An Investigation of the Template Effects in the Synthesis of Monobenzo-15-Crown-5 Ether by Molecular Dynamics Simulation

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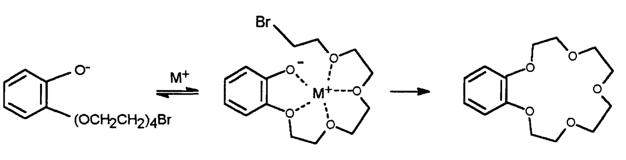
The molecular dynamics simulations of the template effects of alkali metal cations for the synthesis of monobenzo-15-crown-5 were performed. The simulation results qualitatively duplicate the experimental results and Na^+ ion was found to be the best template ion among alkali metal cations.

Template effects in various phases of chemistry are much of recent concern.[1] Particularly, the synthesis of many macrocyclic compounds has been utilized these phenomena to enhance the yield and specificity of the product. Mandolini *et al.* have systematically studied the experimental aspects about the effects of metal ions on the synthesis of crown ethers and verified that the size of the metal ions plays an important role in the synthesis of 18-crown-6 ethers and related molecules.[2] As a first step toward the elucidation of the template effects in organic synthesis, we performed molecular dynamics (MD) simulation for the illumination of the template effects of alkali metal ions on the synthesis of monobenzo-15-crown-5 ether.

The molecular system **1**, precursor for the synthesis of monobenzo-15-crown-5, was built and the minimum energy conformation was determined with MM+ force fields.[3] The AM1 MO calculation was performed with the MM+ minimum energy conformation. The initial structure of the complex **1**-M^+ was constructed by adding appropriate metal template ion to the low energy conformation of precursor **1** and the whole system was optimized again. For the electrostatic interaction energy calculation, the AM1 Mulliken populations were used and the charge of +1e was given for the alkali metal cations.

The MD simulation was carried out for the complex **1**-M^+. After reaching the desired target temperature, 100 ps of the MD simulation was performed under constant temperature condition. During the simulation, the distance between the phenoxide oxygen atom and the bromine bearing carbon atom, r_{CO}, which is critical to the ring closure to form crown ether system, was traced. Representative results for the system of **1**-Na^+ and **1**-Cs^+ at 300 K are given in Figure 1.



1 **1**-M^+

As can be seen from the Figure, the traced distance, r_{CO}, between the reaction sites for **1**-Na^+ oscillates with small amplitude in well-defined fashion. This means that the statistically important conformations of the 1-Na^+ are relatively persistent and the reaction sites are in close proximity during the simulation under the employed conditions. That is a definitely favorable situation for the ring closure to form crown ethers. In contrary to this, **1**-Cs^+ system, which is a clearly misfitting pair, the distance fluctuates considerably with large amplitude and at times diverges into a larger value. The interaction between ether oxygen atoms of **1** and Cs^+ ion is not strong enough to maintain the suitable compact conformation for the ring closure. It is no wonder that the conformation of precursor **1** without any template ion has no consistency at all and the distance between the reaction sites is diverging into a larger value.

To have an insight for the effect of the system temperature and the size of the ion on the reaction, the average distances between the reaction sites of the precursor were obtained as a function of temperature for each ion and are summarized in Table 1. As can be seen from the Table, Li^+ and Na^+ have exerted a markedly favorable effect for keeping the two pertinent atoms in close proximity. The average r_{CO} distance and its standard deviation are remained relatively unchanged with temperature variation. However, with K^+, Rb^+, and Cs^+ ions as a template ion, the average r_{CO} distances increased significantly with the temperature. That also suggests the possible template effect of Li^+ and Na^+ ions in the synthesis of monobenzo-15-crown-5 ether.

For the ring closure reaction, the fraction of time the reaction sites reside within certain effective regions (inside of the reaction field) might be another crucial parameter. So we estimated the fraction of time that the two pertinent atoms are reside in the reaction atmosphere for the reactions. To obatin the effective distance of the r_{CO}, *ab initio* calculations were performed along the minimum energy reaction path (MERP) of the model

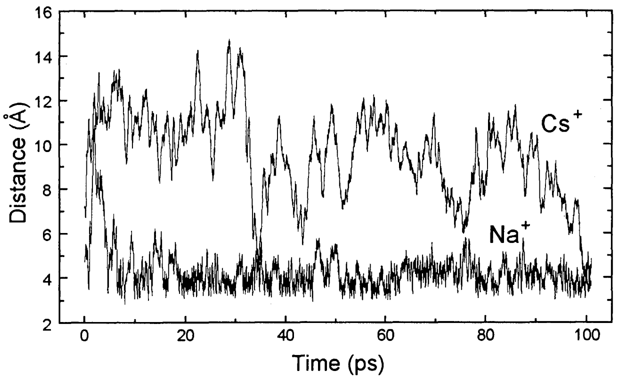


Figure 1. Time evolution of the r_{CO} for the **1**-Na^+ and **1**-Cs^+ systems at 300 K.

