Water-Soluble Calixarenes as New Inverse Phase-Transfer Catalysts. Kinetics of Cyanide Displacement on 4-*tert*-Butylbenzyl Bromide in Aqueous Biphasic Medium

Shoichi SHIMIZU*, Tsuyoshi ISHIZAKA** and Yasuyuki SASAKI***

Abstract

The rates of the nucleophilic substitution reaction of 4-*tert*-butylbenzyl bromide with sodium cyanide catalyzed by water-soluble calix[n]arenes (n = 4, 6 and 8; TACnA) containing trimethylammoniomethyl groups were measured under aqueous biphasic conditions. The effects on the rate were investigated for variations in the concentrations of catalyst, nucleophile and substrate, and the stirring speed as well as the temperature. Furthermore, the transport rate of the alkyl bromide through an aqueous phase using TAC6A as a carrier and surface active property of TAC4A and TAC6A were also measured in order to provide additional independent evidence for a discussion of plausible mechanism. From these results, it can be considered that the reaction takes place predominantly at the heptane-water interface, and that the rate-determining step is the nucleophilic attack of cyanide ions, which interacts electrostatically with TACnA molecule adsorbed at the interface, on the substrate molecules complexed with the same TACnA one.

Keyword: Environmentally benign processes, Water, Inverse phase transfer catalysis, Calixarene, Reaction mechanism

1. Introduction

The use of water as a medium for organic reactions has a number of potential advantages: (i) it is the cheapest solvent available on earth; (ii) it is non-hazardous to the environment and non-toxic; (iii) isolation of the organic products can be performed by simple phase separation.[1] There are beneficial effects of aqueous solvents on rates and selectivities of important organic transformations, *e.g.*, Diels-Alder reactions, aldol reac-

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tions and Michael additions.[1,2] However, its application is limited generally to substrates which have appreciable water solubility. To solve this problem, polar water-miscible organic solvents (co-solvents)[3] or surfactants[4] are frequently used. On the other hand, use of these additives usually complicates workup procedures, particularly in regard to product separation and the recovery of the catalyst and additive itself.

During the past twenty five years, calixarenes have received the increasing attention due to the utilization in supramolecular chemistry.[5] Some functionalized calixarenes were developed as new phase transfer agents for normal PTC reactions.[6] We recently developed new reaction system,[7] which is based on the inverse phase-transfer catalysis (IPTC)[8,9] of water-soluble calix[n]arenes. For example, alkylation reactions of active methylene compounds, alcohols and phenols with alkyl halides proceed smoothly in aqueous NaOH solution without the need for any added organic solvent using water-soluble calix[n]arenes, p-(trimethyl-ammoniomethyl)calix[n]arene methyl ethers (n = 4, 6 and 8; TACnA) as catalysts,[7b,d] as do the aldol-type condensation and Michael addition reactions of activated methyl and methylene compounds.[7c] We have also reported that rhodium complexes with water-soluble calix[4]arenes which contain two phosphine moieties on the wide rim are able to function, not only as homogeneous metal catalysts, but also as inverse phase-transfer catalysts in aqueous biphasic hydroformylation reactions.[10]

The use of IPTC has two major advantages over that of normal phase-transfer catalysis (PTC): (1) the aqueous catalyst solution is easily separated and recycled, and (2) no other organic solvent is necessary if organic reactants are liquid at the conducted reaction temperature. Thus, the IPTC can be expected to make many remarkable contributions to the design and development of environmentally benign processes.

We report here in detail the kinetics of cyanide displacement[7d] on 4-$tert$-butylbenzyl bromide catalyzed by TACnA under aqueous biphasic conditions and discuss the plausible mechanism, because understanding of the catalysis of new inverse phase-transfer agents, water-soluble calixarenes, is important not only from a fundamental viewpoint but also from a practical one. As additional independent evidence for the mechanism, we

also describe the transport rates of 4-$tert$-butylbenzyl bromide through an aqueous phase using TAC6A as a carrier and surface active property of TAC4A and TAC6A.

2. Experimental

2.1 General

Gas-chromatographic (GC) analyses were performed on a Hewlett-Packard GC 5890A instrument equipped with thermal conductivity detector using a J & W Scientific DB-17 bonded phase 30 m megabore, 0.53 mm i.d. column. Melting points were determined on a Yazawa BY-1 micro melting-point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a JEOL JNM-EX90 spectrometer at 89.50 and 22.51 MHz, or Bruker Avance-400 at 400.1 and 100.6 MHz, respectively. MS spectra were measured on a JEOL JMS-AX500 or a Hitachi M-2500 mass spectrometer. IR spectra were recorded on a Bio-Rad FTS-60A spectrometer. Ultraviolet spectra were recorded using a Hitachi 200-10 spectrophotometer. Microanalyses were performed on a Perkin-Elmer 240C or 2400II elemental analyzer.

2.2 Materials

4-$tert$-Butylbenzyl bromide was purchased from Fluka Chemie AG and purified by fractional distillation under reduced pressure (100-101 °C / 2 mmHg). Diethyl ether and tetrahydrofuran (THF) were freshly distilled from Na-benzophenone prior to use. Methanol and ethanol were distilled from Mg turnings. N,N-Dimethylformamide (DMF) stored over molecular sieves (5Å) was distilled under reduced pressure. Unless otherwise noted, starting materials and reagents were commercial materials and used without further purification.

