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HOST-GUEST-TYPE ACID CATALYSTS DERIVED FROM CALIX[6]ARENE

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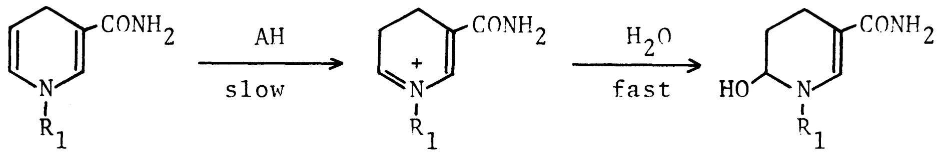
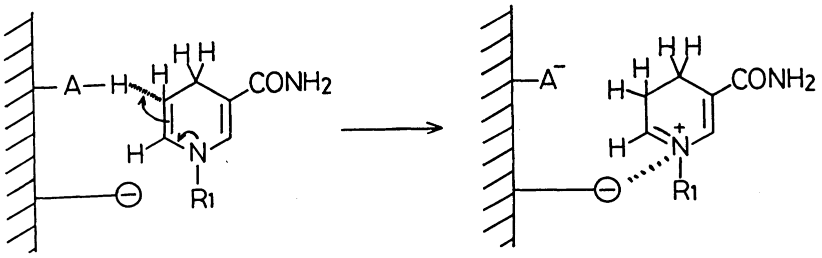
Water-soluble calix[6]arenes bearing both acidic protons and sulfonate groups were synthesized. They catalyzed a hydration reaction of 1-benzyl-1,4-dihydronicotinamide (BNAH) according to Michaelis-Menten kineticts and the rate constants were greater by 426-1220 fold than those for noncyclic analogues. Fluorescence data supported the complexation of BNAH with these water-soluble calixarenes. These findings indicate that calixarenes serve as a new starting material to design functionalized host molecules.

It has been established that NADH and its synthetic model compounds (1,4-dihydronicotinamides) undergo an acid-catalyzed hydration reaction in aqueous solution.$^{1)}$ The hydration reaction causes shifts of a characteristic absorption band of 1,4-dihydronicotinamide in 340-360 nm region downward to around 290 nm. The 290 nm-absorbing compound was later verified to be 6-hydroxy-1,4,5,6-tetrahydronicotinamide.$^{2)}$ The following reaction scheme was thus suggested, in which protonation of 1,4-dihydronicotinamide is involved in the rate-determining step.



(1)

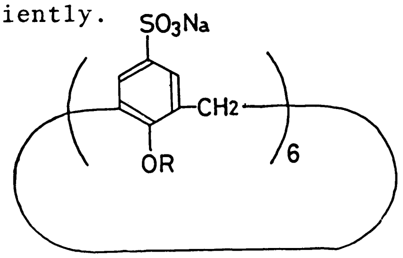
It is known that glyceraldehyde-3-phosphate dehydrogenase can rapidly catalyze this reaction to afford hydrated NADH.$^{3)}$ Although the mechanistic view is not clear yet, some charge-transfer stabilization of the cationic intermediate as well as the presence of some proton-donating group is suggested.$^{4,5)}$ Thus, it would be of value to design such an enzyme model which has within a molecule both an anionic charge and a proton-donating group (Eq. 2).



(2)

Recently, Gutsche and co-workers[6)] have reported on a series of cylindrical molecules called "calixarenes": calixarenes are cyclic oligomers made up of benzene units like cyclodextrins made up of glucose units and thus expected to be useful to design enzyme mimics in totally synthetic systems. We thus synthesized catalytic hosts (1) which are expected to serve as mimics of glyceraldehyde-3-phosphate dehydrogenase. We have found that (1H) and (1CH$_2$COOH) which bear acidic protons as well as anionic sulfonate groups on the two sides of the calixarene cylinder can catalyze Eq. 1 very efficiently.

(1H) :R=H
(1CH$_2$COOH) :R=CH$_2$COOH
(1C) :R=CH$_3$
(1C$_{12}$) :R=n-C$_{12}$H$_{25}$



(1CH$_2$COOH), (1C) and (1C$_{12}$) were prepared from (1H)[7)] by the reaction with corresponding halides and identified by IR, NMR, elemental analysis, and titration of acidic groups. The reaction was carried out at 30 °C in buffered aqueous solution (pH 6.30 with 0.01 M phosphate: 1 M=1 mol dm^{-3}) unless otherwise stated. The titration of (1CH$_2$COOH) showed that at pH 6.30, two of six carboxyl groups remain undissociated. The reaction was followed by monitoring the disappearance of 1-benzyl-1,4-dihydronicotinamide (BNAH: R$_1$=benzyl in Eq. 1) at 357 nm. In all cases, the reaction obeyed the first-order kinetics and the final absorption spectrum was in accord with that of 1-benzyl-6-hydroxy-1,4,5,6-tetrahydronicotinamide (λ_{max} 290 nm).[2)]

