Letter

Cation binding acceleration of Diels–Alder reaction of quinocrown ethers with cyclopentadiene

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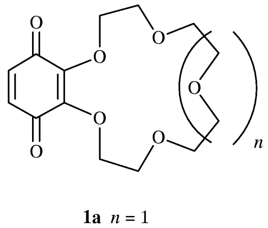
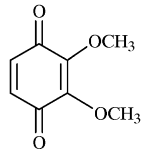
Diels–Alder reactions of 15–21 membered quinocrown ethers **1a**–**c** with cyclopentadiene have been accelerated by the addition of alkali, alkaline-earth, and scandium perchlorates, reflecting the selective cation-binding abilities of crown ethers.

In the study of biological model systems, crown ethers have generated a tremendous amount of interest[1] because of their ability to selectively bind guests by non-covalent interactions. In particular, functionalized crown ethers[2] possessing multiple bonds or reaction groups are expected to play a promising role in the design of new host molecules with highly efficient and selective binding properties. These reactive crowns are of interest in view of the possible control of the reactivities by addition of cation species.[3]



1a $n = 1$
1b $n = 2$
1c $n = 3$



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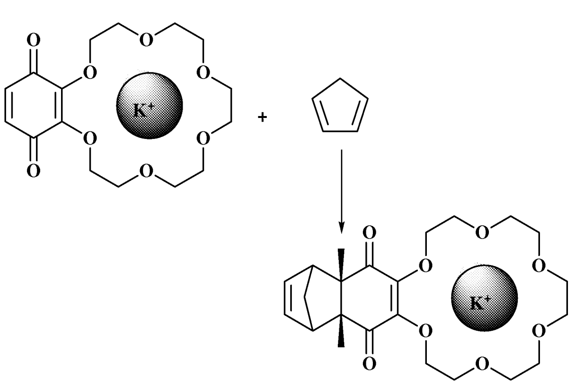
Herein, we report the selective cation-binding effects in the kinetics of Diels–Alder reactions of 15–21 membered ring quinocrown ethers **1a**–**c** with cyclopentadiene in comparison with the reaction of reference 2,3-dimethoxy-1,4-benzoquinone **2**.† Quinocrown ethers **1a** and **1b** are known to react with cyclopentadiene at the outer C=C double bond to give [4 + 2] *endo* adducts in 92–98% yield.[5] We exploited this clear reaction as a probe for exploring the cation-binding features in the kinetics of crown ether reactions as formulated for the reaction of **1b** in the presence of K^+ [eqn. (1)].‡



(1)

The kinetic experiments were performed in acetonitrile solution containing a quinone (0.20–0.80 mM) and 20 equiv. excess of cyclopentadiene (4.0–16.0 mM) with or without added 4.0 mM of alkali and alkaline-earth metal as well as scandium perchlorate. The rates of reactions were determined by monitoring the disappearance of the absorbances due to the quinones **1a**–**c** and **2** at $\lambda_{max} = 391$–399 nm. [The monitored wavelength at $\lambda_{max}(\varepsilon)$ is as follows: **1a** ($\lambda_{max} = 399$ nm, $\varepsilon = 131$ M^{-1} cm^{-1}), **1b** (399, 129), **1c** (399, 130) and **2** (391, 104).] The rates obeyed *pseudo* first-order kinetics up to at least two half lives and the second-order rate constants were obtained by dividing the observed first-order rate constants by the corrected concentration of cyclopentadiene for the consumption of half the amount of quinone.

The kinetic data for the addition of alkali-metal perchlorates are collected in Table 1. In the absence of perchlorates, all quinones used provided comparable rate constants of 4.6–5.3×10^{-2} M^{-1} s^{-1} irrespective of having cyclic or acyclic substituents. However, added salts brought about rate-acceleration depending on the combination of host molecules and guest cations.§ In contrast, the control reaction of dimethoxyquinone **2** showed no appreciable dependency on added salts.

All the kinetic features associated with the selective cation binding can be explicitly visualized in the plots of rate ratios, k_2^M/k_2^0 *vs.* metal ion radius, where k_2^M and k_2^0 represent the respective rate constants for the reactions in the presence and absence of added metal perchlorates (Fig. 1). The rate profiles of quinocrowns **1a**–**c** are taken as reflecting the cation-binding properties. Thus, 15-membered **1a** gave the

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† The quinocrowns **1a**,**b** and 2,3-dimethoxybenzoquinone **2** were synthesized according to the literature.[4] This method was applied for the synthesis of quino[21]crown-7 **1c**.