2.3 Catalysts

The water-soluble calix[n]arenes TACnA·nH$_2$O (n = 4, 6 and 8) were prepared by following literature methods[11] and identified by IR and NMR spectroscopy as well as elemental analysis.[7b]

2.4 Kinetic measurements

The rate of nucleophilic substitution of 4-*tert*-butylbenzyl bromide using TAC*n*A as an inverse phase-transfer catalyst was measured at 50 ± 0.1 °C in 10 mL round-bottomed flask equipped with a septum-capped side arm, magnetic stirring bar (φ4 ×10 mm), and a condenser. In a typical experiment, the flask was charged with an aqueous solution (5 mL) of NaCN 0.882 g (18.0 mmol) and TAC*n*A·*n*H$_2$O (0.036 mmol, 0.40 mol%), and then heated in a silicon oil bath and stirred at 800 rpm. To the flask was added a heptane solution (5 mL) of 4-*tert*-butylbenzyl bromide 2.0 g (9.0 mmol) containing tetradecane 0.16 g (0.80 mmol) as an internal standard, and a timer was started on this addition. At appropriate intervals, the magnetic stirring was stopped, and 0.2-µl samples were removed from the organic layer by using a microsyringe. They were transferred to individual capped microtubes containing xylenes as diluents and then subjected to a GC analysis. In all cases, the detected product was only 4-*tert*-butylbenzyl cyanide. The reaction rates were determined from the product analyses. The product-concentration increments in the conversion region between 5 and 15%, divided by the time required for the reaction progress, were adopted as the initial reaction rates, because an induction period was observed, and because plots of product concentration *vs*. time gave straight lines in this conversion region.

2.5 Transport experiments

All experiments were conducted at 25 °C using the U-tube described by Diederich and Dick.[12] A 10 mL aqueous solution of NaBr (3.6 mol dm^{-3}) and TAC6A or β-CD (7.2 × 10^{-3} mol dm^{-3}) was located at the bottom of the U-tube. Atop this aqueous phase in one arm of the tube, 5 mL of hexane containing 4-*tert*-butylbenzyl bromide (0.2 mol dm^{-3}) was placed as the source phase. In the other arm, 5 mL of hexane was placed atop the aqueous phase as the receiving phase. The aqueous phase was agitated with a magnetic stirring bar (star head type) 10 mm in diameter at 500 rpm. The two arms of the tube were capped with septa during the experiment. Samples were taken from the receiving phase for the determination of the amounts of delivered 4-*tert*-butylbenzyl bromide by ultraviolet absorption at 220

nm. After each determination the sample was returned to the receiving phase. The relative rates of transport of 4-*tert*-butylbenzyl bromide were determined from the slopes of the linear parts of the plots as the increase in the concentration of 4-*tert*-butylbenzyl bromide in the receiving phase per hour, since an induction period appeared.

2.6 Interfacial tension measurements

The interfacial tension at the boundary between hexane and aqueous solutions of TAC*n*A was measured at 25 °C with a Wilhelmy tensiometer (Japan Rheology Instruments NRSF II; micro-roughened glass plates of 2.4 cm width). The aqueous solutions of TAC*n*A were prepared using triple-distilled water. The interfacial tension was adopted at 10 s after pouring hexane over the aqueous solutions.

3. Results and discussion

3.1 Displacement reaction rate

As shown in **Fig. 1**, the cyanide displacement reaction on 4-*tert*-butylbenzyl bromide proceeded quantitatively in mechanical disperse system with the aqueous solution of TAC*n*A and NaCN as disperse medium and the heptane solution of the substrate as disperse phase. The distribution of TAC*n*A into the heptane phase were negligible,[7e] indicating that the reaction catalyzed by TAC*n*A takes place predominantly in bulk aqueous phase and/or at heptane-water interface. The initial reaction rate was determined as a function of several reaction variables as described below.
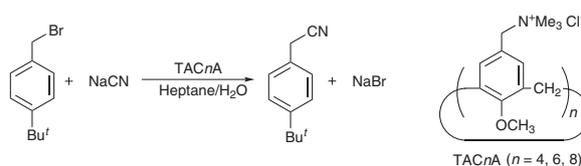
Fig. 1 Nucleophilic substitution reaction of 4-*tert*-butylbenzyl bromide with sodium cyanide catalyzed by water-soluble calix[*n*]arenes (TAC*n*A) in aqueous biphasic medium.

Effect of catalyst concentration. The influence of the catalyst concentration in aqueous solution upon the initial reaction rate is shown in **Fig. 2**. The catalytic activities of TACnA increase in the order of TAC4A < TAC6A < TAC8A. It is assumed that these differences are attributable to their cavity sizes.[7e)] No first-order dependence of reaction rate on the catalyst concentration was obtained. The convex plot in **Fig. 2** may suggest that TACnA can be adsorbed at the heptane-water interface. This is, to the best of our knowledge, the first example of liquid-liquid biphasic reaction in which catalyst exhibits such catalytic feature. On the contrary, in the halogen exchange reactions of alkyl bromides catalyzed by β-CD under IPTC conditions, rate constants of reactions with octyl bromide as a substrate were linearly dependent on the concentration of β-CD.[13)] Furthermore, 1.7th-order dependency, namely concave plot, was observed with dodecyl bromide, which indicated the contribution of a complex between a large substrate and more than one β-CD molecule.[13)]

Effects of nucleophile and substrate concentrations. The influence of the concentration of nucleophile, aqueous sodium cyanide, upon the rate is shown in **Fig. 3**, while the case of substrate, 4-*tert*-butylbenzyl bromide in heptane solution, is depicted in **Fig. 4**. In both cases, the plots exhibit "S" shape curves, excluding two points measured at the substrate concentration above 3 mol

