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Computational study of S_N2 reactions promoted by crown ether: Contact ion pair versus solvent-separated ion pair mechanism

Sung-Sik Lee[1] | Vinod H. Jadhav[2] | Ji-Young Kim[1] | Su-Jin Kim[1] | Dong Wook Kim[2] | Sungyul Lee[1]

[1]Department of Applied Chemistry, KyungHee University, Yongin-si, Gyeonggi-do, 17104, Republic of Korea

[2]Department of Chemistry, Inha University, Nam-gu, Incheon, 22212, Republic of Korea

Correspondence
Sungyul Lee, PhD., Department of Applied Chemistry, KyungHee University, Yongin-si, Gyeonggi-do 17104, Republic of Korea.
Email: sylee@khu.ac.kr and Dong Wook Kim, PhD., Department of Chemistry, Inha University, Nam-gu, Incheon 22212, Republic of Korea.
Email: dwkim@inha.ac.kr

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Abstract

We examined by quantum chemical methods the mechanism of S_N2 reaction using metal bromide MBr (M = Na, K, Cs) and KX (X= F, Cl) in CH_3CN promoted by crown ether (18-crown-6). We focus on whether the metal salts react as a contact ion pair (CIP; M^+ and X^- in close contact) or as a solvent-separated ion pair (SSIP; M^+ and X^- at large distance). In SSIP mechanism, X^- is removed far enough from M^+ for the metal salt to be considered as "separated" by the effects of the crown ether and the solvent. In the CIP picture, conversely, the coordination of 18-crown-6 to M^+ is not sufficient to overcome the powerful Coulombic interactions between M^+ and X^-. We find that the CIP route is favored for S_N2 bromination processes using MBr (M = Na, K, Cs). For S_N2 reaction using KF, the feasibility of the two pathways is essentially equal, whereas for S_N2 chlorination by KCl the SSIP route is predicted to be favored.

KEYWORDS

crown ether, density functional, halogenation, ion pair, mechanism, reaction pathway, S_N2

1 | INTRODUCTION

Rate constants of bimolecular nucleophilic substitution (S_N2) reaction[1–3] are governed by many factors, such as the solvent, the counter-cation, and the presence of catalyst/promotor that determine the reactivity of the nucleophile. The effects of the counter-cation[2–16] are very profound, because its interactions with the nucleophile directly influence its reactivity. It has long been considered to be helpful to reduce this strong Coulombic force exerted by the counter-cation on the nucleophile that is extremely harmful for S_N2 reactions. Use of bulky and polarizable cations such as tetrabutylammonium may help to overcome this retarding influence of the cation. Solvents are also a critical factor in S_N2 reaction rates.[1] Although protic solvents such as the alcohols have been avoided as S_N2 reaction media because of their strong interaction with the nucleophile by hydrogen bonding, it was recently found[9–16] that bulky protic solvents may promote the S_N2 reactions when used in combination with alkali metal halides (especially fluoride). The mechanism of this new type of S_N2 reactions is now well established. The efficiency of promotors (protic solvents, oligoethylene glycols,[15] and ionic liquids[16,17]) for S_N2 reactions using alkali metal salts has been studied in our laboratory in a series of publications.

Among the promotors proposed to increase the S_N2 rate constants, crown ethers[18–21] have been employed with a view to accelerating the reaction by "detaching" the counter-cation from the nucleophile. The electronegative O atoms of crown ethers were envisaged to coordinate the counter-cation, thereby "arresting" the cation and thus "freeing" the nucleophile. To our best knowledge, however, very few[21] systematic study of

Sung-Sik Lee and Vinod H. Jadhav contributed equally to this study.

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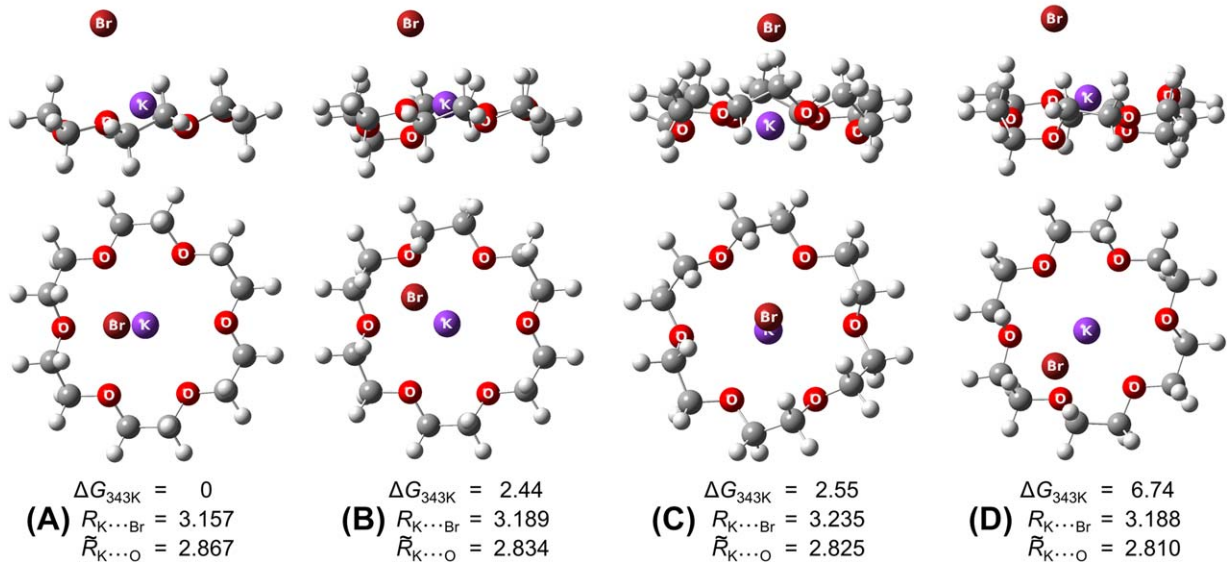


FIGURE 1 Calculated structures of KBr coordinated by 18-crown-6. MPW1K/6–311++G**(for C, H, and O atoms)/LANL2DZ for K and Br atoms with the corresponding effective core potential[30]

the role of crown ethers for promoting the S_N2 reactions was carried out either experimentally or theoretically. Herein, we pose the following question: Do crown ethers really "separate" the counter-cation from the nucleophile, helping to form solvent-separated ion pair(SSIP)[22–26]?

