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Molecular Recognition of Calixarene-Based Host Molecules

SEIJI SHINKAI
Department of Organic Synthesis, Faculty of Engineering, Kyushu University, Higashi-ku, Fukuoka 812, Japan

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Abstract. Water-soluble calixarenes with various functional groups were synthesized. It was found that they are capable of molecular recognition and serve as a new class of catalysts, ligands, and host molecules.

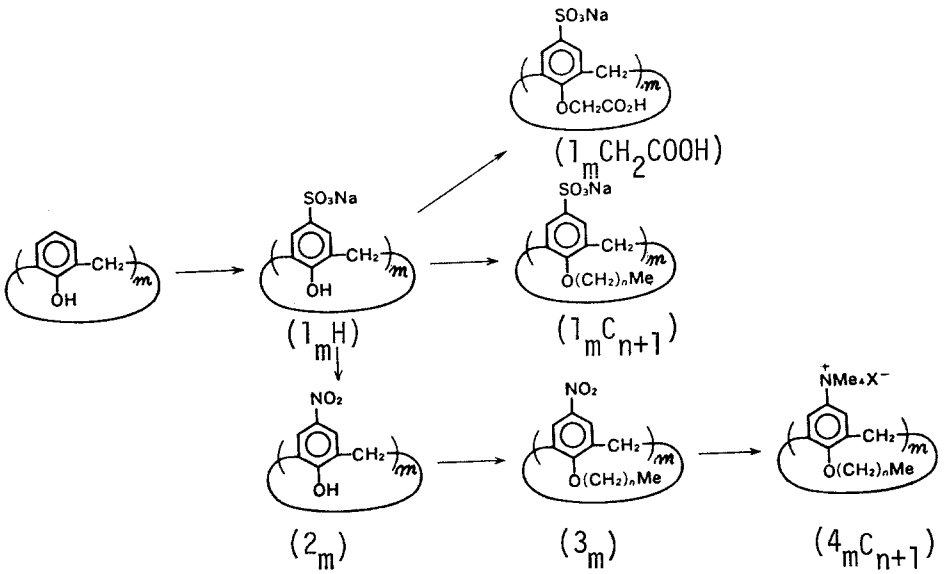
Key words. Calixarene, chiral, catalysis, uranium.

1. Introduction

'Calixarenes' are cyclic oligomers made up of benzene units in a similar way to that in which cyclodextrins are made up of glucose units and thus have been expected to be useful as a new class of host molecules. Although calixarenes can include several small molecules in the solid state, there exist only a few examples for the inclusion properties of calixarenes in solution [1–3]. This is in sharp contrast to cyclodextrins which can form a variety of host–guest-type solution complexes. The difference stems, we believe, from the poor solubility of calixarenes: that is, they are only sparingly soluble in several organic solvents, and insoluble in water. We considered, therefore, that experimental efforts should be directed primarily toward solubilization of calixarenes, which would lead to the exploitation of new host molecules and eventually to the development of refined calixarene-based enzyme mimics. With these objectives in mind, we synthesized several water-soluble anionic and cationic calixarene derivatives [3]. We have found that these water-soluble calixarenes act as excellent host molecules for the selective binding of metal ions and small organic molecules.

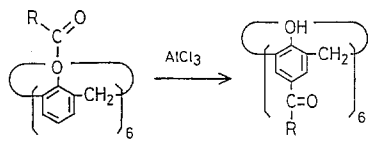
2. Synthesis of Water-Soluble Calixarenes

The synthetic route to water-soluble calixarenes is illustrated in Scheme 1. In order to introduce functional groups into each benzene ring one must choose the reaction having a quantitative yield, because the isolation of a fully-substituted product from lower-substituted by-products is fairly difficult. In Scheme 1 the key step to synthesize water-soluble anionic calixarenes is the sulfonation which proceeds quantitatively under the optimized conditions. The sulfonate group was converted to the nitro group to afford $\mathbf{2}_m$ [4]. Finally, we obtained water-soluble cationic calixarenes, $\mathbf{4}_m\mathrm{C}_{n+1}$ from $\mathbf{3}_m$ via *O*-alkyl-*p*-aminocalixarenes.



