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REVIEW COMMENTARY

MECHANISMS FOR CHIRAL RECOGNITION BY CYCLODEXTRINS

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The mechanisms for chiral recognition by cyclodextrins (CDxs) are discussed. Examples of host–guest systems where the 'lock-and-key mechanism' and the 'three-point rule' are applicable are cited and discussed. Most results reported so far suggest that the ability of native CDxs and chemically modified CDxs to discriminate between enantiomers of guests having a central chirality is low in aqueous solutions. Small $\Delta\Delta G$ values for enantioselective complexation of CDxs with amino acids seem to be due to unpredictably small changes in the structures of the complexes of the guest enantiomers. Therefore, it is very difficult to prove the participation of hydrogen bonding in chiral recognition through the 'three-point rule' in these systems. The use of the Coulomb interaction and the coordinate bonds as point interactions is discussed. CDxs might be good hosts to recognize axial chirality or helicity of guests. Hydrogen bonding in water is assumed in the recognition of the helicity of bilirubin. Very large $\Delta\Delta G$ values have been reported for the chiral recognition of the binaphthyl derivatives. Such a system seems to be a suitable model system to study the mechanism of chiral recognition by CDxs. © 1997 by John Wiley & Sons, Ltd.

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INTRODUCTION

Native cyclodextrin (CDx) is composed of six, seven or eight optically active glucopyranose units (α-, β- or γ-CDx) and has an ability to include hydrophobic guest molecules in its cavity. Therefore, diastereomeric complexes are formed when a racemic guest is included in a CDx cavity. When the stability of an ($R^\star$)-guest complex is larger than that of an ($S^\star$)-guest complex, it can be said that CDx recognizes the chirality of the guest. The first example of chiral recognition by native β-CDx was reported by Cramer and Dietsche,[1] who studied the partial optical resolution of mandelic acid derivatives. After their work, much effort has been directed toward realizing chiral recognition by CDxs.[2] In this paper, we focus on the mechanisms of chiral recognition by native and chemically modified CDxs.

The 'three-point rule' is the general mechanism for chiral recognition in host-guest chemistry.[3] Figure 1 shows the model of a sweet-taste receptor of the tongue presented by Shallenberger *et al*.[4] In general, D-amino acids can be bound to the receptor at two points through hydrogen bonding whereas L-amino acids cannot because of the steric hindrance due to the protein. Two hydrogen-bonding interactions and one steric hindrance determine the stability of the guest enantiomer–host receptor protein complex. As shown in this example, the three attractive interactions between host and guest are not needed in this rule. Two attractive and one repulsive interaction, for example, can be used for chiral recognition. Therefore, this mechanism is different from the 'three-point binding' proposed by Ogston.[5] Another model for chiral recognition might be the 'lock-and-key mechanism' originally proposed by Emil Fischer.[6] In CDx chemistry, this can be regarded as a classical shape-fitting model including the 'induced-fit

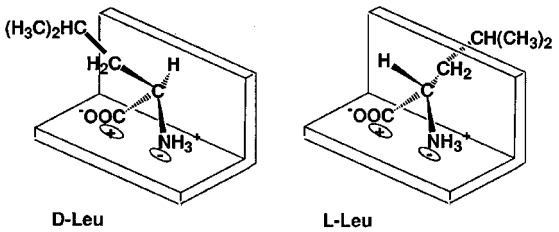

Figure 1.

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mechanism'.[7]

This review focuses on the mechanisms of chiral recognition by CDxs in aqueous solutions which have been reported in recent years. The use of CDxs for analytical purposes has been reviewed elsewhere.[3c,8]