Here, we address this intriguing question for the case of MBr (M = Na, K, Cs) and KX (X= F, Cl) for S_N2 reactions under the influence of 18-crown-6 in CH_3CN. This would be a most stringent test for the role of crown ethers (whether it helps to separate the counter-cation and the nucleophile for S_N2 reactions or not), because of the strong Coulombic influence of the alkali metal cation M^+ on the nucleophile that may or may not be overcome by the crown ether (18-crown-6). By systematic quantum chemical investigations, we show that the CIP mechanism mostly prevails for S_N2 bromination (with the exception of S_N2 chlorination by KCl for which the two mechanisms may compete), indicating that the metal salts react as CIP in which the counter-cation and the nucleophile are in close contact. For S_N2 processes using KF and KCl, either the two processes may compete, or the SSIP route is favored. The role of crown ether is as a Lewis base coordinating the counter-cation to reduce its retarding Coulombic influence on the nucleophile to "activate" the latter for S_N2 reactions, which in line with our previous view of S_N2 promotion by bulky protic solvents, oligo-ethylene glycols,[15] and ionic liquids.[16,17]

2 | COMPUTATIONAL DETAILS

We obtained the structures of prereaction complexes, transition states, and postreaction complexes by the M06-2X[27]/6–311 + G** (for C, H, O, F, S, and Cl atoms)/LANL2DZ(for alkali metal and Br atoms) and MPW1K[28,29]/6–311++G**(for C, H, and O atoms)/LANL2DZ(for K and Br atoms) methods with effective core potential[30] for alkali metal and Br, SMD-PCM[31] for the solvent continuum (CH_3CN) implemented in Gaussian 09 suite of programs.[32] Stationary structures are obtained by confirming that all the harmonic frequencies are real. Structures of the transition states are obtained by observing only one imaginary harmonic frequency, and also by carrying out the intrinsic reaction coordinate analysis along the reaction pathway. Zero point energies (ZPEs) are taken into account. Default criteria are used for all optimizations. Relative Gibbs energies (at 70°C, ΔG_{343K}) of prereaction complexes were calculated to compare their thermodynamic stability, and activation barriers $G^{\ddagger}$ of alternative reaction paths were evaluated to determine the most feasible reaction pathway. Here, -OMs is taken as the leaving group for S_N2 reactions, because it proved to perform best in our previous experiments.[11,14–16]

3 | RESULTS AND DISCUSSION

To examine the interactions between the metal salt and the crown ether in gas phase (i.e., without the effects of solvent), we present in Figure 1 the calculated gas phase structures of KBr/18-crown-6 complex, in which the counter-cation K^+ is coordinated by the six O atoms of 18-crown-6. In this gas phase situation without the substrate and solvent, KBr would have no choice but exist as a contact ion pair (CIP) because of strong Coulombic force between of K^+ and Br^-. The $R_{K\text{-}Br}$ distances in the prereaction complexes are 3.157–3.235 Å, indicating that indeed KBr forms ion-pair. Due to the coordination by the O atoms, however, the $R_{K\text{-}Br}$ distances are somewhat larger than the gas phase value of 2.821 Å.[33] It can be seen that the structures (a)–(d) differ mostly in the configuration of crown ether relative to KBr which lies more or less perpendicular to the plane of