dm^{-3} in **Fig. 4**. It is considered that the local decrease in reaction rate at the high substrate concentration is ascribed to an increase in viscosity of the heptane solution of substrate as disperse phase and consequently an increase in the droplet size, since in the case of disperse phase with low viscosity, its droplet size is independent of the viscosity, whereas in the case of highly viscous disperse phase, the droplet size strongly depends on the
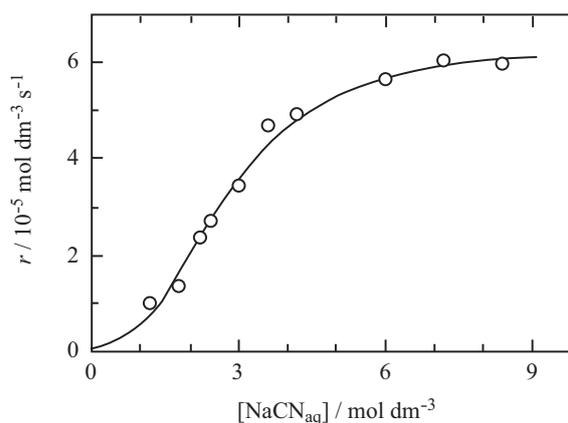
Fig. 3 Influence of nucleophile concentration upon reaction rate. Reaction conditions are the same as in Fig. 2 except the nucleophile concentration and the catalyst concentration of aqueous solution (TAC6A: 0.40 mol %, 7.2×10^{-3} mol dm^{-3}).

Fig. 2 Influence of catalyst concentration upon reaction rate. Reaction conditions are as follows: NaCN (18.0 mmol) and TACnA in water, 5 mL; 4-*tert*-butylbenzyl bromide (9.0 mmol) in heptane, 5 mL; temp. 50 °C; stirring speed 800 rpm.
(○) TAC4A; (△) TAC6A; (□) TAC8A.
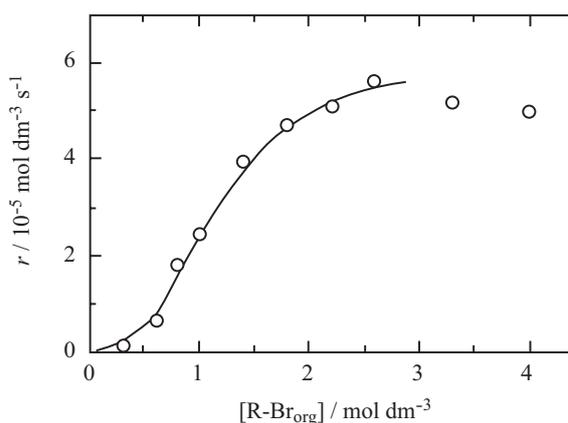
Fig. 4 Influence of substrate concentration upon reaction rate. Reaction conditions are the same as in Fig. 2 except the substrate concentration and the catalyst concentration of aqueous solution (TAC6A: 0.40 mol %, 7.2×10^{-3} mol dm^{-3}).

viscosity.[14] In fact, the heptane solution with high substrate concentration of 4 mol dm^{-3} which is near to neat (5.4 mol dm^{-3}) becomes highly viscous. Accordingly, this high viscosity may bring about the decrease in the interface area.

Since the plots in **Figs. 3** and **4** exhibit "S" shapes, the rate data can be described by Hill eqn. (1),[15, 16] where r_{max}, K_H and m are constants, and C is the concentration of material.

$$r = \frac{r_{max} C^m}{K_H + C^m} \qquad (1)$$

That is, C corresponds to the molar concentration of sodium cyanide in aqueous solution, [NaCN$_{aq}$], or that of substrate in heptane solution, [R-Br$_{org}$], in this biphasic system. The curves are calculated from eqn. (1) using the optimum values of parameters in **Table 1**. The good agreement is obtained between the observed and calculated values. This may imply that the catalyst TAC6A interacts simultaneously with m molecules of nucleophile and substrate independently, and then resulting complex gives the product, according to the fundamental mechanism postulated by Lineweaver and Burk[16] for some enzyme reactions which is represented by eqn. (2). The symbols E, S and P express enzyme,

$$\text{E} + m\,\text{S} \rightleftharpoons \text{ES}_m \longrightarrow \text{E} + \text{P} \qquad (2)$$

substrate and product, respectively. For instance, it may be considered that the value of m for nucleophile refers the number of cyanide ions interacting electrostatically with the quaternary ammonium groups of one TAC6A molecule, and hence the fraction of dissociation of the ammonium groups is estimated to be 0.458 from $m = 2.75$.

When β-CD[13] and its *O*-(2-hydroxy-3-trimethyl-ammoniopropyl) derivatives[17] were employed as catalysts in the halogen exchange reactions of alkyl halides with an excess of aqueous inorganic salt, pseudo-first-order rate constants were obtained. It is therefore particularly interesting that the TAC6A-catalyzed reaction showed no first-order dependence of reaction rate not only on the concentration of substrate in organic phase, but also on that of nucleophile in aqueous phase, where practically almost all of catalyst is present.

Effects of stirring speed and reaction temperature. The influence of the stirring speed upon the reaction rate is shown in **Fig. 5**. The rate of reaction using TAC6A as a catalyst increases in direct proportion to the stirring speed from 200 to 700 rpm, and then attains the optimal value (plateau region) at around 800 rpm, after which a certain decrease occurs up to 1100 rpm. Also when β-CD was used, the rate found to exhibit such a tendency to some extent.