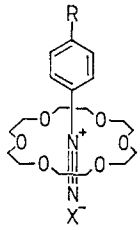
Scheme 1.

Another method to obtain *p*-substituted calixarenes is the rearrangement from the OH group. Gutsche *et al.* [5, 6] introduced the Claisen rearrangement but the products, *p*-allylcalixarenes, are fairly useless as intermediates for water-soluble calixarenes. We have found that $\mathbf{2}_m$ is soluble in basic aqueous solution because of the lowered pK_a of the OH groups [7]. This suggests that introduction of electron-withdrawing *para* substituents may make the calixarene water soluble. We found that the Fries rearrangement of *O*-acylcalixarenes to *p*-acylcalixarenes occurs in 29–34% yield [8]. As expected, *p*-acylcalixarenes are soluble in water at pH > 10.



3. Stabilization of Arenediazonium Salts

In 1973, Gokel and Cram [9] found that crown ethers of the proper dimensions can solubilize several arenediazonium salts in nonpolar media. Subsequent spectroscopic studies established that the solubilization is caused by complexation, like the complexation between crown and metal cations, the linear Ar—N^+≡N inserting into the hole of the crown ring with its oxygen atoms turned inward toward the positive charge as shown in **5**. It was already found that hexasulfonated calix[6]arenes $\mathbf{1}_6C_{n+1}$ strongly bind cationic guest molecules [10]. Also, they can include amines through protonation and the apparent pK_a values are significantly lowered [11]. We thus considered that $\mathbf{1}_6C_{n+1}$ may form stable complexes with the arenediazonium salt **6R**.



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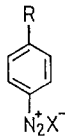
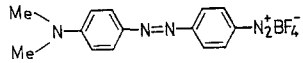


6R



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The first-order rate constants (k_d) for the dediazonation of **6H** and **6C$_6$** to the corresponding phenols are summarized in Table I. Examination of Table I reveals that in an aqueous system, neither 18-crown-6 nor anionic micelle suppresses the thermal decomposition of **6R** to a significant extent, but the k_d values decrease with increasing $\mathbf{1}_6C_{n+1}$ concentration and in particular $\mathbf{1}_6C_{12}$ can reduce the k_d to 20–23% of those observed in the absence of $\mathbf{1}_6C_{n+1}$ [11]. To obtain insight into the stabilization mechanism, we examined the solvent effect on the dediazonation rate because the hydrophobic effect, which is partly reproduced by the solvent effect, may significantly contribute to the rate suppression [11]. We used 4-(4-dimethylaminophenylazo)benzenediazonium tetrafluoroborate **7** as a spectroscopic probe. Through the correlation of λ_{max} in a water–dioxane mixture we estimated the hydrophobicity of $\mathbf{1}_6C_6$ and $\mathbf{1}_6C_{12}$ in water to be 25 and 85 vol% of dioxane, respectively. However, the k_d values for $\mathbf{1}_6C_6$ and $\mathbf{1}_6C_{12}$ are incomparably smaller than those obtained in these mixed solvents. We believe, therefore, that the specific stabilization effect is due to the strong anionic field brought about by six sulfonate groups arranged on the edge of the calixarene cavity.

Table I. First-order rate constants (k_d) for thermal decomposition of **3R** at 30°C

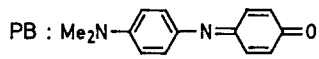
Additive (conc./mM)	**3H**		**3C$_6$**	
	$10^5 \cdot k_d/s^{-1}$	k_d/k_0	$10^5 \cdot k_d/s^{-1}$	k_d/k_0
None	9.52(=k_0)	1.00	1.60(=k_0)	1.00
$\mathbf{1}_6C_1$ (5.00)	8.62	0.91	1.27	0.79
$\mathbf{1}_6C_6$ (5.00)	2.92	0.31	0.37	0.23
$\mathbf{1}_6C_{12}$ (2.00)	1.91	0.20	0.37	0.23
18-crown-6 (24.4)	9.25	0.96	–	–
SDS[a] (20.0)	8.84	0.93	–	–

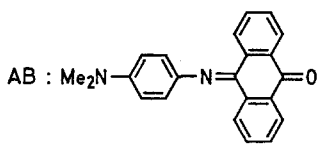
[a] Sodium dodecylsulfate.