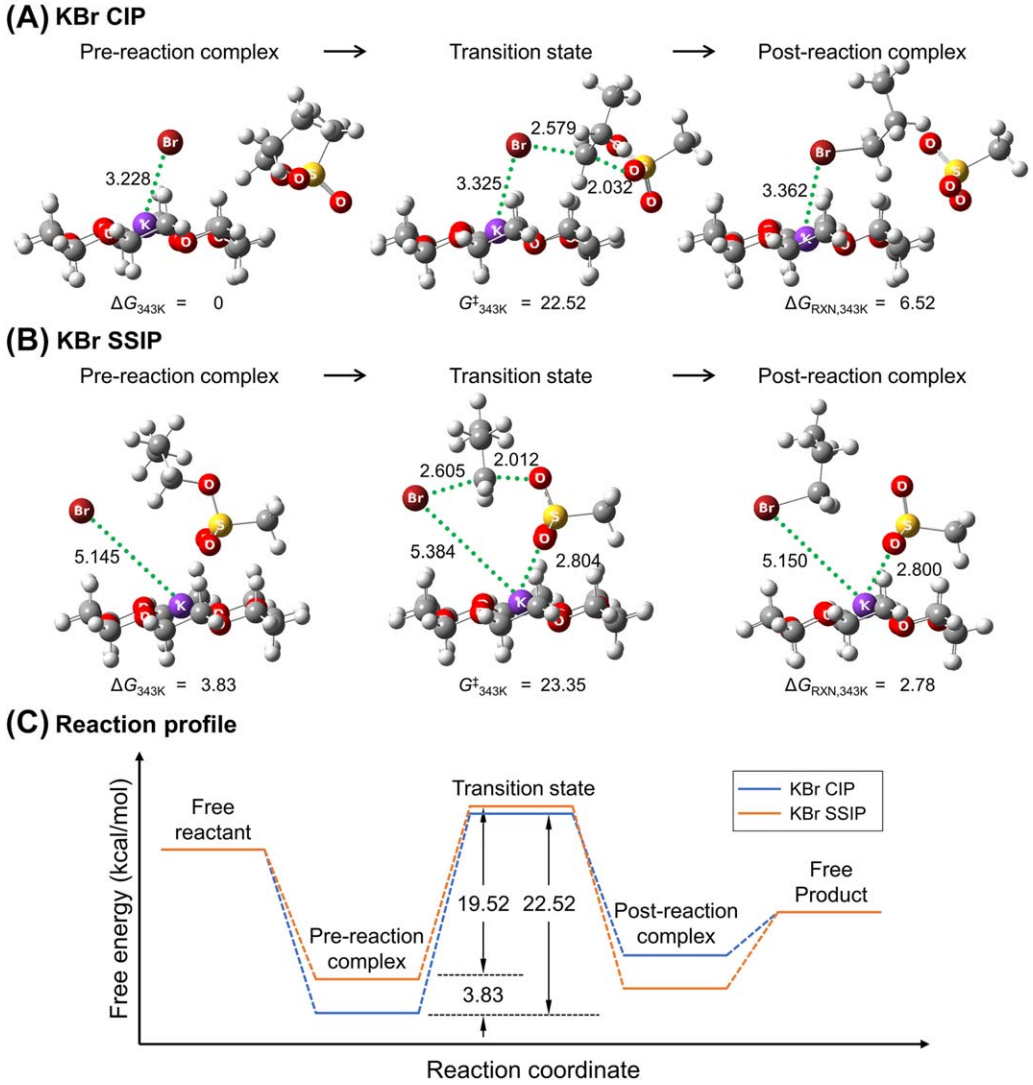


FIGURE 2 Mechanism of S_N2 bromination using KBr via (a) the CIP and (b) SSIP mechanism promoted by 18-crown-6 in CH_3CN, and (c) energetics of the reaction. (M06-2X/6–311 + G**(for C, H, O, and S atoms)/LANL2DZ for K and Br atoms with the corresponding effective core potentials[30])

crown ether. In the most stable structure (a), the crown ether is D_{3d} symmetric with respect to KBr, with the six O atoms lying on a plane.[34] In other structures, the crown ether is distorted in various ways. In (b)–(d), whose Gibbs free energy at 343 K is 2.44–6.74 kcal/mol higher than that of (a), the crown ether is distorted in a symmetrical fashion.

In the most stable complex (a), Br^- is positioned over the center of 16-crown-8, and the structure is symmetrical with respect to the plane formed by these three atoms. In (b) Br^- locates between K^+ and two O atoms, and the crown ether ring is a bit distorted. The nucleophile Br^- lies right above the counter-cation K^+ which is at the center of the crown ether ring in (c). In this structure, K^+ and Br^- are positioned at the opposite sides of the crown ether, making their $R_{K\text{-}Br}$ distance largest. The structure (d) exhibits the largest distortion of the crown ether ring with no symmetry. Br^- lies quite off the center of the crown ether ring.

Figure 2 describes the mechanism and energetics of S_N2 bromination using KBr under the influence of crown ether in CH_3CN, for which we carried out experiments reported earlier.[16] The solvent here is treated as a continuum (PCM) by employing the SMD method.[31] Figure 2A shows the structure of the lowest energy prereaction complex for the reaction [$K^+Br^- + C_3H_7$-OMs → K^+ $OMs^- + C_3H_7$-Br] in CH_3CN in which K^+Br^- reacts as a CIP ($R_{K\text{-}Br}$ = 3.228 Å). The crown ether maintains its symmetry, and Br^- locates above K^+ which is more or less at the center of the crown ether. The leaving group -OMs is far (6.052 Å) from K^+. In the SSIP prereaction complex (Figure 2B) K^+ and Br^- are solvent-separated ($R_{K\text{-}Br}$ = 5.145 Å). The distance between the -OMs oxygen and K_+ is small (2.833 Å). This SSIP prereaction complex and the corresponding transition state have usually been envisioned in organic chemistry community to account for the role of crown ethers promoting the S_N2 reactions.

Two kinds of factors (first, the thermodynamic stability [that is, the Gibbs free energy ΔG_{343K}] of prereaction complexes for alternative reaction pathways, and second, the Gibbs free energies of activation $G^{\ddagger}_{343K}$) should be considered in general to elucidate the reaction mechanism. The first