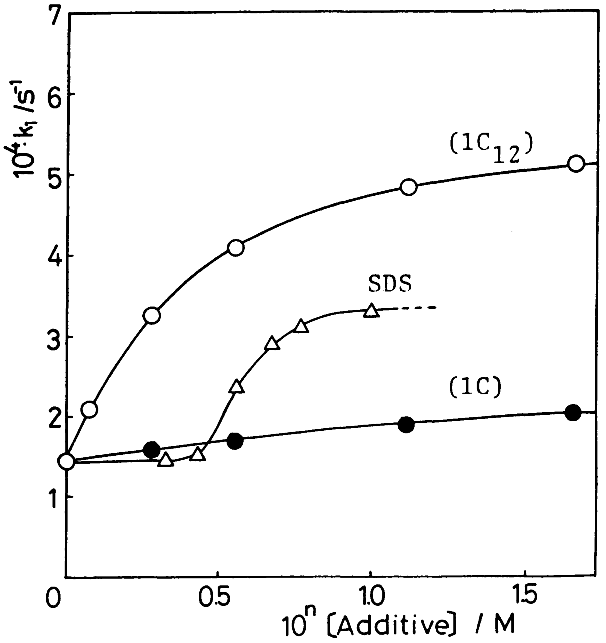


Fig. 1. First-order rate constant vs. additive concentration (for the reaction conditions see Table 1). n=2 for SDS; n=3 for (1C) and (1C$_{12}$).

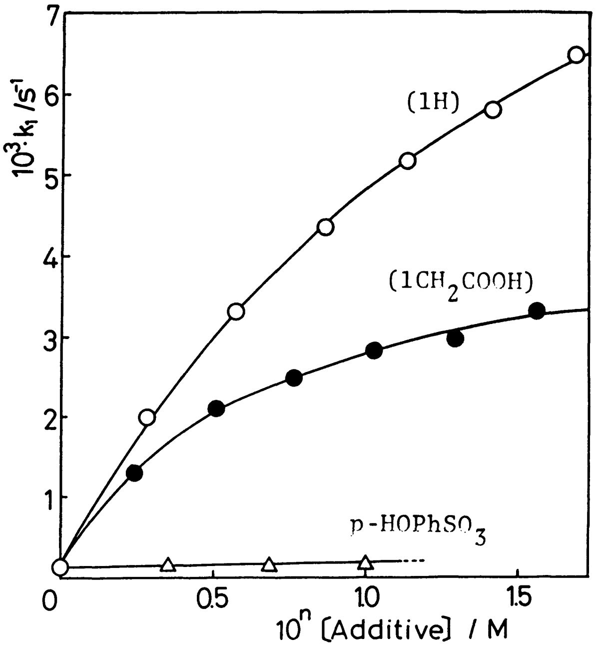


Fig. 2. First-order rate constant vs. additive concentration (for the reaction conditions see Table 1). n=2 for p-hydroxybenzenesulfonate; n=3 for (1H) and (1CH$_2$COOH).

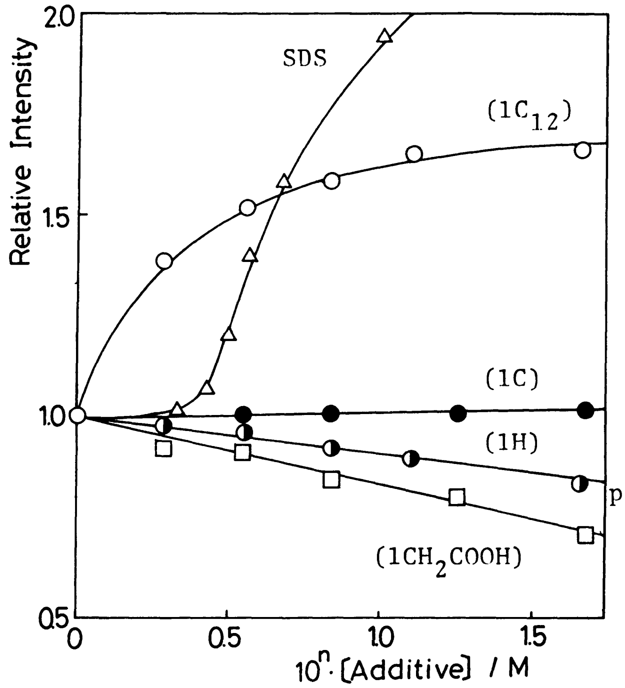


Fig. 3. Fluorescence intensity vs. additive concentration. 30 °C, pH 10.11 (0.01 M carbonate), [BNAH]=3.16×10^{-5} M, excitation 361 nm, emission 460 nm. n=2 for SDS; n=3 for others.