4. 'Hole-Size Selectivity' in Calixarene Complexes

Several groups have so far reported the metal ion selectivity of calixarenes which have ether or ester groups on the edge of the cylindrical architecture [12–14]. In contrast, almost nothing is known with certainty as to the selectivity of the calixarene cavity for neutral guest molecules. Does the calixarene cavity recognize the size of guest molecules? To answer this question we examined the host-guest

behavior of water-soluble calixarenes with the different cavity size, $\mathbf{1}_4C_4$, $\mathbf{1}_6C_4$, and $\mathbf{1}_8C_5$ [15]. As guest molecules we selected Phenol Blue (PB) and Anthrol Blue (AB) with different molecular size.





When PB (or AB) is bound to $\mathbf{1}_mC_4$, the distinctive color change from blue to pink is observed. This occurs because of the stabilization of included protonated species (PBH^+, ABH^+) by the sulfonate groups [10, 11]. The total scheme for the complex formation (e.g., with PB) is illustrated as below.

$$\begin{array}{ccc} PB + (\mathbf{1}_mC_4) & \overset{K^0}{\rightleftharpoons} & PB\cdot(\mathbf{1}_mC_4) \\ \Big\Vert\!\uparrow K_a^0 & & \Big\Vert\!\uparrow K_a^+ \\ PBH^+ + (\mathbf{1}_mC_4) & \overset{K^+}{\rightleftharpoons} & PBH^+\cdot(\mathbf{1}_mC_4) \end{array}$$

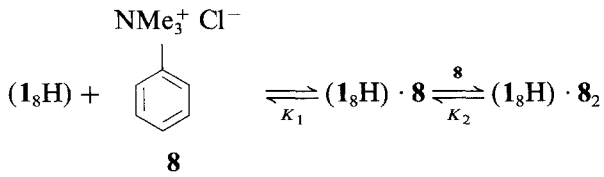
First, we confirm that PB and AB form 1 : 1 complexes with $\mathbf{1}_mC_4$ on the basis of a continuous variation method. Based on the computer-assisted curve-fitting of the photo-titration data, we could determine the pK_a^0, pK_a^+, and K^+ values independently (Table II) [15]. Clearly, the K^+ values change sensitively in response to the cavity size: PB (small guest molecule) shows the selectivity order of $\mathbf{1}_6C_4 > \mathbf{1}_4C_4 > \mathbf{1}_8C_4$ while AB (large guest molecule) shows the selectivity order of $\mathbf{1}_8C_4 > \mathbf{1}_6C_4 > \mathbf{1}_4C_4$. The result suggests that PB can fit the cavity of $\mathbf{1}_4C_4$ and $\mathbf{1}_6C_4$ while AB is too large to be included in the cavity of these calixarenes. The largest difference in K^+ (31-fold) was attained between $\mathbf{1}_6C_4$–PB (largest K^+, $5.57 \times 10^4\ M^{-1}$) and $\mathbf{1}_4C_4$–AB (smallest K^+, $1.82 \times 10^3\ M^{-1}$). Thus, one may predict the guest selectivity of calixarenes (to some extent) on the basis of the 'hole-size selectivity'.

Table II. pK_a shifts and binding constants (K^+) for the calixarene complexes (30°C)

Guest		Calixarene		
		$\mathbf{1}_4C_4$	$\mathbf{1}_6C_4$	$\mathbf{1}_8C_4$
PB[a]	ΔpK_a[c]	1.68	1.75	0.73
	$10^{-3}\cdot K^+(M^{-1})$	47.2	55.7	13.5
AB[b]	ΔpK_a[c]	1.02	0.54	2.84
	$10^{-3}\cdot K^+(M^{-1})$	1.82	9.30	15.0

[a] pK_a^0 (in the absence of $\mathbf{1}_mC_4$) = 4.60.
[b] pK_a^0 (in the absence of $\mathbf{1}_mC_4$) = 4.34.
[c] $\Delta pK_a = pK_a^+ - pK_a^0$.