Gas being drawn into the center of the liquid phase was observed clearly at the stirring speed of 1100 rpm. It appears most likely that this phenomenon results in aggregation of the heptane droplets dispersed in aqueous phase,[18] which consequently contributes in decreasing the reaction rate at higher stirring speeds due to the decreases in interfacial area. It is well-known that the reaction rate is directly proportional to stirring speed (from 600 to 1700 rpm) in imidazole-catalyzed ester hydrolysis at a heptane-water interface.[19] On the other hand, the reaction rate of cyanide displacement on octyl chloride shows no longer dependence on the stirring speed beyond just enough to obtain moderate mixing (*ca.* 250 rpm) under normal PTC conditions, which supports the assumption that mass transport across the interface is very fast relative to the organic-phase displacement reaction.[20]
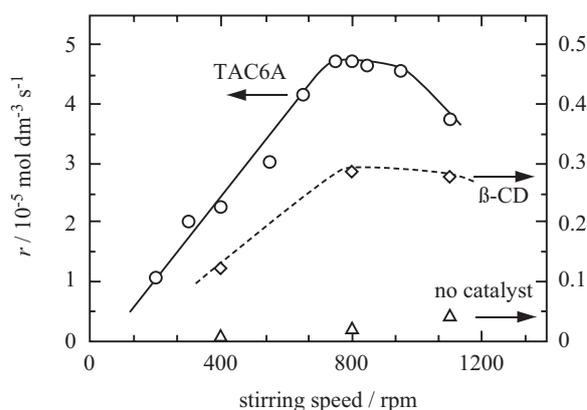
Fig. 5 Effect of stirring speed. Reaction conditions are the same as in Fig. 2 except the stirring speed and the catalyst concentration of aqueous solution (0.40 mol %, 7.2×10^{-3} mol dm^{-3}).

Table 1 The best-fit values of parameters in Hill eqn. (1).

Reactant (C_H)	$10^5\, r_{max}$	K_H	m
[NaCN$_{aq}$]	6.35	15.1	2.75
[R-Br$_{org}$]	6.01	1.44	2.87

Fig. 6 shows the temperature dependences of the observed reaction rate. Apparent activation energies are nearly equal for the reactions using TAC6A at 500 and 800 rpm, and they are 12.5 and 13.5 kcal mol⁻¹, respectively. The close proximity of numerical values of these two activation energies indicates that rate-limiting diffusion of the organic halide through the heptane-water interface or through the bulk heptane phase can be ruled out, and chemical reaction is rate determining at both stirring speeds of 500 and 800 rpm. The following points in addition to this consideration suggest that the reaction takes place predominantly at the heptane-water interface. Firstly, the reaction rate is proportional to the stirring speed from 200 to 700 rpm as already mentioned. Secondly, the plot showing the influence of catalyst concentration on the reaction rate is convex up. Thirdly, apparent activation energies of the reactions using β-CD and without catalyst are *ca.* 4 and *ca.* 30 kcal mol⁻¹ at 800 rpm, and they appear to be assigned to diffusion-and reaction-controlled processes, respectively.

On the other hand, it has been reported that, even under normal PTC conditions, there is a possible participation of an interfacial reaction process in nucleophilic substitution reactions of 1-bromodecane with aqueous inorganic salts using water-insoluble alcohols as organic solvents, owing to surface active cetyltrimethylammo-

nium ions adsorbed selectively at the interface.[21] In oxidation of piperonal with aqueous KMnO₄ and hydrolysis of α,α,α-trichlorotoluene with aqueous NaOH, it has been suggested that cetyltrimethylammonium bromide operates by both emulsification and micellization.[22]

3.2 Transport rate

Inverse phase-transfer catalysts TAC6A and β-CD were investigated as carriers for transport of the lipophilic substrate, 4-*tert*-butylbenzyl bromide, through an aqueous sodium bromide solution from hexane source into hexane receiving phases. The relative rates of transport were determined from the slopes of the linear parts of the plots shown in **Fig. 7**, which were 2.64 × 10⁻⁶, 28.7 × 10⁻⁶ and 1.37 × 10⁻⁶ mol dm⁻³ h⁻¹ in the presence of TAC6A and β-CD, and in the absence of a carrier, respectively.

Diederich and Dick[12] have found an approximate proportionality between the relative rates of transport and the extractability of neutral substrate from hexane into the aqueous phase mediated by carriers. The extractability can be expressed by the extraction constant K_e (eqn. (3)) provided a 1:1 host-guest complex is formed.

$$K_e = \frac{[(H \supset G)_{aq}]}{[G_{org}][H_{aq}]} = K_d K_a \qquad (3)$$
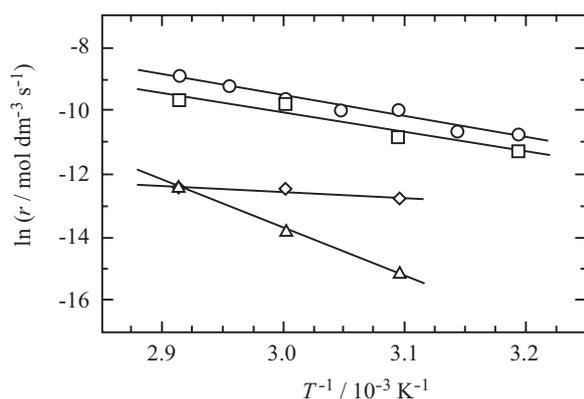
Fig. 6 Dependence of reaction rate on temperature. Reaction conditions are the same as in Fig. 2 except the temperature, the stirring speed and the catalyst concentration of aqueous solution (0.40 mol %, 7.2 × 10⁻³ mol dm⁻³). (○) TAC6A, 800 rpm; (□) TAC6A, 500 rpm ; (◇) β-CD, 800 rpm ; (△) no catalyst, 800 rpm.
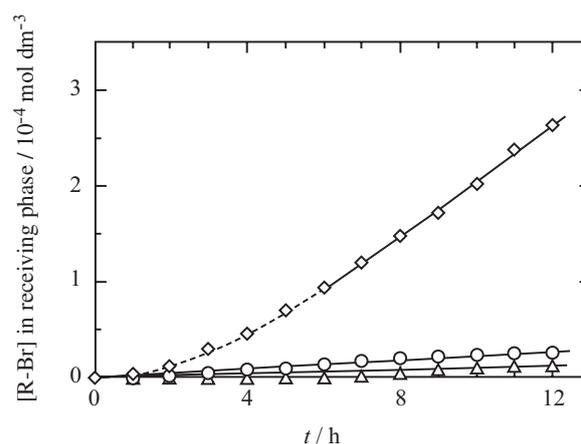
Fig. 7 Transport of 4-*tert*-butylbenzyl bromide through an aqueous solution of TAC6A or β-CD (7.2 × 10⁻³ mol dm⁻³) containing NaBr (3.6 mol dm⁻³). Initial concentration of 4-*tert*-butylbenzyl bromide in the hexane source phase is 0.2 mol dm⁻³; temp. 25 ˚C. (○) TAC6A; (◇) β-CD; (△) no catalyst.