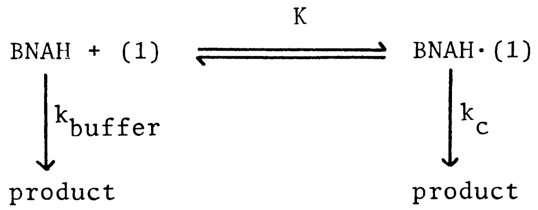
Table 1. Kinetic parameters$^{a)}$

Additive	$10^4 \cdot k_1$$^{b)}$ / s^{-1}	$10^4 \cdot k_c$$^{e)}$ / s^{-1}	$K^{e)}$ / M^{-1}
(1H)	46.2	131	564
$(1CH_2COOH)$	26.6	47.5	1340
(1C)	0.36	3.08	287
$(1C_{12})$	3.31	6.23	2160
SDS	≈0	—	—
SDS$^{c)}$	1.13	—	—
$p\text{-HOPhSO}_3^-$	0.038	—	—
$(1CH_2COOH)^{d)}$	328	668	1020
$p\text{-HOOCCH}_2\text{OPhSO}_3^-$$^{d)}$	0.77	—	—

a)30 °C, pH 6.30(0.01 M phosphate), [BNAH]=1.01×10^{-4} M. b)First-order rate constant($k_1 = k_{obs} - k_{buffer}$) at [additive]= 1.00×10^{-3} M.
c)[SDS]=6.00 mM. The cmc of SDS was estimated to be ca. 5 mM. d) pH 4.00 (0.01 M acetate). e) k_c and K are defined in Scheme 1.

It has been established that anionic micelles can catalyze Eq. 1.[8,9] As shown in Fig. 1, first-order rate constants (k_1) in the presence of sodium dodecylsulfate (SDS) increase above its cmc (about 5 mM). Examination of Figs. 1 and 2 reveals that (i) (1C) acts as a weak catalyst whereas $(1C_{12})$ catalyzes Eq. 1 more efficiently than SDS, (ii) (1H) and $(1CH_2COOH)$ which have acidic protons on the calixarene edge serve as very efficient catalysts, the rate constants at 1.0 mM (Table 1) being greater by 426-1220 fold than those for noncyclic analogues such as p-hydroxybenzenesulfonate and p-carboxymethoxybenzenesulfonate, and (iii) most importantly, plots of k_1 vs. calixarene concentration provide simple saturation curves. The finding (iii) suggests that the reaction catalyzed by these calixarene derivatives should proceed via BNAH·calixarene complexes. Gutsche[10] described in his recent review article that there are no published data in support of solution complexes of calixarenes. Hence, this problem merits further investigation.

The fluorescence intensity (I/I_0) of BNAH increases when it is bound to hydrophobic domain constructed in water.[11] As shown in Fig. 3, I/I_0 increases with $(1C_{12})$ concentration indicating that $(1C_{12})$ can provide the hydrophobic cavity in aqueous solution. On the other hand, it decreases with increase in the concentration of (1H) and $(1CH_2COOH)$. Conceivably, the latter two calixarenes provide, apparently, the microenvironment more polar than water.[12] Noncyclic analogues showed no effect on the fluorescence intensity. These fluorescence data support that BNAH is bound into the cavity of the calixarene derivatives and the reaction proceeds according to Scheme 1.



Scheme 1.

K and k_c determined on the basis of Scheme 1 are summarized in Table 1. Similarly, we could estimate the K for ($1C_{12}$) from Fig. 3: K=2860 M^{-1}(at pH 10.11) is in good accord with the kinetically-determined K (2160 M^{-1}: at pH 6.30). These fluorescence and kinetic data support consistently that BNAH included in the cavity of the calixarene derivatives undergoes the catalytic action. The efficient catalytic effect observed for (1H) and ($1CH_2COOH$) arises from a characteristic architecture of the calixarenes bearing both of the acidic protons and the anionic groups.

In conclusion, the present study demonstrated for the first time that calixarens serve as very useful host molecules, like cyclodextrins,[13,14] to design enzyme mimics. Further applications are now continued in this laboratory.

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