The binding constants (K) for nonchromophoric guest molecules can be determined by a ^{1}H-NMR method. We estimated the K (25°C, D_2O) for the complexation of $\mathbf{1}_m$H and trimethylanilinium chloride **8**. In $\mathbf{1}_4$H and $\mathbf{1}_6$H, the resonance peaks of **8** shifted monotonously to higher magnetic field with increasing $\mathbf{1}_m$H concentration. The resultant plots of δ vs. $[\mathbf{1}_m\mathrm{H}]/[\mathbf{8}]$ could be analyzed assuming the formation of 1 : 1 complexes: $K = 5610\,\mathrm{M}^{-1}$ for $\mathbf{1}_4$H and $550\,\mathrm{M}^{-1}$ for $\mathbf{1}_6$H. In contrast, the plot for $\mathbf{1}_8$H was biphasic with a break point at $[\mathbf{1}_8\mathrm{H}]/[\mathbf{8}] = 0.5$. The finding supports, we believe, the proposed that $\mathbf{1}_8$H binds two **8** molecules in a stepwise manner.



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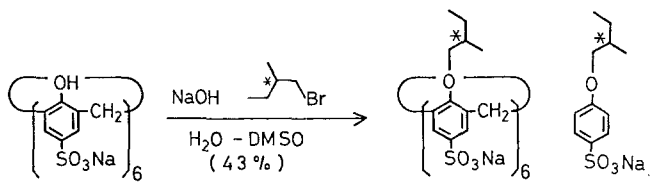
This unexpected result for $\mathbf{1}_8$H is the second example to prove the 'hole-size selectivity' in calixarene complexes.

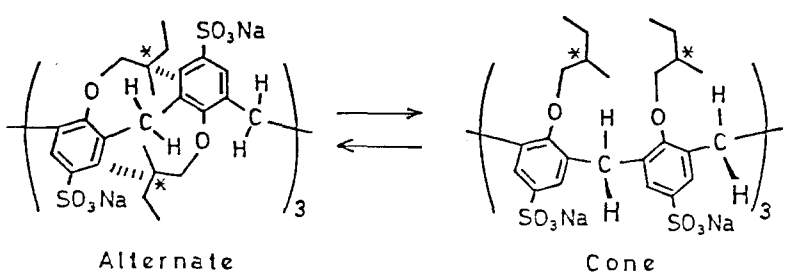
5. Chiral Calixarenes

As described above, calixarenes are capable of including small molecules in solution. It thus occurred to us that introduction of chiral substituents into calixarenes would be of great value for development of a new class of chiral host molecules.



9 **10**

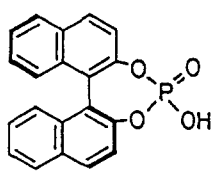
We synthesized chiral calixarene **9** by the reaction of ($\mathbf{1}_6$H) and (*S*)-1-bromo-2-methylbutane [16]. In an aqueous system *p*-(*S*)-2-methylbutyloxybenzenesulfonate **10**, a noncyclic analogue, did not give a perceptible CD spectrum at 220–300 nm. Probably, the asymmetric carbon in **10** is too far from the chromophoric benzene ring to affect it intramolecularly. In contrast, **9** gave a clear CD spectrum in this



wavelength region [λ_{max}236 ([θ] − 14 100) and 269 nm ([θ] 3300)] [16]. These results suggest that the CD band of the benzene chromophore is induced by the (*S*)-2-methylbutyl groups in the neighboring benzene units but not by that in the same benzene unit. This situation is commensurate with the 'alternate' conformation in which (*S*)-2-methylbutyl group and the benzene ring are arranged alternately on the same side of the calixarene cavity.

Interestingly, we found that the CD band of **9** is weakened when the guest molecule is included in the cavity [16]. From the plots of [θ] vs. guest concentration we estimated the binding constants: $K = 1.4 \times 10^2\ M^{-1}$ for hexan-1-ol, $1.2 \times 10^3\ M^{-1}$ for heptan-1-ol, and $7.8 \times 10^3\ M^{-1}$ for octan-1-ol. The result is rationalized in terms of the conformational change from 'alternate' to 'cone' upon inclusion of guest molecules, because the 'cone' conformation can arrange the (*S*)-2-methylbutyl groups and the benzene rings on the different sides of the calixarene cavity. Conceivably, the calixarene with the 'cone' conformation can provide a cavity more suitable to substrate-binding than that with the 'alternate' conformation.

