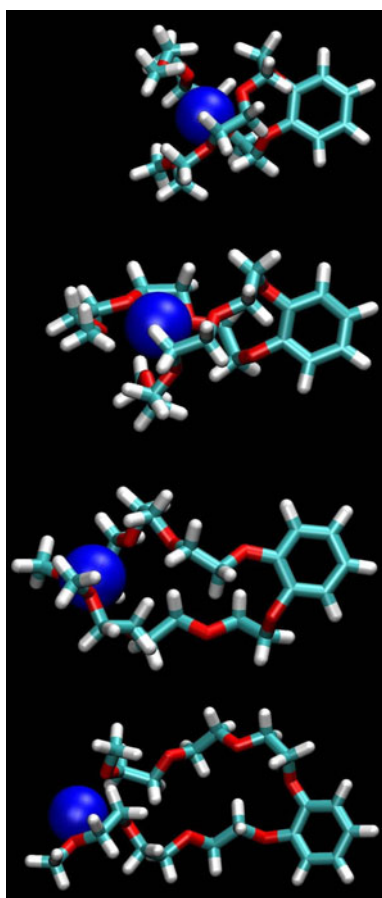
Interestingly, as the Na$^+$ cation was pulled from its initial position, the mean coordination number was seen to increase. Due to its small size, initially the Na$^+$ cation was kept close to the central oxygen atoms and the podand adopted conformations that sterically hinder close interactions of the cation with the terminal oxygen atoms (less than 2.6 Å). When pulled slightly from the vicinity of the central oxygen atoms, the terminal ones were allowed to establish close interactions and the mean coordination number increased. This was observed to a much lesser
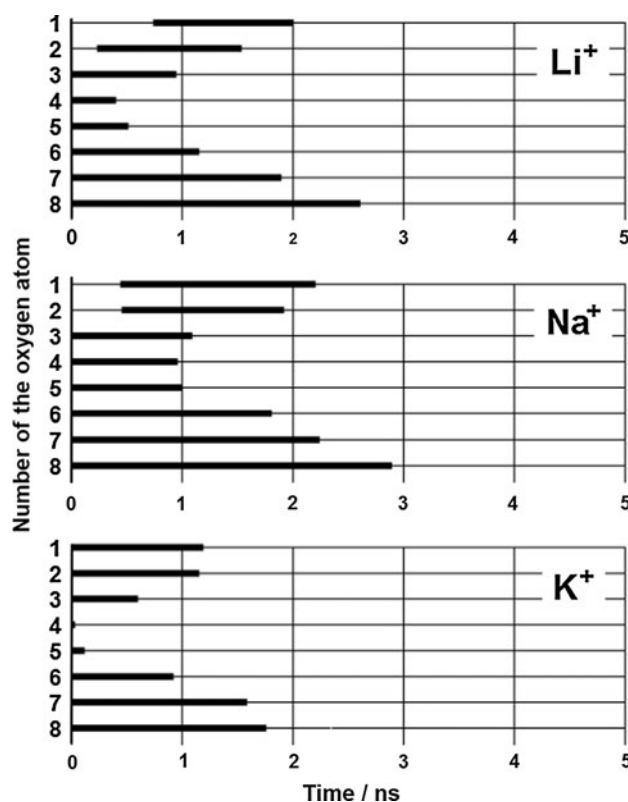
Fig. 2 *Graphical* representation of the typical duration (*broad line*) of strong interactions between each cation and each podand oxygen atom along the full simulation time (the numbering scheme is as in Fig. 1)

degree in the Li^+ case: the size of this cation is too small to effectively allow more than six close interactions with the podand oxygen atoms (less than 2.3 Å), even when slightly pulled from its initial position. When the much bulkier K^+ cation was pulled from its initial position, close interactions (less than 2.9 Å) were quickly broken. As an example, a sequence of snapshots from the decomposition of the $[K\ b33]^+$ complex is shown in Fig. 3.