The symbols G, H and (H⊃G) in eqn. (3) stand for guest, host and host-guest complex, respectively; subscripts "aq" and "org" refer to aqueous and organic phases. That is to say, the constant K_e is defined as the product of the distribution coefficient K_d of the substrate and the association constant K_a of complex formation. Poh *et al.*[23] have also proposed a relationship between the relative transport rate and the association constant K_a. Although their findings are inapplicable directly to our system due to the possible formation of multi-guest: one-host complex as mentioned above, it is quite likely that an increase in the relative transport rate implies an increase in the concentration of complexed substrate in aqueous phase. Hence, we can discuss a relationship between the rates of cyanide displacement reactions catalyzed by TAC6A and β-CD and the relative transport rates. The corresponding reaction rates are 4.71×10^{-5}, 0.285×10^{-5}, and 0.022×10^{-5} mol dm^{-3} s^{-1} in the presence of the same concentration of TAC6A and β-CD (7.2×10^{-3} mol dm^{-3}), and in the absence of a catalyst, respectively. If the rate-determining step is the diffusion process through the heptane-water interface or chemical reaction process in aqueous phase, a simple relationship between those is supposed to be obtained. Actually the relative rate of transport in the presence of β-CD is 13 times greater than that in the absence of a carrier, and the rate of reaction catalyzed by β-CD is 21 times. This harmony has supported that, in the reaction catalyzed by β-CD, the rate-determining step is diffusion process. In contrast, a 214-fold enhancement in the rate of reaction catalyzed by TAC6A, in spite of only a 2-fold enhancement in the relative transport rate, has strongly pointed that the reaction takes place predominantly at the heptane-water interface.

3.3 Adsorption at hexane-water interface

Interfacial tension at the boundary between hexane and aqueous solutions of TAC4A and TAC6A was measured at 25 °C for understanding the catalytic feature of TAC*n*A in this liquid-liquid reaction system. The plots of interfacial tension *vs.* logarithm of molar concentration for TAC4A and TAC6A are shown in **Fig. 8**. The interfacial tension for both water-soluble calixarenes decreased gradually with the increase in their concentrations. That a significant reduction in the interfacial

tension is brought by the water-soluble calixarenes bearing only methyl groups at narrow rim as hydrophobic substituents, to the best of our knowledge, is the first finding. While several surface-active calixarenes have been synthesized,[24] all of them contain hydrophobic alkyl groups larger than butyl at wide or narrow rim of calixarene platform as well as hydrophilic groups at the opposite rim. This finding may suggest that hydrocarbon molecule(s) binding weakly to TAC*n*A by hydrophobic and/or CH/π [25] interactions in their cavities behaves as hydrophobic alkyl chain(s) for TAC*n*A surfactants over a certain period of time only at the interface, though it is clear from the results of the transport experiment that such complex is unstable in bulk water phase.

When it is adopted as a working hypothesis that TAC*n*A are electrolytes as represented by eqn. (4), where *l* is the fraction of dissociation of their quaternary ammonium groups, and further the value of 0.458 estimated from *m* for NaCN is adopted as that of *l*, the surface excess concentration $\Gamma_{(n)}$ can be expressed by eqn. (5) according to Gibbs adsorption eqn.,[26] where

$$\text{TAC}n\text{A} \rightleftharpoons \text{TAC}n\text{A}^{nl+} + nl\, \text{Cl}^- \qquad (4)$$
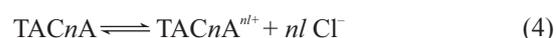
$$\Gamma_{(n)} = \frac{-1}{2.303(nl+1)RT} \left(\frac{\partial \gamma}{\partial (\log a_\pm)} \right) \qquad (5)$$

γ is the interfacial tension and $a_\pm$ the mean activity of TAC*n*A electrolytes, and subscript "(*n*)" refers to *n* of TAC*n*A. It can be tactically presumed that the mean
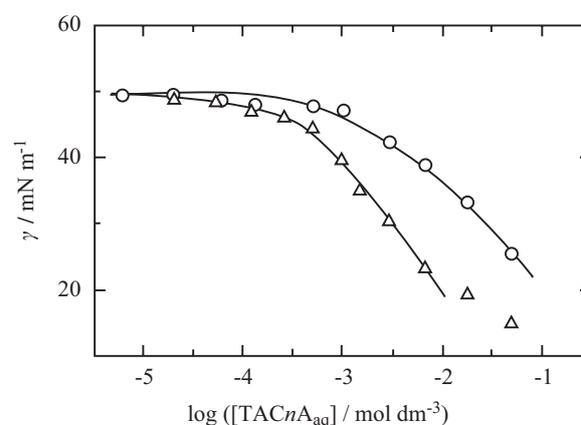
Fig. 8 Interfacial tension at hexane-water interface *vs.* logarithm of concentration for (O) TAC4A and (△) TAC6A in aqueous phase at 25 ˚C.