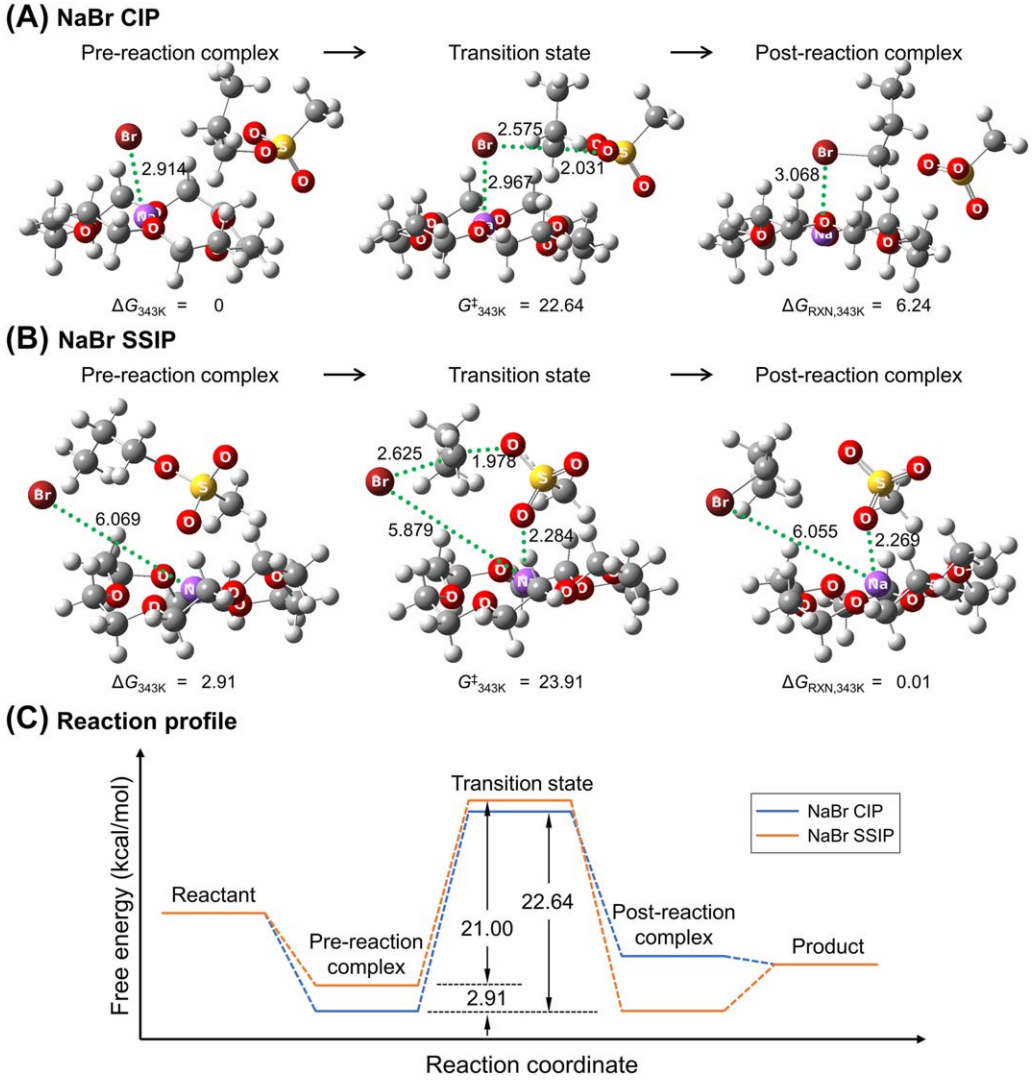


FIGURE 3 Mechanism of S_N2 bromination using NaBr via (a) CIP and (b) SSIP prereaction complexes promoted by 18-crown-6 in CH_3CN, and (c) energetics of the reaction. (M06-2X/6–311 + G**(for C, H, O, and S atoms)/LANL2DZ for Na and Br atoms with the corresponding effective core potentials[30])

factor determines the relative population of prereaction complexes from which the reactions proceed, and the second (kinetic) factor is related to the relative reaction rates from the prereaction complexes to the transition states (and subsequently to products). It would be extremely useful to discuss the present results by invoking the Curtin–Hammet principle[35–38]: the relative amounts of products formed depend only on the difference in free energy of the transition states, provided the rates of reaction are slower than the rates of interconversion between the reactants. Since the time scale of the reactions studied here is typically a few hours, the equilibration of the CIP/SSIP prereactions complexes may be safely presumed. Thus, the Curtin–Hammet principle applied to our system dictates that relative rates of S_N2 reactions via the CIP vs. SSIP prereaction complexes are determined by the relative Gibbs free energy of the corresponding transition states. That is, the reaction route via the transition state of lower Gibbs free energy would prevail.

The Gibbs free energy of the CIP prereaction complex is thermodynamically much more stable (G_{343K} lower by ~3.8 kcal/mol, which corresponds to ~60 times larger population) than the SSIP prereaction complex. This difference stems, of course, from the strong Coulombic attraction between K^+ and Br^- in the CIP complex. The calculated Gibbs free energy of the transition state via the CIP path is lower than that for the SSIP route by 0.83 kcal/mol, thus according to the Curtin–Hammet principle the S_N2 bromination via the CIP mechanism is favored, because the relaxation of prereaction complexes to solvent would be complete, and the rates of equilibration between the CIP and SSIP prereaction complexes would be much larger than the S_N2 reaction rates considering that S_N2 bromination was observed to typically take place in 3–6 hours.[16] It would also be useful to point out that the calculated $G^{\ddagger}_{343K}$ (19.5 kcal/mol) for the SSIP mechanism seems to be too small in comparison with the activation barrier (23.2 kcal/mol) of S_N2 fluorination promoted by pentaethylene glycol previously studied[14,39] previously in our laboratory, which gave excellent S_N2 yield (95%) in 1.5 hour at 100°C (although the calculated $G^{\ddagger}_{343K}$ seems to underestimate the experimental values by a few kcal/mol, our DFT calculations looks to be enough for our purpose of comparing the S_N2 reactions via CIP/SSIP routes).