From the continuous breaking and forming of close interactions between the cations and the podand oxygen atoms observed during the simulations, it may be inferred that individual interactions are not very strong, but as a group, they provide extra stability to these complexes in dichloromethane. In fact, the cation-dipole interactions in the complexes are stronger than the cation-dipole interactions between the cation and the solvent molecules and the dipole-dipole interactions between the podand oxygens and the solvent molecules. This accounts for the complex stabilities in dichloromethane [3, 5].
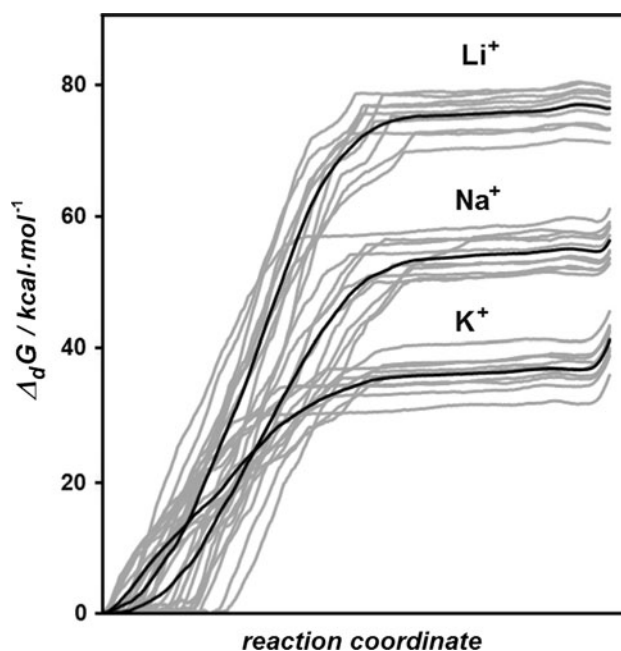
3.2 Decomposition and complexation free energies

The total work performed on the systems during the decomposition processes of the Li^+, Na^+ and K^+ complexes with $b33$ corresponds to the decomposition free energy and is graphically represented in Fig. 4 as a function of the reaction coordinate.

The total decomposition free energy values found for the Li^+, Na^+ and K^+ complexes are, respectively, 76.0 (±2.7), 54.6 (±2.7) and 36.6 (±2.5) kcal mol^{-1} (Table 1). The accuracy of the calculated decomposition free energy is associated to the work fluctuation found [63]. For the operational conditions used in the SMD runs, the free energies for the decomposition processes of the Li^+, Na^+ and K^+ complexes show standard deviations that are 4.4, 4.4 and 4.1 times k_BT, corresponding to 3.6, 4.9 and 6.9% mean errors, respectively. This validates our choice of parameters [30] and provides an indication of the accuracy

Fig. 3 Snapshots from a typical SMD run, showing the K^+ cation (*blue sphere*) in four stages of the decomplexation process (increasing time from *top to bottom*)

Fig. 4 Plots of the free energies of decomposition (Δ_dG) for the [M $b33$]$^+$ complexes (M = Li, Na, K), along the reaction coordinate for the various SMD runs (*light grey lines*) and the corresponding mean value (*black line*)

Table 1 Free energy values (in kcal/mol) determined for the total decomposition processes, Δ_dG (by SMD), calculated for the unitary formation processes, $\Delta_{uf}G$, and for the complex formation, Δ_fG, in dichloromethane (experimental) [2], for each cation

	Δ_dG	$\Delta_{uf}G$	Δ_fG(exp)
Li^+	76.0 (±2.7)	-9.5	-26
Na^+	54.6 (±2.7)	-6.8	-30
K^+	36.6 (±2.5)	-4.6	-35

of the free energy values estimated from ten SMD trajectories.

One must note that during the decomposition process, the smaller cations establish a few close interactions while simultaneously others are broken. In all cases, eight close interactions are broken, but in average, two to four of them were non-existent in the starting structures of the Li^+ complex [3, 5] and one to three of them were non-existent in the starting structure of the Na^+ complex [3, 5], due to the smaller size of these cations when compared to the K^+ cation [3, 5] as referred previously.

Considering, in a first approximation, that the breaking of each close interaction involves an equal amount of free energy, that is, that

$$\Delta_d G = 8 \times \Delta_{ud} G \qquad (2)$$

where $\Delta_d G$ is the total free energy variation involved in the decomposition processes as performed by our SMD experiments, and $\Delta_{ud} G$ is the unitary mean decomposition free energy variation (involved in the breaking of a single close interaction); the values of these unitary free energy variations are 9.5, 6.8 and 4.6 kcal mol^{-1}, respectively, for the Li^+, the Na^+ and the K^+ complexes with $b33$.

Work done while stretching the podand arms seems not to be statistically significant as the mean of the electronic energies calculated at the B3LYP/6-31G(d,p)* level of theory for five sampled initial conformations (without the cation) is not statistically different (at a confidence level of 95%) to the ones calculated for five fully stretched conformations (also without the cation), just prior to the loss of the cation. Thus, the whole work determined by SMD for the decomposition process practically corresponds to the breaking of the cation-oxygen close interactions.