activity $a_\pm$ is equal to $f_\pm[\text{TAC}n\text{A}_{aq}]$, and that the mean activity coefficient $f_\pm$ is related to the individual activity coefficients of TACnA cation and counterion by $f_\pm = (f_+ f_-^{nl})^{1/(nl+1)}$. These individual ones, f_+ and f_-, are given by eqn. (6), where I is the total ionic strength of the aqueous solution expressed by eqn. (7). The value of

$$\log f_{+/-} = \frac{-D\sqrt{I}}{1 + 0.33d\sqrt{I}} \qquad (6)$$

$$I = \frac{1}{2}\{[\text{TAC}n\text{A}_{aq}](+nl)^2 + nl[\text{TAC}n\text{A}_{aq}](-1)^2\}$$

$$= \frac{1}{2} nl(nl+1)[\text{TAC}n\text{A}_{aq}] \qquad (7)$$

D is 0.509 at 25 °C, and d is taken as 0.6 for TACnA cation and 0.3 for the inorganic counterion Cl⁻.[27] Thus the surface excess concentrations were determined from the slopes of lines tangent to the interfacial tension *vs.* log $a_\pm$ curves, excluding two points measured at the TAC6A concentration above 0.01 mol dm⁻³, and could be in accord with Langmuir adsorption isotherm[28] in linear form (eqn. (8)) as shown in **Fig. 9**. $\Gamma_{\infty(n)}$ and $K_{L(n)}$ represent the saturated surface excess concentration and the adsorption equilibrium constant, respectively. The values of $\Gamma_{\infty(n)}^{-1}$ are evaluated from the slopes of these lines in **Fig. 9**, and then limiting molecular areas $A_{0(n)}$ of TACnA adsorbed at the hexane-water interface also can be given by eqn. (9), where N_A is Avogadoro's

$$\frac{[\text{TAC}n\text{A}_{aq}]}{\Gamma_{(n)}} = \frac{1}{\Gamma_{\infty(n)} K_{L(n)}} + \frac{[\text{TAC}n\text{A}_{aq}]}{\Gamma_{\infty(n)}} \qquad (8)$$

$$A_{0(n)} = \frac{1}{\Gamma_{\infty(n)} N_A} \qquad (9)$$

number. They are 126 Å²/molecule for TAC4A and 150 Å²/molecule for TAC6A. The value for TAC4A is quite in agreement with that (*ca.* 125 Å²/molecule) which is predicted on the basis of the molecular mechanics (MM2) geometry, assuming that TAC4A retaining the 1,3-alternate conformation[11a] lies at the hexane-water interface in a tetragonal packed array, and that its annulus is faced to the interface. When the cone conformation is assumed for TAC4A, larger value (*ca.* 140 Å²/molecule) is predicted. In addition, the value for TAC6A also agree very closely with that (*ca.* 150 ± 8 Å²/molecule) of mercurated calix[6]arenes forming a stable monolayer.[29] These agreements may indicate that the working hypothesis, eqn. (4) and $l = 0.458$, is reasonable, and that m for NaCN is certainly related

to the fraction of dissociation of ammonium groups in TACnA, although there are significant differences between the reaction conditions in aqueous biphasic system and the conditions for interfacial tension measurement, *e.g.*, temperature and total ionic strength of aqueous solution. Moreover, it can be considered that molar adsorption of TACnA at the interface is represented by Langmuir adsorption isotherm not only in the system for measuring the interfacial tension but also in the aqueous biphasic reaction system.

3.4 Kinetics and plausible mechanism

As we have so far described in this article, eqn. (10)−(12) summarize the pathway for this cyanide displacement on 4-*tert*-butylbenzyl bromide in aqueous biphasic system. Subscripts "int" refers to heptane-water

$$^{\phi}\text{TAC}n\text{A}^{nl+}{}_{int} + \alpha_{(n)}\text{R-Br}_{org}$$
$$\rightleftharpoons (^{\phi}\text{TAC}n\text{A}^{nl+} \supset \text{R-Br}\alpha_{(n)})_{int} \qquad (10)$$

$$^{\pm}\text{TAC}n\text{A}^{nl+}{}_{int} + nl\ \text{CN}^-{}_{aq}$$
$$\rightleftharpoons (^{\pm}\text{TAC}n\text{A}^{nl+}//\text{CN}^-{}_{nl})_{int} \qquad (11)$$

$$(^{\phi}\text{TAC}n\text{A}^{nl+} \supset \text{R-Br}\alpha_{(n)})_{int} + (^{\pm}\text{TAC}n\text{A}^{nl+}//\text{CN}^-{}_{nl})_{int}$$
$$\longrightarrow \text{R-CN}_{org} + (\alpha_{(n)}-1)\ \text{R-Br}_{org} + {}^{\phi}\text{TAC}n\text{A}^{nl+}{}_{int}$$
$$+ {}^{\pm}\text{TAC}n\text{A}^{nl+}{}_{int} + (nl-1)\ \text{CN}^-{}_{aq} + \text{Br}^-{}_{aq} \qquad (12)$$
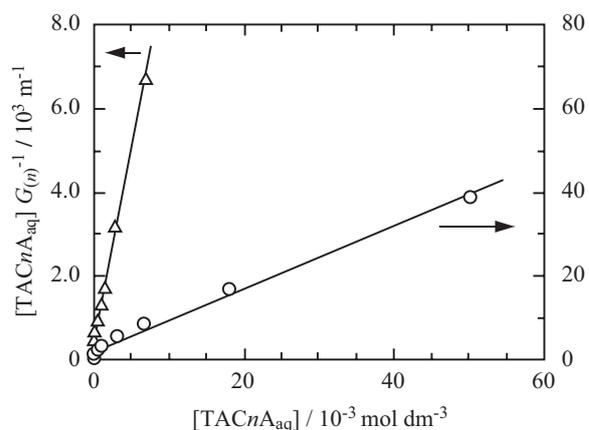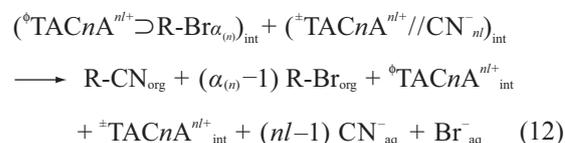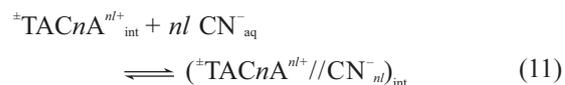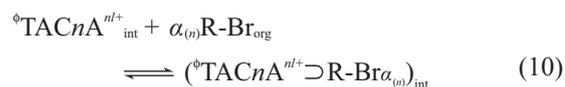
Fig. 9 Adsorption of (○) TAC4A (right-hand vertical scale) and (△) TAC6A (left-hand vertical scale) at hexane-water interface graphed according to Langmuir eqn. in linear form.