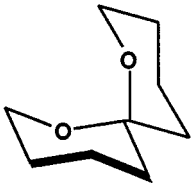
LOCK-AND-KEY MECHANISM

The simplest example of chiral recognition by CDx through the 'lock-and-key mechanism' is the formation of a chiral pyrene dimer in the γ-CDx cavity.[9] The asymmetric nature of the pyrene dimer in the cavity has been established by its strong circularly polarized fluorescence (CPF). A strong left-handed CPF signal at the wavelength region corresponding to the pyrene excimer fluorescence band shows that the pyrene dimer in the γ-CDx cavity preferentially takes an asymmetric conformation having an (*M*)-helicity.[10] Since no hydrogen-bonding site exists in the system, the 'lock-and-key mechanism' seems to be adequate. Similar phenomena have been observed for 4-helicene and 1,1′-binaphthalene.[11] Both 4-helicene and 1,1′-binaphthalene are achiral in solution at room temperature. However, the conformations of these compounds are fixed upon complexation with β- and γ-CDxs. 4-Helicene in the γ-CDx cavity shows a (*P*)-helicity and binaphthalene included in the β-CDx cavity takes an (*R*)-configuration. Although detailed structures of these complexes with the CDx-induced chiralities have not been clarified, it can be concluded that native CDxs act as asymmetric keyholes in host–guest interactions. Recently, the optical resolution of (±)-1,7-dioxaspiro[5.5]undecane by hexakis(2,3,6-tri-*O*-methyl)-α-CDx (TMe-α-CDx) was reported.[12] The optically pure (*R*)-enantiomer of the guest precipitates in water as a complex with TMe-α-CDx. Fundamentally, in optical resolution by a diastereomeric method, it is not necessary for the binding constant (*K*) of the (*R*)-enantiomer complex to be much larger than that of the (*S*)-enantiomer complex. The structure of the (*R*)-enantiomer complex should differ from that of the (*S*)-enantiomer complex. Indeed, the (*R*)-enantiomer complex is very stable and no racemization occurs whereas the (*S*)-enantiomer complex racemizes in water over several days to enrich the (*R*)-enantiomer complex. Since TMe-α-CDx can act only as a hydrogen acceptor, no hydrogen bonding interaction occurs in this system. Induced fit-type shape fitting might be the mechanism for this chiral recognition. Induced fit-type enantiomer recognition is also suggested for the α-pinene–TMe-α-CDx system by chemical calculation using the CVFF method.[13]

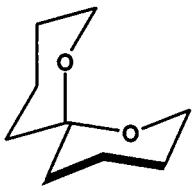
POINT INTERACTIONS THROUGH HYDROGEN BONDING

Intermolecular hydrogen bonds are hardly formed in aqueous systems because of strong hydration to hydrogen bonding sites of both host and guest molecules. Biological systems, however, clearly suggest that hydrogen bonds can be formed in a microscopically hydrophobic environment in water. Such an effect might be called 'hydrophobic effect on hydrogen bond formation.' Another way to form a hydrogen bond in water is suggested by the pK_a values of salicyclic acid. The very low pK_1 (2·81) and high pK_2 values (13·4) of salicylic acid are ascribed to the intramolecular hydrogen bonding interaction between the CO_2^- group and the OH group at the *ortho*-position. Such an effect can be regarded as the 'proximity effect on hydrogen bond formation.' Therefore, a hydrogen bond is expected to be formed in water when the hydrogen bonding sites are located in a microscopically hydrophobic environment and/or are situated very close to each other.

Although several examples have been reported of inclusion complexes of CDxs where hydrogen bonding participates in complexation,[14] no direct evidence for the formation of a hydrogen bond in water has been obtained. We do not have a good method which proves hydrogen bond formation in water. The conformational enantiomerism of (4*Z*,15*Z*)-bilirubin IXα (BR) induced by native α-, β- and γ-CDxs[15] might be one of the novel examples where hydrogen bonding participates in chiral recognition.[16] Lightner *et al*.[15] found that BR bound to a native CDx shows the (−) to (+) bisignate Cotton effect in its circular dichroism (CD) spectrum. The exciton-coupling theory for CD spectroscopy[17] suggests that the conformation of BR is fixed selectively to take an (*M*)-helicity.[15] When heptakis(2,3,6-tri-*O*-methyl)-β-CDx (TMe-β-CDx), which can act only as an acceptor in the hydrogen bonding interaction, is used in place of native CDxs, the conformational enantiomerism does not occur at all.[18] In addition, noncyclic oligosaccharides such as maltose (G2), maltotriose (G3) and maltoheptaose (G7)[18] as well as nucleosides,[19] bile acids[20] and glycolipid micelles[21] also fix the conformation of BR, yielding optically active BR, indicating that inclusion of the BR molecule in the CDx cavity is not essential in this conformational enantiomerism. Indeed, the addition of