The combination of chromophoric calixarene and chiral guest, which may give the ICD spectrum, is also interesting. As $\mathbf{2}_m$ is soluble in basic aqueous solution and gives a λ_{max} at around 400 nm [7], we measured the CD spectrum of $\mathbf{2}_m$ in the presence of chiral guest molecules (20°C, pH 12.8) [17]. Among them **11** ((*R*)-1,1′-binaphthyl-2,2′-phosphoric acid) afforded a distinct ICD band, and the greatest [θ] values were observed for $\mathbf{2}_6$ ([θ] = −19 000 (392 nm), 2400 (450 nm)) and the next for $\mathbf{2}_8$ ([θ] = −5900 (410 nm)). In contrast, the ICD band was not detected at all for $\mathbf{2}_4$. A continuous variation plot showed that **11** and $\mathbf{2}_6$ form a 1 : 1 complex. One may conclude, therefore, that **11** fits the cavity of $\mathbf{2}_6$ (and probably of $\mathbf{2}_8$) but is too large to be included in the cavity of $\mathbf{2}_4$. On the basis of X-ray studies [2] and CPK molecular models the upper-rim diameters of calix[4]arene and calix[6]arene are estimated to be 3.8 Å and 5.0 Å, respectively. Thus, the molecular recognition pattern of calix[6]arene, found for the first time for **11**, is comparable with that of β-cyclodextrin (diameter 5.5–5.9 Å).



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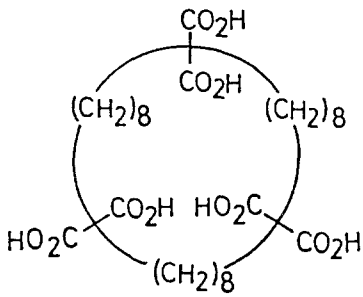
6. Molecular Design of Calixarene-Based Uranophiles

The selective extraction of uranium from sea water has attracted extensive attention from chemists because of its importance in relation to energy problems. In order to design a ligand that can selectively extract uranyl ion (UO_2^{2+}), one has to overcome a difficult problem: i.e., the ligand must strictly discriminate UO_2^{2+} from other metal ions present in great excess in sea water. A possibly unique solution to this difficult

problem is provided by the unusual coordination structure of UO_2^{2+} complexes. X-ray crystallographic studies have established that UO_2^{2+} complexes adopt either a pseudoplanar pentacoordinate or hexacoordinate structure, which is quite different from the coordination structures of other metal ions. This suggests that a macrocyclic host molecule having a nearly coplanar arrangement of either five or six ligand groups would serve as a specific ligand for UO_2^{2+} (i.e., as a uranophile). This approach has been investigated by several groups [18–21]. For example, Tabushi *et al.* [19] synthesized a macrocyclic host molecule **12** having six carboxylate groups in the ring. Although the stability constant for **12** and UO_2^+ is pretty high (log K_{uranyl} = 16.4 at pH 10.4 and 25°C), the selectivity for UO_2^{2+} is not satisfactory (e.g., $K_{uranyl}/K_{M^{n+}}$ = 80–210 for Ni^{2+} and Zn^{2+}) and the synthesis is not easy [19].



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In the course of our studies on calixarenes, we noticed that calix[5]arene and calix[6]arene have an ideal architecture for the design of uranophiles, because the introduction of ligand groups into each benzene unit of these calixarenes provides exactly the required pseudoplanar penta- and hexacoordinate structures [22, 23]. We thus applied $\mathbf{1}_m$H and $\mathbf{1}_m$CH$_2$COOH as uranophiles. We found that, as shown in Tables III and IV $\mathbf{1}_5$H, $\mathbf{1}_5$CH$_2$COOH, $\mathbf{1}_6$H, and $\mathbf{1}_6$CH$_2$COOH not only have high stability constants (log K_{uranyl} = 18.4–19.2) but also an unusually high selectivity for UO_2^{2+} ($K_{uranyl}/K_{M^{n+}} = 10^{12}$–$10^{17}$) [23]. In contrast, the K_{uranyl} for $\mathbf{1}_4$H and $\mathbf{1}_4$CH$_2$COOH were dramatically decreased: they were smaller by about 16 log units than those for the pentamers and the hexamers [23]. The high affinity is rationalized in terms of the 'coordination-geometry selectivity': that is, the pentamers and the