interface. $(^{\phi}\mathrm{TAC}n\mathrm{A}^{nl+}\supset\mathrm{R\text{-}Br}_{\alpha_{(n)}})_{\mathrm{int}}$ and $(^{\pm}\mathrm{TAC}n\mathrm{A}^{nl+}//\mathrm{CN}^{-}nl)_{\mathrm{int}}$ stand for $\alpha_{(n)}$ molecules of substrate R-Br binding weakly to TACnA by CH/π, π/π and/or hydrophobic interactions at the interface, and cyanide ions interacted electrostatically with TACnA, respectively. The presumption that the multiple substrate molecules are complexed with TACnA (n = 6, 8) at the interface is consistently supported by their substrate selectivities reported previously.[7e)] It could be assumed that the solvent-separated ion pair, $(^{\pm}\mathrm{TAC}n\mathrm{A}^{nl+}//\mathrm{CN}^{-}nl)_{\mathrm{int}}$, is stabilized by forming a spatial electrostatic network within itself. This may be the reason why the property of TACnA^{nl+} is enriched with cooperative and allosteric effect on the interaction with nl cyanide ions. TACnAs adsorbed at the interface can be regarded as a receptor monolayer equipped with two kinds of sites for interacting independently with substrates and nucleophiles, where total surface densities are exactly identical, $[^{\phi}\mathrm{TAC}n\mathrm{A}^{nl+}{}_{\mathrm{int}}]_0 = [^{\pm}\mathrm{TAC}n\mathrm{A}^{nl+}{}_{\mathrm{int}}]_0$. As shown in eqn. (12), one of cyanide ions interacting with one TACnA molecule reacts with one of substrate molecules complexed with the same TACnA molecule at the interface to give product, and this nucleophilic attack on benzyl carbon is rate determining. Hence, the initial rate of reaction is represented by eqn. (13), because the rate of reaction of distributed substrate in bulk aqueous phase with cyanide ion are negligible compared with that of TACnA-catalyzed one.

$$r_{(n)} = k_{(n)}[(^{\phi}\mathrm{TAC}n\mathrm{A}^{nl+}\supset\mathrm{R\text{-}Br}_{\alpha_{(n)}})_{\mathrm{int}}][(^{\pm}\mathrm{TAC}n\mathrm{A}^{nl+}//\mathrm{CN}^{-}nl)_{\mathrm{int}}] \tag{13}$$

For the two equilibria (10) and (11), their dissociation constants can be express by eqns. (14) and (15), respectively, where superscripts "Su" and "Nu" refer to substrate and nucleophile reagent. The product and Br$^-$ are present only very small amounts at the initial

$$K_{\mathrm{H}(n)}^{\mathrm{Su}} = \frac{[^{\phi}\mathrm{TAC}n\mathrm{A}^{nl+}{}_{\mathrm{int}}][\mathrm{R\text{-}Br}_{\mathrm{org}}]^{\alpha_{(n)}}}{[(^{\phi}\mathrm{TAC}n\mathrm{A}^{nl+}\supset\mathrm{R\text{-}Br}_{\alpha_{(n)}})_{\mathrm{int}}]} \tag{14}$$

$$K_{\mathrm{H}(n)}^{\mathrm{Nu}} = \frac{[^{\pm}\mathrm{TAC}n\mathrm{A}^{nl+}{}_{\mathrm{int}}][\mathrm{CN}^{-}{}_{\mathrm{aq}}]^{nl}}{[(^{\pm}\mathrm{TAC}n\mathrm{A}^{nl+}//\mathrm{CN}^{-}nl)_{\mathrm{int}}]} \tag{15}$$

stage of reaction, so that the surface densities $[^{\phi}\mathrm{TAC}n\mathrm{A}^{nl+}{}_{\mathrm{int}}]$ and $[^{\pm}\mathrm{TAC}n\mathrm{A}^{nl+}{}_{\mathrm{int}}]$ can be given by eqns. (16) and (17). Substituting eqns. (16) and (17) into eqns.

(14) and (15), respectively, eqns. (18) and (19) are obtained. Consequently, combination of eqns. (13),

$$[^{\phi}\mathrm{TAC}n\mathrm{A}^{nl+}{}_{\mathrm{int}}] = [^{\phi}\mathrm{TAC}n\mathrm{A}^{nl+}{}_{\mathrm{int}}]_0 \\ - [(^{\phi}\mathrm{TAC}n\mathrm{A}^{nl+}\supset\mathrm{R\text{-}Br}_{\alpha_{(n)}})_{\mathrm{int}}] \tag{16}$$

$$[^{\pm}\mathrm{TAC}n\mathrm{A}^{nl+}{}_{\mathrm{int}}] = [^{\pm}\mathrm{TAC}n\mathrm{A}^{nl+}{}_{\mathrm{int}}]_0 \\ - [(^{\pm}\mathrm{TAC}n\mathrm{A}^{nl+}//\mathrm{CN}^{-}nl)_{\mathrm{int}}] \tag{17}$$