(*R*)-1,7-dioxaspiro[5.5]undecane



(*S*)-1,7-dioxaspiro[5.5]undecane

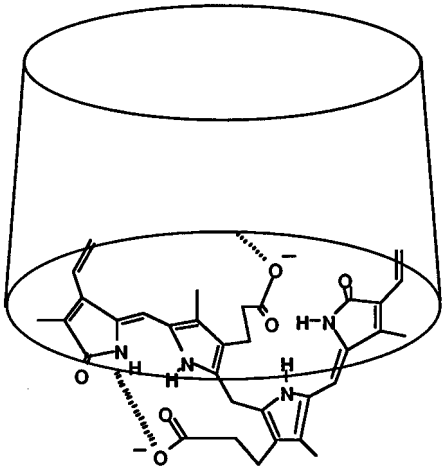


Figure 2.

cyclooctanol, which is a good guest for β-CDx, enchances the CD intensities of BR bound to β-CDx.[16] Such a second guest seems to enhance the dehydration from the secondary OH group side of β-CDx to promote the formation of hydrogen bonds between the secondary OH groups of β-CDx and the CO_2^- groups of BR. The lack of interaction between BR and β-CDx in water at pH 12 also supports the existence of a hydrogen-bonding interaction between the OH groups of β-CDx and the CO_2^- groups of BR. At pH 12, the secondary OH groups are partially dissociated,[22] leading to electrostatic repulsion between the host and the guest.[16] Although no direct evidence has been obtained, all the experimental results strongly support the hydrogen-bonded complex of BR and native CDx (Figure 2). Such a complexation might be explained by the hydrophobic effect on hydrogen bond formation. Similar lid-type CDx complexes have been assumed without direct evidence.[23] It is plausible that we would be able to find many hydrogen-bonded complexes of CDxs formed in water if hydrogen bond formation could easily be detected in water.

The thermodynamic parameters determined for complexation of azo dyes having a CO_2^- group with native CDxs suggest that inclusion of such anionic dyes in the CDx cavity occurs much more favorably in water than in organic solvents while the interaction between the anionic species and the OH-group sides of native CDx which are located near the chiral centers preferentially occurs in organic solvents such as DMF.[24] It is well known that CDx derivatives are good chiral selectors for HPLC and GLC.[3c,8] Chiral recognition by CDxs in organic solvents might be a useful future research subject.

Computer chemistry is very useful for discussing the mechanisms of chiral recognition. NMR spectroscopy indicates that zwitterionic D-Trp is bound to α-CDx more tightly than L-Trp.[25] Molecular modeling using CHARMM force field suggests that D-Trp forms a larger number of multiple contact hydrogen bonds with α-CDx than the L-enantiomer does. Although the results of the computer calculations provide one possibility, we have to prove the mechanism experimentally.

POINT INTERACTIONS THROUGH COULOMB FORCES

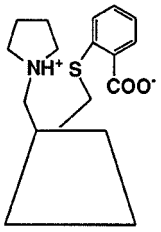
Most hydrogen-bond lengths have been reported to be less than 0·2 nm.[26] The angles around H are in the range 90–180°, with 165° most populated. The interaction between point charges (Coulomb force of attraction) is proportional to R^{-1}, where R is the distance between the point charges. Such a long-distance interaction might be effective even if both host and guest molecules are hydrated. Therefore, Coulomb interaction is a good point interaction for molecular recognition in water in host–guest chemistry.[27] Pioneering work on chiral recognition using Coulomb interaction has been carried out by Tabushi *et al*.[28] They used 6^A-amino-6^B-carboxy-6^A, 6^B-dideoxy-β-CDx (AmCar-β-CDx) and 6^B-amino-6^A-carboxy-6^A,6^B-dideoxy-β-CDx (CarAm-β-CDx) as zwitterionic hosts and studied the chiral recognition of tryptophan (Trp) (in this review, zwitterionic hydrogen bonds such as $NH_3^+ \ldots O^-$ are classified as Coulomb interaction). The results are shown in Table 1. The K values are small and the ability of these hosts to discriminate between the enantiomers of Trp is poor. Similar binding constants and a small $\Delta\Delta G$ value (0.65 kJ mol^{-1}) have been obtained in the enantioselective complexation of phenylalanine (Phe) with α-CDx where no Coulomb interaction participates[29] (in this review, $\Delta\Delta G$ is defined as the absolute value of the difference between the ΔG values for complexation of the enantiomers).