Table III. Stability constants (K_{uranyl}) for calixarene derivatives and UO_2^{2+} (25°C)

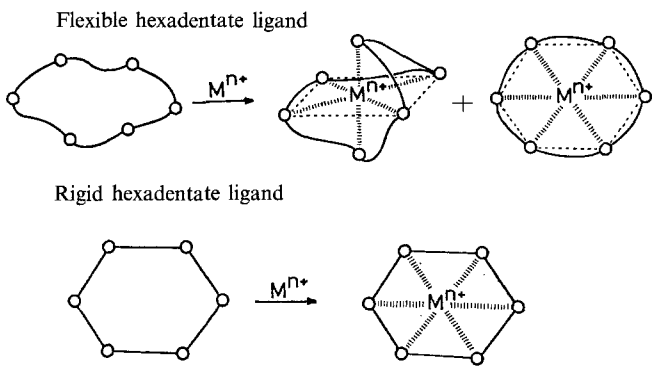
Calixarene	pH	log K_{uranyl}
$\mathbf{1}_4$H	6.5	3.2
$\mathbf{1}_4$CH$_2$COOH	6.5	3.1
$\mathbf{1}_5$H	10.4	18.9
$\mathbf{1}_5$CH$_2$COOH	10.4	18.4
$\mathbf{1}_6$H	10.4	19.2
$\mathbf{1}_6$CH$_2$COOH	10.4	18.7
$\mathbf{1}_6$C$_1$	6.5	3.2
12	10.4	16.4

Table IV. Selectivity factors for UO_2^{2+} ($K_{uranyl}/K_{M^{n+}}$)

Calixarene	Metal (M^{n+})	log $K_{M^{n+}}$	$K_{uranyl}/K_{M^{n+}}$
$\mathbf{1}_6H$	UO_2^{2+}	(19.2)	1.0
$\mathbf{1}_6H$	Mg^{2+}	[a]	$>10^{17}$
$\mathbf{1}_6H$	Ni^{2+}	2.2	$10^{17.0}$
$\mathbf{1}_6H$	Zn^{2+}	5.5	$10^{13.7}$
$\mathbf{1}_6H$	Cu^{2+}	8.6	$10^{10.6}$
$\mathbf{1}_6CH_2COOH$	UO_2^{2+}	(18.7)	1.0
$\mathbf{1}_6CH_2COOH$	Mg^{2+}	[a]	$>10^{17}$
$\mathbf{1}_6CH_2COOH$	Ni^{2+}	3.2	$10^{15.3}$
$\mathbf{1}_6CH_2COOH$	Zn^{2+}	5.6	$10^{13.1}$
$\mathbf{1}_6CH_2COOH$	Cu^{2+}	6.7	$10^{12.0}$

[a] The $K_{M^{n+}}$ is too small to determine by the polarographic method.

hexamers can provide the ligand groups arranged in a suitable way required for pseudoplanar penta- or hexacoordination on the edge of the calixarenes but the tetramers cannot. Similarly, the high selectivity is rationalized in terms of the moderate rigidity of the calixarene skeleton: that is, $\mathbf{1}_6H$ and $\mathbf{1}_6CH_2COOH$ firmly maintain the pseudoplanar hexacoordination geometry and cannot accommodate either to tetrahedral or to octahedral coordination geometry (Scheme 2).



In general, there are two possible strategies for improving the metal selectivity of macrocyclic ligands: the first one is to enhance the stability constant for the target metal cation and the second one is to lower the stability constants for competing metal cations. The present study shows that calixarenes provide an ideal basic skeleton for the second strategy: they are moderately rigid, allowing the high metal selectivity to be realized although their conformational freedom still remains.

7. Conclusions

The foregoing results indicate that calixarenes are very useful as a basic skeleton to design a new class of catalysts, ligands, and host molecules.

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