$$[(^{\phi}\mathrm{TAC}n\mathrm{A}^{nl+}\supset\mathrm{R\text{-}Br}_{\alpha_{(n)}})_{\mathrm{int}}] \\ = \frac{[\mathrm{R\text{-}Br}_{\mathrm{org}}]^{\alpha_{(n)}}[^{\phi}\mathrm{TAC}n\mathrm{A}^{nl+}{}_{\mathrm{int}}]_0}{K_{\mathrm{H}(n)}^{\mathrm{Su}} + [\mathrm{R\text{-}Br}_{\mathrm{org}}]^{\alpha_{(n)}}} \tag{18}$$

$$[(^{\pm}\mathrm{TAC}n\mathrm{A}^{nl+}//\mathrm{CN}^{-}nl)_{\mathrm{int}}] \\ = \frac{[\mathrm{CN}^{-}{}_{\mathrm{aq}}]^{nl}[^{\pm}\mathrm{TAC}n\mathrm{A}^{nl+}{}_{\mathrm{int}}]_0}{K_{\mathrm{H}(n)}^{\mathrm{Nu}} + [\mathrm{CN}^{-}{}_{\mathrm{aq}}]^{nl}} \tag{19}$$

(18) and (19), and $[^{\phi}\mathrm{TAC}n\mathrm{A}^{nl+}{}_{\mathrm{int}}]_0 = [^{\pm}\mathrm{TAC}n\mathrm{A}^{nl+}{}_{\mathrm{int}}]_0 = [\mathrm{TAC}n\mathrm{A}_{\mathrm{int}}]_0$ leads to eqn. (20). Provided molar adsorption of TACnA at the interface can be represented by Langmuir adsorption isotherm, eqn. (20) may be transformed into eqn. (21). The values of reaction rate

$$r_{(n)} = \frac{k_{(n)}[\mathrm{R\text{-}Br}_{\mathrm{org}}]^{\alpha_{(n)}}[\mathrm{CN}^{-}{}_{\mathrm{aq}}]^{nl}[\mathrm{TAC}n\mathrm{A}_{\mathrm{int}}]_0^2}{(K_{\mathrm{H}(n)}^{\mathrm{Su}} + [\mathrm{R\text{-}Br}_{\mathrm{org}}]^{\alpha_{(n)}})(K_{\mathrm{H}(n)}^{\mathrm{Nu}} + [\mathrm{CN}^{-}{}_{\mathrm{aq}}]^{nl})} \tag{20}$$

$$r_{(n)} = \frac{k_{(n)}[\mathrm{R\text{-}Br}_{\mathrm{org}}]^{\alpha_{(n)}}[\mathrm{CN}^{-}{}_{\mathrm{aq}}]^{nl}}{(K_{\mathrm{H}(n)}^{\mathrm{Su}} + [\mathrm{R\text{-}Br}_{\mathrm{org}}]^{\alpha_{(n)}})(K_{\mathrm{H}(n)}^{\mathrm{Nu}} + [\mathrm{CN}^{-}{}_{\mathrm{aq}}]^{nl})}\left(\frac{\Gamma_{\infty(n)}K_{\mathrm{L}(n)}[\mathrm{TAC}n\mathrm{A}_{\mathrm{aq}}]}{1 + K_{\mathrm{L}(n)}[\mathrm{TAC}n\mathrm{A}_{\mathrm{aq}}]}\right)^2 \tag{21}$$

calculated from eqn. (21), where $K_{\mathrm{L}(4)}$, $K_{\mathrm{L}(6)}$ and $K_{\mathrm{L}(8)}$ are 130, 189 and 372 dm^3 mol^{-1}, respectively, are indicated by the full line curves in **Fig. 2**. The agreements between the observed and calculated values are satisfactory. This result provides support to the assumption that molar adsorption of TACnA at the interface can be represented by Langmuir adsorption isotherm. Moreover, the kinetic data shown in **Figs. 3** and **4** is consistent with eqn. (21), substituting the optimum values of $\alpha_{(6)}$ and $K_{\mathrm{H}(6)}^{\mathrm{Su}}$, and nl and $K_{\mathrm{H}(6)}^{\mathrm{Nu}}$ which correspond to m and K_{H} for substrate, and for nucleophile listed in **Table 1**. Accordingly, the mechanism of the aqueous biphasic reaction which is proposed above with eqns. (10) – (12) is quite reasonable.

In conclusion, we have shown herein that the aqueous biphasic reaction of lipophilic 4-*tert*-bu-

tylbenzyl bromide with aqueous sodium cyanide catalyzed by TACnA takes place predominantly at the interface, and that the nucleophilic attack of cyanide ion on the substrate is rate determining. The catalytic features of TACnA are quite interesting, for there are striking similarities between those of TACnA and enzymes.

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新規な逆相間移動触媒としての水溶性カリックスアレーン：
水相−有機相二相系での 4-*tert*-ブチルベンジルブロミドのシアン化物イオンによる求核置換反応の速度論的研究

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概　　要

　水溶性のトリメチルアンモニオカリックス [n] アレーン ($n = 4, 6, 8$; TACnA) を触媒とする 4-*tert*-ブチルベンジルブロミドとシアン化物イオンとの求核置換反応を水相−有機相二相系で行い，その反応速度を測定した。触媒濃度，求核試薬濃度，基質濃度，撹拌速度，温度の反応速度への影響を調べた。さらに，反応機構を考察するために TAC6A をキャリヤーとし，水を液膜とするアルキルブロミドの輸送実験を行った。また，TAC4A と TAC6A の界面活性能の測定も行った。これらの結果から，反応はヘプタン−水界面で優先的に起こり，反応律速であると考えられる。具体的には，界面に吸着した TACnA 分子と静電的に相互作用したシアン化物イオンが，その TACnA 分子に包接されている基質分子 (アルキルブロミド) を求核攻撃する段階が律速と考えられる。

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