Brown *et al*.[30] studied the chiral recognition of 2-phenylpropanoic acid by 6^A-amino-6^A-deoxy-β-CDx (6-NH_2-β-CDx). Some of their results is shown in Table 2. Protonated 6-NH_2-β-CDx (6-NH_3^+-β-CDx) has a low ability to include a neutral guest. Although the K value for the complex of 2-phenylpropanoate anion and 6-NH_3^+-β-CDx is larger than those for the systems where no Coulomb interaction exists, the $NH_3^+ \ldots O^-$ interaction is not so remarkable in the stabilization of the complex. In all cases, the $\Delta\Delta G$ values seem to be too small to discuss the mechanism of chiral recognition. The small $\Delta\Delta G$ can be

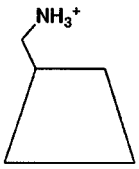
Table 1. Binding constants (K) for tryptophane with cyclodextrin derivatives[a]

Guest	Host	K/M^{-1}	$\Delta\Delta G$/kJ mol^{-1}
D-Trp	AmCar-β-CDx	45·5	0·69
L-Trp	AmCar-β-CDx	34·5	
D-Trp	CarAm-β-CDx	54·0	0·59
L-Trp	CarAm-β-CDx	42·5	

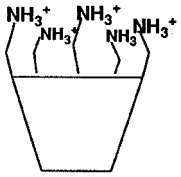
[a] I. Tabushi, Y. Kuroda and T. Mizutani, *J. Am. Chem. Soc.* **108**, 4514–4518 (1986).



AmCar-β-CDx
CarAm-β-CDx



6-NH_3^+-β-CDx



polyNH_3^+-β-CDx

explained by the sum of the unpredictably small difference in intermolecular interactions such as van der Waals, hydrophobic and/or electrostatic interactions between (*R*)- and (*S*)-enantiomers. Therefore, it is very difficult to deduce the mechanism for chiral recognition when $\Delta\Delta G$ is very small. The 2-phenylpropanoate anion–6-NH_2-*β*-CDx system shows a fairly large $\Delta\Delta G$ value. In this case, however, the *K* values are too small to study the mechanism.

Kitae and Kano[31] determined the *K* values for complexation of 6-NH_3^+-*β*-CDx and heptakis(6-amino-6-deoxy)-*β*-CDx (polyNH_3^+-*β*-CDx) with anionic *N*-acetylated Trp, Phe and leucine (Leu) in D_2O. The results are summarized in Table 3. In all cases, the *K* values of the polyNH_3^+-*β*-CDx complexes are much larger than those of the 6-NH_3^+-*β*-CDx complexes. Protonated amino-*β*-CDxs binds preferentially with the L-enantiomers. The small $\Delta\Delta G$ values (0·2–1·1 kJ mol^{-1}) in enantioselective complexation might be explained by the small difference in the structures of the complexes of the acetylated L- and D-amino acids. ^{1}H NMR spectroscopy suggests that one Coulomb interaction between host and guest, one inclusion of a hydrophobic part of guest and probably one hydrogen bonding or van der Waals repulsion determine the stability of the complex.

The conformational enantiomerism of BR is very effectively induced by polyNH_3^+-*β*-CDx.[32] BR bound to polyNH_3^+-*β*-CDx shows a (+) to (−) bisignate CD Cotton effect, indicating that the conformation of BR is selectively fixed to take a (*P*)-helicity. In this case, the interaction between the CO_2^- groups of BR and the NH_3^+ groups of CDx at two points and one inclusion of a part of the BR molecule in the CDx cavity are required to promote the conformational enantiomerism.