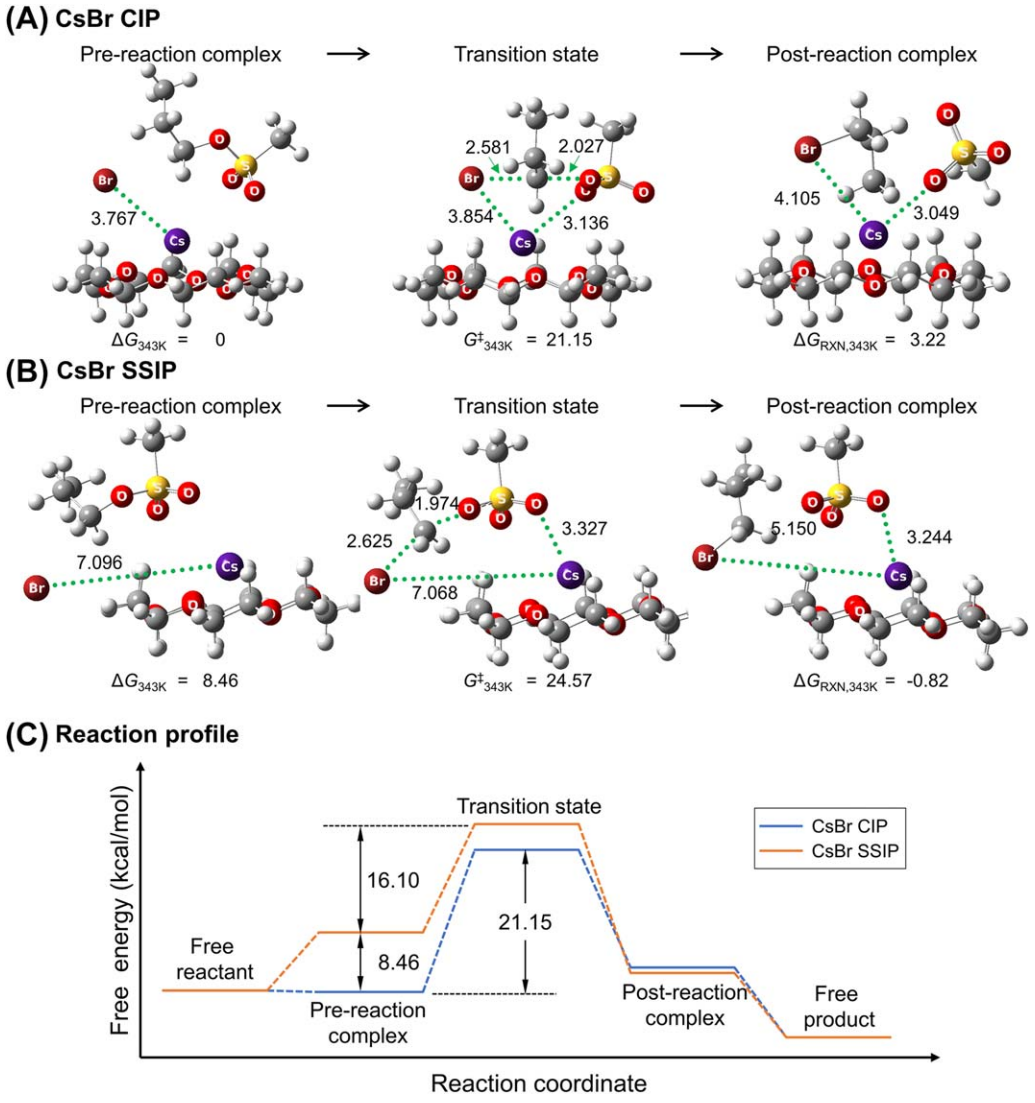


FIGURE 4 Mechanism of S_N2 bromination using CsBr via (a) CIP and (b) SSIP prereaction complexes promoted by 18-crown-6 in CH_3CN, and (c) energetics of the reaction. (M06-2X/6–311 + G**(for C, H, O, and S atoms)/LANL2D for Cs and Br atoms with the corresponding effective core potentials[30])

Figures 3 and 4 depict the mechanisms of S_N2 bromination using NaBr and CsBr, respectively, along with the energetics. The Gibbs free energy of prereaction for the CIP ($R_{Na\text{-}Br}$ = 2.914 Å) mechanism for NaBr is calculated to be 2.91 kcal/mol lower than that for the SSIP ($R_{Na\text{-}Br}$ = 6.069 Å) mechanism. Since the Gibbs free energy of transition state for CIP route is lower (by 1.27 kcal/mol) than that for prereaction for the SSIP mechanism, the former pathway is favored here. The Gibbs free energy of prereaction of CsBr bromination for the CIP mechanism is much lower (by 8.5 kcal/mol) than that for the SSIP mechanism, whereas the difference between the transition state is now as much as 3.4 kcal/mol. This large difference in Gibbs free energies of the two prereaction complexes reflects the larger differences in $R_{Cs\text{-}Br}$ in prereaction complex (3.329 Å) and in the transition state (3.214 Å) than those (3.155, 1.912 Å for NaBr and 1.917, 2.059 Å for KBr) in the reactions using NaBr or KBr. It is also to be noted that the counter-cation Cs^+ lies above the crown ether ring. The large Cs-Br distance (7.096 Å) in SSIP prereaction complex makes it far less stable than the CIP case, suggesting that the CIP mechanism also prevails here. For S_N2 bromination using CsBr, the difference in Gibbs free energies of transition states for the two mechanisms is much larger (3.41 kcal/mol), making the CIP route much more dominant over the SSIP pathway.

Table 1 summarizes the energetics of S_N2 bromination using MBr (M = Na, K, Cs) promoted by 18-crown-6 in CH_3CN. The effective barriers of bromination are in the order of NaBr > KBr > CsBr, indicating that they decrease as a function of the size and the polarizability of the counter-cation M^+. This is in accordance with the order of the strength of Coulombic force ($Na^+ > K^+ > Cs^+$) between the counter-cation and the nucleophile (hence, the most harmful effects on S_N2 reactions) Br^- that exerts retarding influence on the reaction rates.