‡ Reaction of **1b** (1 mM) with 20 equiv. excess of cyclopentadiene at 25 °C for 1 h in acetonitrile solution containing 4 mM of $K(ClO_4)$ also led to almost the quantitative formation of [4 + 2] *endo* adduct as confirmed by ^1H-NMR spectroscopy.

Selected data for **1c**: ^1H-NMR (270 MHz, $CDCl_3$) δ 3.66 (s, 8H), 3.68 (s, 8H), 3.81–3.85 (m, 4H), 4.45–4.49 (m, 4H) and 6.58 (s, 2H); IR(KBr) 2917, 1655, 1591, 1351, 1298, 1180, 1108, 951 and 845 cm^{-1}; MS(EI) *m*/*z* 388 (M^+, 20%), 298 (18%), 194 (30%), 179 (15%), 166 (100%), 138 (82%), 117 (21%), 89 (36%), 82 (49%), 73 (60%), 45 (98%). Found C, 56.11; H, 7.08; calcd for $C_{18}H_{26}O_9$: C, 55.95; H, 6.78%.

§ Recently stimulating role of Li^+ in diethyl ether has been reported to accelerate Diels–Alder reactions. The source of this effect has been discussed in terms of internal high pressure of solvent or Lewis acid catalysis.[6] The effect of the counter anion was investigated for the cycloaddition of **2** (0.8 mM) with cyclopentadiene (16 mM) by addition of 18-crown-6 ether (0.8 mM) in the acetonitrile solution containing potassium perchlorate (4 mM) at 30 °C. Under these conditions, a rate decrease (9%) occurred as compared with the salt-free reaction. Keeping in mind that added 18-crown-6 alone did not affect the rate, this small decline may be ascribed to some weak interaction of free perchlorate with **2** owing to the selective complexation of K^+ by the added crown ether.

Table 1 Rate constants (k_2/M^{-1} s^{-1}) for Diels–Alder reactions of quinocrowns **1a**–**c**, dimethoxyquinone **2** with cyclopentadiene in the presence and absence of added metal perchlorates in acetonitrile at 30 °C[a]

		10^{-2} k_2/M^{-1} s^{-1}					
Quinone	Additive[b] =	None	Li^+	Na^+	K^+	Rb^+	Cs^+
1a		5.23	11.2	13.9	10.0	7.87	6.91
1b		4.60	6.68	9.13	17.1	13.7	9.55
1c		4.76	8.20	7.29	8.27	11.8	12.3
2		5.33	5.51	5.33	5.55	5.53	5.44

[a] Reactions were carried out under pseudo-first-order conditions by using 20 equiv. excess of cyclopentadiene (4.0–16.0 mM) with respect to quinone (0.20–0.80 mM). [b] Counter anion perchlorate was omitted; 4.0 mM solution of alkali, alkaline-earth metal perchlorate was used.

maximum rates for Na^+ (ion radius 0.95 Å) by analogy with the complexation of comparable 15-crown-5 (cavity radius 0.86–1.1 Å).[7] A much more selective rate-profile accompanied by the peak shift to K^+ (1.33 Å) was observed for 18-membered **1b**. The high K^+ binding ability of 18-crown-6 (cavity radius 1.3–1.6 Å) is well recognized.[7] As found for 21-membered **1c**, one more oxyethylene unit enlargement produced somewhat strange plots with a small peak at Li^+, although the maximum rate was still attained at the cavity-fitted cation Rb^+ (1.48) or Cs^+ (1.69 Å). The additional peak may be due to the formation of a dinuclear complex $[\mathbf{1c}\cdot 2Li]^{2+}$. In fact, such multi-incorporated complexes are known for dibenzo-24-crowns-8 with Na^+ or K^+ cations.[8]¶

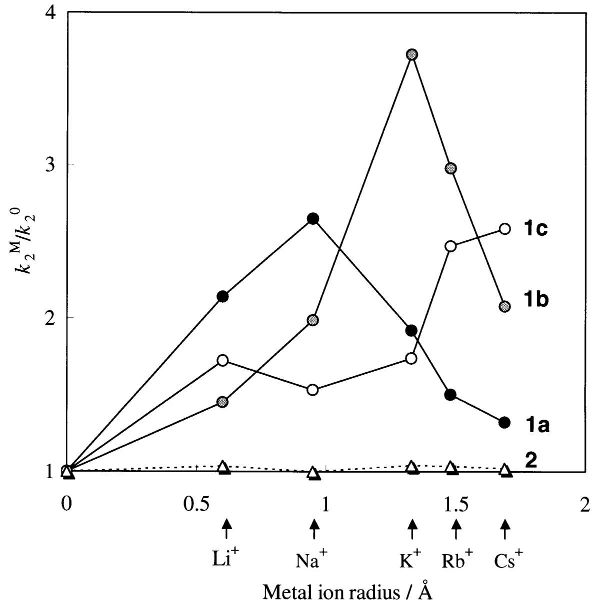

Fig. 1 Plot of rate ratios for k_2^M/k_2^0 *vs.* the metal ion radius, where k_2^M and k_2^0 represent the rate constants for the reactions in the presence and absence of added perchlorate salts, respectively