One may consider that the unitary mean decomposition free energy variation ($\Delta_{ud} G$) is symmetrical to the unitary mean formation free energy variation ($\Delta_{uf} G$),

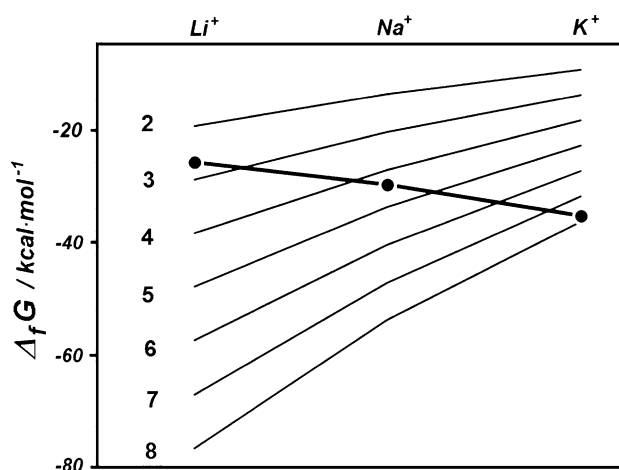$$\Delta_{ud} G = -\Delta_{uf} G. \qquad (3)$$

The formation free energy variation may be estimated by use of the expression

$$\Delta_f G = n \times \Delta_{uf} G \qquad (4)$$

where n corresponds to the mean number of close interactions established in the complex. It is known by experimental [2] and theoretical [3, 5] works that n depends on the size of the cation and may go up to 6 for Li^+, up to 7 for Na^+, and up to 8 for K^+, in the complexes with $b33$ [3, 5] but may be strongly reduced by the presence of water molecules [4].

In extraction experiments, when considering the complexation process in the bulk organic solvent as hinted by theoretical studies [3], the extraction constants (K_{extr}) are related to the formation constants in the organic solvent (K_f) by [64]

Fig. 5 Plots of the formation free energy ($\Delta_f G$) for the Li^+, Na^+ and K^+ cations with the podand $b33$ determined experimentally (*bold line*) and estimated by SMD, by considering the unitary free energy variations ($\Delta_{uf} G$), with $n = 2$ to 8 podand oxygen atoms (*thin lines*)

$$K_{extr} = D \times K_f \qquad (5)$$

where D corresponds to the cation distribution quotients.[1] This expression allows the determination of the experimental formation constant values, from which the corresponding free energies may be calculated by use of the expression

$$\Delta G = -RT \ln K_f. \qquad (6)$$

The graphical comparison (Fig. 5) of theoretical values determined by SMD (using expression (4) with n values varying from 3 to 8) with the experimental values determined using expression (6) hints that, in solution, the number of strong interactions between the Li^+ cation and the podand is somewhat reduced from its ideal coordination number of five to about three. The same happens with the Na^+ cation, for which the coordination number seems to lower from seven to about four, whereas in the case of the K^+ cation, there seems to be no lowering of the coordination number of eight.

This lowering of the podand denticity may be rationalized by considering that the hydration enthalpy for these cations increases from K^+ to Li^+, suggesting a stronger hydration of the smaller cations and to a concomitant reduction of the podand denticity due to the presence of water molecules dragged from the water layer in the liquid-liquid extraction studies, as already hinted by MD studies [4, 55, 65–68] and experimentally observed for other systems [69, 70].

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[1] Unpublished results from our laboratory: D(Li picrate) = 8.0($\pm$0.3) $\times$ 10^{-2}; D(Na picrate) = 5.3($\pm$0.1) $\times$ 10^{-2} and D(K picrate) = 3.5($\pm$0.1) $\times$ 10^{-2} for the K^+ picrate, at 298 K, from water to dichloromethane.

4 Conclusions

By use of SMD, we were able to determine the total decomposition free energies of alkali cation complexes with a podand in dichloromethane. The corresponding values were used to estimate the complexation free energies in this solvent. The resulting values compared very well with the experimental (liquid-liquid extraction) ones as long as a lowering of the podand denticity was considered, which may very well be the case as it is known that in liquid-liquid extraction studies, water molecules do diffuse into the organic layer and compete with the extraction agents for the alkali cations.

Double solvent box SMD studies are under way to clarify the crossing of the water-dichloromethane interface by alkali cations and picrate anion, in order to achieve a fuller understanding of the extraction process at the atomic level.

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