Finally, we present the mechanism of S_N2 reactions of KF and KCl to probe the effects of the nucleophiles (F^- and Cl^-) other than Br^-. Figures 5 and 6 depict the mechanism, and Table 2 lists the energetics of reactions. For S_N2 fluorination using KF, the gibbs free energy of prereaction complex for the CIP mechanism is somewhat lower (by 2.0 kcal/mol) than that for the SSIP mechanism. The Gibbs free energies of the transition states are, however, very similar (to within 0.14 kcal/mol, indicating that the two reaction pathways are almost equally feasible. For S_N2 chlorination by

TABLE 1 Energetic (kcal/mol) of S_N2 bromination using MBr (M = Na, K, Cs) under the influence of 18-crown-6 in CH_3CN

Reaction pathway from	Relative Gibbs free energy ΔG_{343K} of pre-rxn complex	Relative Gibbs free energy ΔG_{343K} of TS	Gibbs free energy of activation $G^{\ddagger}_{343K}$	R(M-Br) of pre-rxn complex	R(M-Br) of TS	$\tilde{R}$(M-6O) of pre-rxn complex	$\tilde{R}$(M-6O) of TS
(a) NaBr CIP	0	0	22.6	2.914	2.967	2.725	2.736
(b) NaBr SSIP	2.91	1.27	21.0	6.069	5.879	2.669	2.731
(a) KBr CIP	0	0	22.5	3.228	3.325	2.819	2.800
(b) KBr SSIP	3.83	0.83	19.5	5.145	5.384	2.812	2.819
(a) CsBr CIP	0	0	21.2	3.767	3.853	3.224	3.209
(b) CsBr SSIP	8.46	3.42	16.2	7.096	7.068	3.198	3.207

Bond lengths in Å. (M06-2X/6–311 + G**(for C, H, O, and S atoms)/LANL2DZ for Na, K, Cs, and Br atoms with the corresponding effective core potentials[30]).
Abbreviations: pre-rxn, prereaction; TS, transition state.

KCl, the Gibbs free energy of the transition state via the SSIP prereaction complex in lower by 0.9 kcal/mol than that for the CIP route, thus in this case the SSIP pathway seems to be more favorable. Another interesting feature of this reaction is much larger activation barriers (> 24.5 kcal/mol) as compared with others (< 22.5 kcal/mol). In fact, this large activation barrier of S_N2 chlorination does not exhibit a smooth trend of the calculated

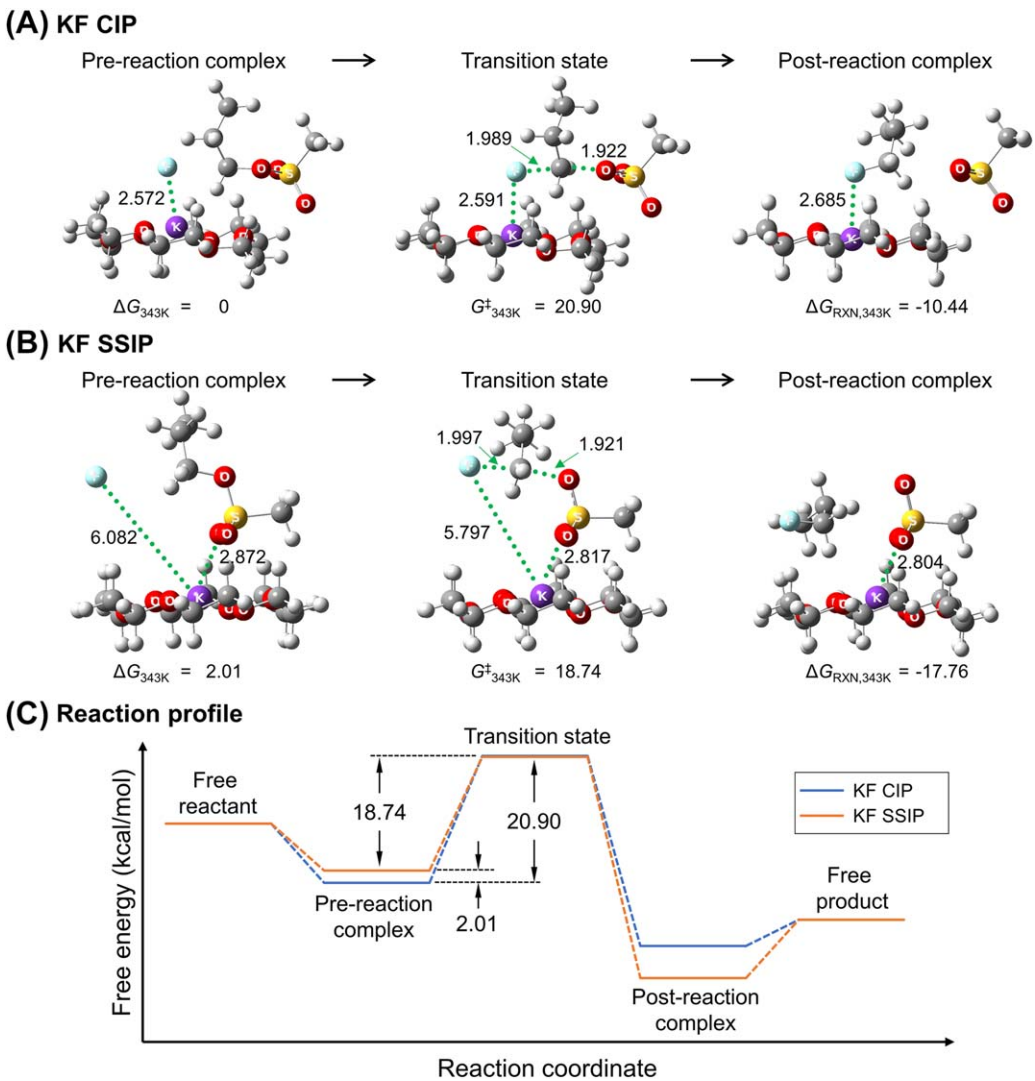


FIGURE 5 Mechanism of S_N2 chlorination using KF via (a) CIP and (b) SSIP prereaction complexes promoted by 18-crown-6 in CH_3CN, and (c) energetics of the reaction. (M06-2X/6-311 + G**(for C, H, O, S, and F atoms)/LANL2DZ for K atom with the corresponding effective core potentials[30])