Table 2. Binding constants (*K*) for 2-phenylpropanoic acid (PPA) with cyclodextrins at 298·2 K[a]

Guest	Host	K/M^{-1}	$\Delta\Delta G$/kJ mol^{-1}
(*R*)-PPA	*β*-CDx	1090	0·1
(*S*)-PPA	*β*-CDx	1010	
(*R*)-PPA	6-NH_3^+-*β*-CDx	580	0·5
(*S*)-PPA	6-NH_3^+-*β*-CDx	480	
(*R*)-PPA$^-$	*β*-CDx	63	0·5
(*S*)-PPA$^-$	*β*-CDx	52	
(*R*)-PPA$^-$	6-NH_3^+-*β*-CDx	150	0·7
(*S*)-PPA$^-$	6-NH_3^+-*β*-CDx	110	
(*R*)-PPA$^-$	6-NH_2-*β*-CDx	36	2·52
(*S*)-PPA$^-$	6/NH_2-*β*-CDx	13	

[a] S. E. Brown, J. H. Coates, P. A. Duckworth, S. F. Lincoln, C. J. Easton and B. L. May, *J. Chem. Soc. Faraday Trans.* **89**, 1035–1040 (1993).

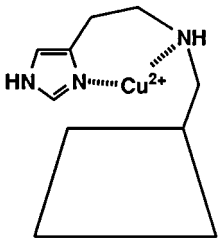
Table 3. Binding constants (*K*) for complexation of *N*-acetylated amino acids with protonated aminocyclodextrins at 25 °C and pD 6·0

Guest	Host	K/M^{-1}	$\Delta\Delta G$/kJ mol^{-1}
Ac-L-Trp	6-NH_3^+-*β*-CDx	99 ± 4	1·1
Ac-D-Trp	6-NH_3^+-*β*-CDx	64 ± 6	
Ac-L-Phe	6-NH_3^+-*β*-CDx	167 ± 8	0·2
Ac-D-Phe	6-NH_3^+-*β*-CDx	155 ± 7	
Ac-L-Leu	6-NH_3^+-*β*-CDx	68 ± 4	0·8
Ac-D-Leu	6-NH_3^+-*β*-CDx	50 ± 3	
Ac-L-Trp	polyNH_3^+-*β*-CDx	2670 ± 100	0·8
Ac-D-Trp	polyNH_3^+-*β*-CDx	1930 ± 90	
Ac-L-Phe	polyNH_3^+-*β*-CDx	2180 ± 130	0·3
Ac-D-Phe	polyNH_3^+-*β*-CDx	2000 ± 130	
Ac-L-Leu	polyNH_3^+-*β*-CDx	2480 ± 130	0·1
Ac-D-Leu	polyNH_3^+-*β*-CDx	2380 ± 110	

[a] T. Kitae and K. Kano, *Abstracts of 11th Symposium on Biofunctional Chemistry*, (1996).

POINT INTERACTIONS THROUGH COORDINATIVE BONDS

Native amino acids are very strongly bound to a copper(II) complex of histamine monofunctionalized *β*-CDx (Cu–His-*β*-CDx).[33] Some of the results are listed in Table 4. The *K* values are extremely large and a considerably large $\Delta\Delta G$ value is found in the case of Trp–Cu–His-*β*-CDx. The coordination geometry in the D-Trp complex seems to allow the inclusion of the indole moiety in the CDx cavity while the indole moiety of L-Trp complex is located outside the cavity. Essentially the same results were obtained by using 6^A-(3-aminopropylamino)-6^A-deoxy-*β*-CDx.[34] Such a chiral recognition may also be classified according to the 'three-point rule.'



Cu-His-β-CDx

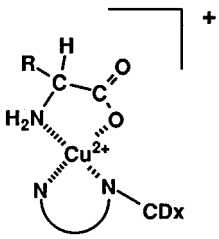


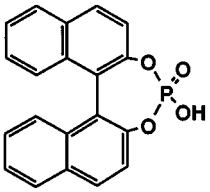
Table 4. Binding constants (K) for amino acids with cyclodextrin derivative[a]

Guest	Host	K/M^{-1}	$\Delta\Delta G$/kJ mol^{-1}
D-Ala	Cu-His-β-CDx	$3{\cdot}39\times10^{15}$	0·12
L-Ala	Cu-His-β-CDx	$3{\cdot}24\times10^{15}$	
D-Phe	Cu-His-β-CDx	$7{\cdot}08\times10^{15}$	0·97
L-Phe	Cu-His-β-CDx	$4{\cdot}79\times10^{15}$	
D-Trp	Cu-His-β-CDx	$2{\cdot}95\times10^{16}$	2·00
L-Trp	Cu-His-β-CDx	$1{\cdot}32\times10^{16}$	

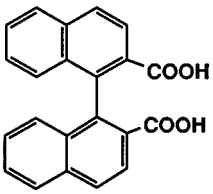
[a] R. Corradini, A. Dossena, G. Impellizzeri, G. Maccarrone, R. Marchelli, E. Rizzarelli, G. Sartor and G. Vecchio, *J. Am. Chem. Soc*. **116**, 10267–10274 (1994).