Table 1. The average distances and standard deviations[a]

	100	200	300	400 (K)
Li^+	3.705 ± 0.268	3.848 ± 0.361	3.988 ± 0.577	4.130 ± 0.723
Na^+	3.740 ± 0.223	3.712 ± 0.376	3.976 ± 0.522	4.244 ± 0.852
K^+	4.571 ± 0.806	6.231 ± 0.996	6.568 ± 1.038	7.685 ± 2.182
Rb^+	5.629 ± 0.326	5.823 ± 0.848	6.784 ± 1.517	8.752 ± 2.523
Cs^+	5.723 ± 0.323	6.005 ± 0.766	7.509 ± 1.414	9.457 ± 2.142

[a] Average of r_{CO} for 100 ps of MD simulation at the specified temperatures.

Table 2. Fraction of time reside within 4.0 Å and the corrected values with nucleophilicity changes

	Fraction of time (%)		Corrected value[a]		k_{obsd}[b]
	300	400 (K)	300	400 (K)	($\times 10^{-2}$)
Li^+	60.37	36.18	< 0.604	< 0.362	0.19
Na^+	50.53	41.40	1.768	1.449	9.27
K^+	3.05	1.07	0.214	0.075	4.68
Rb^+	3.48	2.68	0.244	0.188	2.96
Cs^+	4.44	0.79	0.311	0.055	1.70

[a] Corrected with the reported nucleophilicity changes by metal ions.[8] [b] Observed rate constants for the formation of monobenzo-15-crown-5 in the presence of metal bromide (1.0 x 10^{-2} M, at room temperature). Taken from reference 2.

compounds.[4] The calculations were performed between the reactant and reactant complex. In Figure 2, the binding energy between model compounds is plotted against the MERP. The attraction force, the first derivative of the binding energy, increases rapidly as the r_{CO} decreases from r_{CO} = 4.5 Å. If solvent molecules are included in the *ab initio* calculations, the r_{CO} of the reactant complex may decrease. In this work, therefore, 4.0 Å was used somewhat arbitrarily as the r_{rxn}^{o} and the fraction of time spent within r_{rxn}^{o} is summarized in Table 2.

The results indicate that the fraction of time reside in a specified region, r_{rxn}^{o}, is generally decreasing in the following manner: $Li^+ \approx Na^+ >> K^+ \approx Rb^+ \approx Cs^+$. It is obvious that the longer the atoms reside in close proximity, the more likely the reaction to occur in the present system.[5,6] However, the trend of the fraction of time variation is not well correlated with the observed reaction rate k_{obsd}, particularly for the Li^+ ion. That is partly due to the ignorance of the changes in nucleophilicity of phenoxide ions upon ion pairing with metal cations: lithium ion with small and high charge density forms more tight ion pair, that reduces the nucleophilicity of the reaction site significantly than larger metal ions.[7] The fraction of time was, therefore, corrected with the nucleophilicity changes as referenced to the work of Mandolini[8] (Li^+, < 0.01; Na^+, 0.035; $K^+ = Rb^+ = Cs^+$, 0.07) and shown in the middle columns of the Table 2. The corrected values, although some discrepancies exist, qualitatively parallel the experimental work for the synthesis of the benzo-15-crown-5 ether, that exhibited a bell-shaped reaction rate profile centered around Na^+ ion.[2]

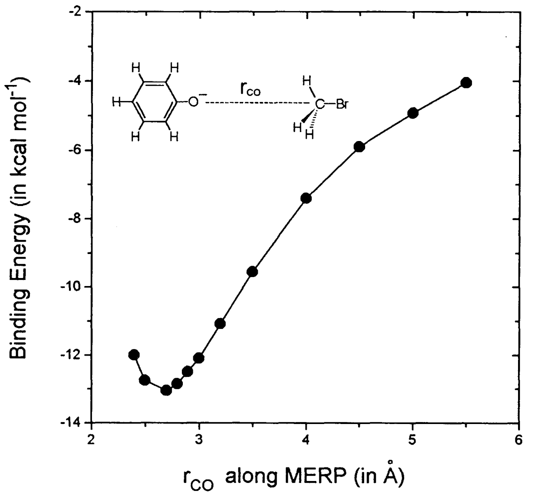


Figure 2. The MERP of the model complex was plotted against the r_{CO}. The MERP was obtained between reactant and reactant complex (see the inset).

In conclusion, we have simulated semi-quantitatively the template effect of Na^+ ion in the preparation of benzo-15-crown-5 ether in terms of the greater proximity of chain ends in the metal ion associated reactant than in the unassociated one. Further works concerning the other crown ether systems and appropriate considerations of solvent as the reaction medium are underway.

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References and Notes

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