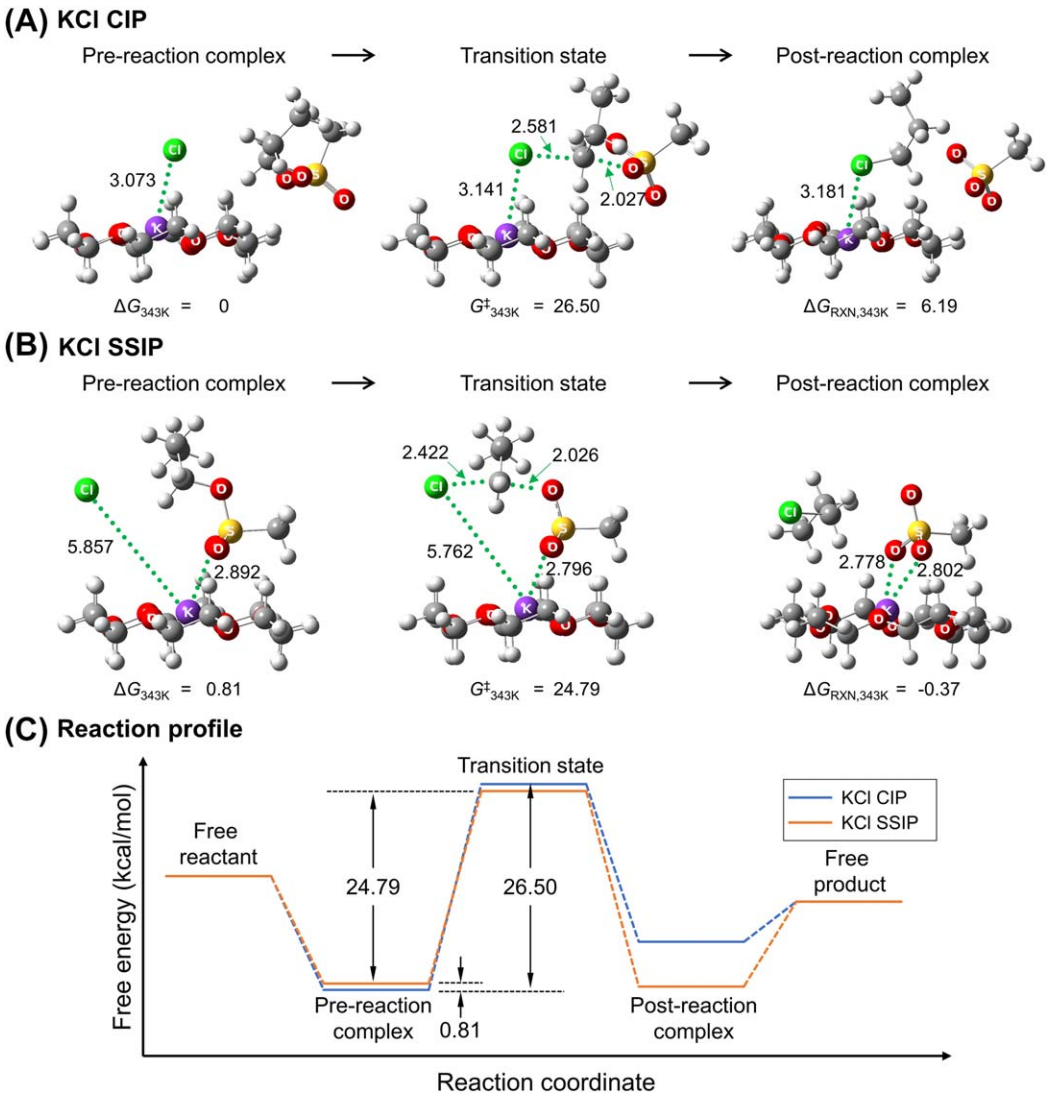


FIGURE 6 Mechanism of S_N2 chlorination using KCl via (a) CIP and (b) SSIP prereaction complexes promoted by 18-crown-6 in CH_3CN, and (c) energetics of the reaction. (M06-2X/6-311 + G**(for C, H, O, S, and Cl atoms)/LANL2DZ for K atom with the corresponding effective core potentials[30])

activation barriers (20.9, 24.9–26.5, 22.5 kcal/mol) for reactions of KX (X = F, Cl, Br) as expected from the effects of electrostatic interactions between the counter-cation K^+ and the nucleophile X^-.

In Tables 3 and 4 a decomposition of the activation energy $E^‡$ into various components is carried out to elucidate this apparently irregular pattern of the activation barriers. $E^‡$ is composed of three components: (1) Difference in energy of the substrate (E_{Sub}), (2) difference in energy of KX-crown ether complex (E_{KX-CE}), and (3) difference in interaction energy of KX-crown ether complex and the substrate (E_{int}), all between the prereaction complex and the transition state for reactions of KX (X = F, Cl, Br): $E^‡ = \Delta E_{KX-CE} + \Delta E_{Sub} + \Delta E_{int}$. The magnitude of ΔE_{KX-CE} is rather small

TABLE 2 Energetic (kcal/mol) of S_N2 reaction using KX (X= F, Cl) under the influence of 18-crown-6 in CH_3CN

Reaction pathway from	Relative Gibbs free energy Δ G_{343K} of pre-rxn complex	Relative Gibbs free energy Δ G_{343K} of TS	Gibbs free energy of activation $G^‡_{343K}$	R(M-Br) of pre-rxn complex	R(M-Br) of TS	$\tilde{R}$(M-6O) of pre-rxn complex	$\tilde{R}$(M-6O) of TS
(a) KCl CIP	0	0.90	26.50	3.091	3.141	2.811	2.795
(b) KCl SSIP	0.81	0	24.79	5.857	5.762	2.832	2.822
(a) KF CIP	0	0.14	20.90	2.598	2.591	2.822	2.797
(b) KF SSIP	2.01	0	18.74	6.082	5.797	2.803	2.819

Bond lengths in Å. (M06-2X/6–311 + G**(for C, H, O, F, S, and Cl atoms)/LANL2DZ for K atom with the corresponding effective core potentials[30]).
Abbreviations: pre-rxn, prereaction; TS, transition state.