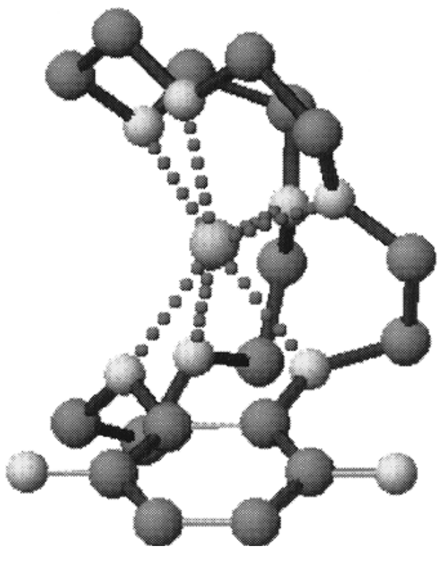

Fig. 2 Calculated structure of the complex $[\mathbf{1c}\cdot Sc]^{3+}$

With respect to the divalent alkaline-earth cations, a greater rate-acceleration was observed, reflecting the selective cation-binding abilities. The rate constants of **1b** at 30 °C were 6.66 ($\times 10^{-2}$ M^{-1} s^{-1}) for Mg^{2+} (0.65 Å), 33.6 for Ca^{2+} (0.99 Å), 56.3 for Sr^{2+} (1.13 Å), and 47.1 for Ba^{2+} (1.35 Å). Thus, 18-membered **1b** demonstrated 1.5-, 6-, 12-, and 10-fold acceleration by the addition of 4 mM of alkaline-earth perchlorates. Again, reference quinone **2** did not enjoy such a divalent cation-induced rate acceleration; $k = 5.40$–5.93×10^{-2} M^{-1} s^{-1}. The selective rate-accleration by the smaller sized Sr^{2+} rather than the expected Ba^{2+} is probably due to the decline in the effective ring cavity owing to steric repulsion between quinone carbonyls and adjacent oxyethylene units. Such repulsion was anticipated in X-ray analysis[9] and PM3 calculations of **1a**.

Of special interest is that the trivalent salt, $Sc(ClO_4)_3$ brought about an astonishing rate-acceleration of 117-fold for **1a**, 160 for **1b**, and 404 for **1c** (only 4.1-fold for **2**). The rate constants at 30 °C were 61.2 ($\times 10^{-1}$ M^{-1} s^{-1}) for **1a**, 73.7 for **1b**, 1930 for **1c**, and 2.20 for **2**. The order of rate-acceleration in going from **1a** to **1c** by the smaller Sc^{3+} (0.81 Å) apparently contradicts the size-fitting concept.[10] Therefore, the maximum rate for 21-membered **1c** may be rationalized by considering a wrapping structure, where the counter anions and solvent molecules can be more effectively excluded from the bound Sc^{3+} (Fig. 2).[11] Such charge-separated incorporation of Sc^{3+} would result in the unexpected rate acceleration.

Bearing in mind that quinocrowns **1a**–**c** exhibit rate profiles reflecting their cation-binding abilities as well as the cation valency, it can be easily envisaged that the incorporating guest cation behaves as an electron-withdrawing group on the quinone dienophile, thus lowering its LUMO energy suitable for the frontier orbital interaction with the HOMO of cyclopentadiene. In Diels–Alder reactions it is well known that the stronger the electron-withdrawing ability of the substituents then the more reactive the dienophile due to the diminished HOMO(diene) – LUMO(dienophile) energy difference.[12]

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¶ As unambiguous evidence for the selective alkali-metal cation binding of quinocrowns **1a**–**c**, we also used ESI-MS which exhibited essentially the similar binding behaviors as the above rate profiles. Furthermore, specially designed ESI-MS analysis showed the presence of the above-mentioned dinuclear complex $[\mathbf{1c}\cdot 2Li]^{2+}$; details will be described elsewhere.

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