EFFECTS OF DIPOLE–DIPOLE INTERACTION ON CHIRAL RECOGNITION

The importance of the dipole–dipole interaction in inclusion phenomena has been demonstrated.[35] It has been reported that TMe-β-CDx discriminates well between the enantiomers of binaphthyl derivatives.[35–38] The K values determined for BNP at pH 5·5 and BNC at pH 2·0 are listed in Table 5. It can be seen that TMe-β-CDx preferentially binds to (*S*)-BNP in its anionic form and (*R*)-BNC in its neutral form. The $\Delta\Delta G$ values for the enantioselective complexation are large in both cases. These $\Delta\Delta G$ values are the largest among the values reported for chiral recognition by CDxs. Analysis of the NMR data and MM–MD calculations suggests the structures for the (*S*)- and (*R*)-BNP complexes of TMe-β-CDx.[38] Interestingly, the hydrophilic group of (*S*)-BNP is located inside the hydrophobic cavity of CDx (axial complex) whereas for (*R*)-BNP part of the naphthalene moiety is incorporated in the CDx cavity and the hydrophilic group of the guest is situated outside the CDx cavity (equatorial complex). The structure proposed for the (*S*)-BNP complex seems to be abnormal. However, a recent study demonstrated that the insides of the cavities of native and *O*-methylated CDxs are composed of positively polarized carbon and hydrogen atoms and, therefore, are preferable for penetration of anionic guests.[39]



BNP



BNC

Table 5. Binding constants (K) for BNP and BNC with cyclodextrins at 25 °C[a]

Guest	Host	K/M^{-1}	$\Delta\Delta G$/kJ mol^{-1}
(*S*)-BNP	β-CDx	346	0·67
(*R*)-BNP	β-CDx	263	
(*S*)-BNP	DMe-β-CDx	210	0·04
(*R*)-BNP	DMe-β-CDx	207	
(*S*)-BNP	TMe-β-CDx	398	3·94
(*R*)-BNP	TMe-β-CDx	81	
(*S*)-BNC	β-CDx	ca. 0	—
(*R*)-BNC	β-CDx	28	
(*S*)-BNC	DMe-β-CDx	583	0·36
(*R*)-BNC	DMe-β-CDx	675	
(*S*)-BNC	TMe-β-CDx	114	4·47
(*R*)-BNC	TMe-β-CDx	691	

[a] K. Kano Y. Kato, and M. Kodera, *J. Chem. Soc., Perkin Trans. 2* 1211–1217 (1996).

Presumably, the geometric conditions of the wider side of the TMe-β-CDx cavity allow the penetration of the (*S*)-BNP molecule whose head is the hydrophilic phosphate group whereas the penetration of the (*R*)-BNP molecule from the head is sterically prohibited, leading to the formation of the complexes of (*S*)- and (*R*)-BNPs having significantly different structures. This complex formation follows essentially the lock-and-key mechanism. However, in order to discriminate between the enantiomers, dipole interaction between the host and the guest is required. Since the mechanism proposed here has not been verified completely, chiral recognition through the 'lock-and-key mechanism' assisted by dipole interactions should be studied in more detail.

CONCLUSION

All results reported so far suggest that native CDxs and chemically modified CDxs are poor hosts for the chiral recognition of guests with a central chirality. In contrast, CDxs seem to be good hosts for the recognition of axial chirality or helicity. In addition to the chiral recognition of the binaphthyl derivatives and the conformational enantiomerism of BR, we are studying the recognition of helicity by native and chemically modified CDxs. Preliminary results indicate that CDxs recognize well the helicity of some guest molecules,[40] providing novel characteristics of cyclic oligosaccharides.

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