TABLE 3 Interaction energies (E_{int}) between substrate and metal salt/crown ether and the distance between C and O of -OMs

X	Type of complex	E_{int}	$R_{C\ldots O}$	X	Type of complex	E_{int}	$R_{C\ldots O}$
F (CIP)	**Pre-rxn complex**	−6.9	1.460	F (SSIP)	**Pre-rxn complex**	−11.8	1.464
	Transition state	−16.0	1.922		**Transition state**	−22.2	1.921
Cl (CIP)	**Pre-rxn complex**	−6.2	1.467	Cl (SSIP)	**Pre-rxn complex**	−12.4	1.468
	Transition state	−16.1	2.036		**Transition state**	−23.2	2.026
Br (CIP)	**Pre-rxn complex**	−8.5	1.470	Br (SSIP)	**Pre-rxn complex**	−15.5	1.472
	Transition state	−20.6	2.032		**Transition state**	−28.9	2.012

E_{int}, $E_{KX\text{-}CE}$ - ($E_{KX\text{-}CE\text{-}Sub} + E_{Sub}$) (kcal/mol)
$E_{KX\text{-}CE}$ (Single point energy of [KX/18-crown-6] complex), E_{Sub} (Single point energy of C_3H_7OMs), $E_{KX\text{-}CE\text{-}Sub}$ (Single point energy of [KX/18-crown-6/C_3H_7OMs]) are presented in the Supporting Information Table S1.

TABLE 4 Decomposition of activation energy $E^{‡}$ into energy differences accompanying structural changes of substrate, metal salt/crown ether complex, and difference in metal salt/crown ether–substrate interaction energy, all between prereaction complexes and transition states

X	$\Delta E_{KX\text{-}CE}$	ΔE_{int}	ΔE_{Sub}	$E^{‡}$
F (CIP)	0.05	−9.1	30.3	21.22
F (SSIP)	0.67	−10.4	29.2	19.56
Cl (CIP)	−0.31	−9.9	36.9	26.68
Cl (SSIP)	0.54	−10.8	35.5	25.23
Br (CIP)	0.72	−12.1	36.1	24.75
Br (SSIP)	1.30	−13.4	34.0	21.91

$\Delta E_{KX\text{-}CE}$, $E_{KX\text{-}CE}$ (Transition state) - $E_{KX\text{-}CE}$ (Prereaction complex) (kcal/mol) ΔE_{int}, E_{int} (Transition state) - E_{int}(Prereaction complex) (kcal/mol) ΔE_{Sub}, E_{Sub} (Transition state) - E_{Sub}(Prereaction complex) (kcal/mol) $E^{‡}$, $E_{KX\text{-}CE\text{-}Sub}$ (Transition state) - $E_{KX\text{-}CE\text{-}Sub}$ (Prereaction complex) = $\Delta E_{KX\text{-}CE} + \Delta E_{Sub} + \Delta E_{int}$ (kcal/mol)

(< 1.3 kcal/mol) for all cases, thus this term may be neglected. Compared with ΔE_{Sub} for S_N2 fluorination, ΔE_{Sub} for (29–31 kcal/mol), the corresponding term (35–37 kcal/mol) for S_N2 chlorination is significantly larger, whereas the magnitudes of is similar in these two reactions. This indicates that the substrate C_3H_7OMs becomes much more unstable in the transition state in S_N2 chlorination as compared with S_N2 fluorination to give higher activation barrier. This difference in $E^{‡}$ may arise from the separation of the -OMs group from methyl chain (C_3H_7-) in the transition states with respect to than in the prereaction complex: For S_N2 fluorination the increase in the distance $R_{C\ldots O}$ between the reaction center (C atom) and the O atom of the -OMs group from the prereaction complex to the transition state is ∼0.46 Å, whereas the corresponding value for S_N2 chlorination is 0.56 Å. Conversely, the higher activation barrier for S_N2 chlorination as compared with S_N2 bromination seems to result from the larger difference in interaction energy of KX-crown ether and the substrate between the prereaction complex and the transition state: The magnitude of ΔE_{int} (12.1–13.4 kcal/mol) S_N2 bromination is larger than that (9.9–10.8 kcal/mol) for S_N2 chlorination, indicating that the KX/crown ether/substrate substrate is stabilized in the transition state to a larger degree in S_N2 bromination than in S_N2 chlorination. This may be due to the larger van der Waals radius of Br atom allowing larger sphere of interactions with the substrate than Cl.

4 | CONCLUSION

Our present analysis clearly demonstrates that the crown ether 18-crown-6 may not separate the counter-cation M^+ from the nucleophile X^- in most S_N2 halogenation reactions in acetonitrile promoted by crown ether in contrast with the conventional view. The contact ion pair mechanism proposed here is in line with those observed in S_N2 reactions promoted by bulky protic solvent (t-butanol, t-amyl alcohol), oligo-ethylene glycol, and ionic liquid, in that 18-crown-6 acts as a Lewis base on the counter-cation M^+, significantly reducing the latter's Coulombic influence on the nucleophile, thereby "freeing" it for efficient S_N2 reactions. Experimental works on the mechanism of crown ether promoted reactions would be highly desirable.

ORCID

Sungyul Lee http://orcid.org/0000-0002-6370-2662

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