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Theoretical Investigations and Mechanisms of the Inclusion Processes of Bi(3-sulfonatophenyl) (4-tert-butylphenyl) Phosphine in the β-cyclodextrin

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Abstract

Quantum mechanical calculations on the bi(3-sulfonatophenyl) (4-tert-butylphenyl) phosphine/β-cyclodextrin inclusion complex (TPP/CD) are carried out using semiempirical quantum calculations. Inclusion process pathways described in the present work lead straight to the most probable structures of the 1:1 association. These investigations suggest that the most stable structure obtained is that where the aromatic ring bearing the tert-butyl (tBu) group is included into the hydrophobic cavity of the β-cyclodextrin from the side of the primary hydroxyl groups. Theoretical investigations of the Hartree-Fock level of the inter-proton proximity between the host and guest molecules in the inclusion complex and their corresponding electronic properties suggest a deep insertion of the tBu group into the cavity. The host-guest interaction energy of the complex at different levels of the insertion pathway is reported with the corresponding basis set superposition error (base). The host–guest association is thermodynamically stable when compared to the separated states and the calculated binding energy is 40.6 kcal mol^{-1}.

Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides in which D-glucopyranose units combine with each other through α-(l, 4) glycosidic oxygen bridges in a chair-like conformation. The most abundant forms are (α-CD), (β-CD), and (γ-CD). Cyclodextrins have a torus geometry and are very often described as having a shallow truncated cone [1] with a narrower and a wider end. Their structure has a hydrophobic central cavity coated with C-3–H and C-5–H hydrogen atoms (Figure 1) and a hydrophilic rim lined with primary O-6–H hydroxyl groups (the primary face) at the narrow side and secondary O-2–H, O-3–H hydroxyl groups (the secondary face) at the wide side [2]. They have the ability to selectively incorporate various inorganic or organic compounds, which lead to widespread applications in pharmaceutical chemistry, food technology, analytical chemistry, chemical synthesis, and catalysis [3–6]. We have recently reported that the β-CD forms in aqueous solution a 1:1 inclusion complex with the sodium salt of the trisulfonated triphenyl phosphine ($P(m\text{-}C_6H_4SO_3Na)_3$,TPPTS) [6], as it does with the sodium salt of the monosulfonated triphenyl phosphine ($P(m\text{-}C_6H_4SO_3Na)(C_6H_5)_2$,TPPmS) [6, 7]. These two molecules are well known to be standard water-soluble ligands in aqueous phase organometallic catalysis.

Intensive experimental [8–10] and theoretical [11–25] investigations have been performed over the past few years on cyclodextrin inclusion complexes and their stability. Different approaches with computer calculations, mainly Molecular Mechanics [11, 13, 14, 17] and Molecular Dynamics [16, 23], with various force fields, were applied. For instance, stochastic Molecular Dynamics and Molecular Mechanics calculations [23, 24] were used with empirical MM2 and AMBER force fields implemented in MACROMODEL [25]. Early quantum calculations were performed with semi-empirical CNDO methods [26, 27] followed by several semi-empirical quantum calculations [12, 20, 28, 29] with the use of the AM1 Hamiltonian (Austin Model 1) [30]. Over the past few years, all attempts made to investigate such processes have focused mainly on CD complexation. At a higher level of theory, SCF/Hartree-Fock methods or the Density Functional theory [19, 21] were carried out with a minimal basis set on single points for structures obtained at a lower level of theory. In a recent work [7] we described a methodology to approach a complete potential surface scan of the inclusion process and to seek the complexation of (4-tert-butylphenyl)(3-sulfonatophenyl) (phenyl) phosphine (TPPmSptBu) in β-CD. In recent studies we also found that such soluble ligands are used to dissolve the catalyst in the aqueous phase [31],

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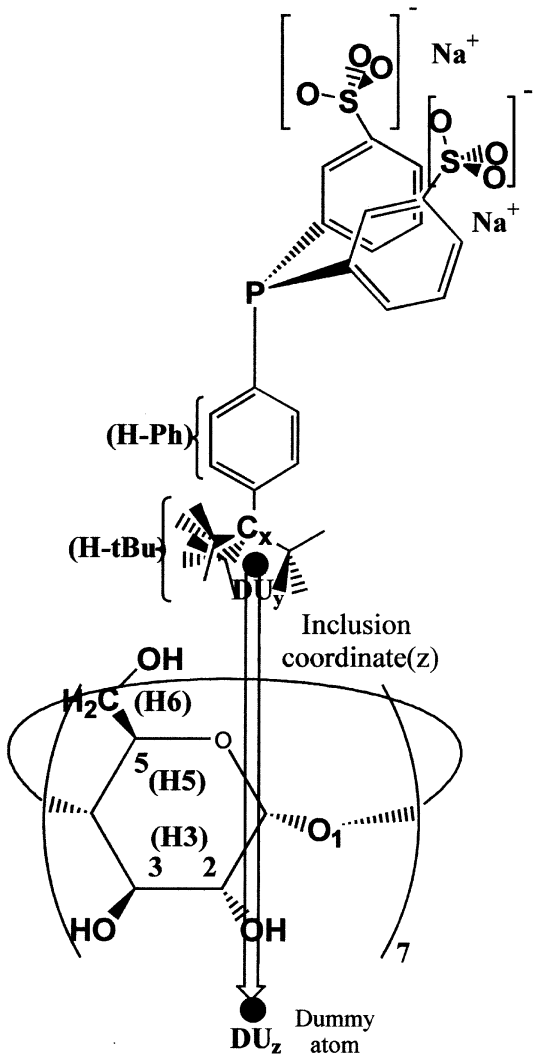

Figure 1. Starting configuration of the inclusion process, z is the approaching distance between the two dummy atoms (DU_y, DU_z).

and therefore, complexes formed between the β-CD or modified β-CD and phosphines, are intensively studied. One of the most important application of these Phosphines is to employ them in the hydroformylation of olefins [32], which is an important process for the production of aldehydes and alcohols [33, 34]. Although the rhodium-based process widely dominates in the hydroformylation of C_2–C_4 olefins, the hydroformylation of higher olefins is exclusively carried out with cobalt catalysts. Actually, separation of products from rhodium solution by distilling the aldehydes becomes troublesome with increasing molecular weight of olefin. Among the different approaches that have been described to solve this crucial problem, the two-phase catalysis where the catalyst is dissolved in a phase which contains neither the substrate nor the products is of great interest [35, 36], in that the aqueous-organic two-phase system is one of the most attractive systems in that it is very economical. In the case of the hydroformylation, several studies show that the sodium salt of the TPPTS [32] increases the catalytic activity [37] and that by the use of this salt as ligand in the aqueous phase [38], there is a possibility of trapping the catalyst and enhancing the reaction [10].

In the present work we shall address the insertion process of the bi (3-sulfonatophenyl) (4-tert-butylphenyl) phosphine ($P(m\text{-}C_6H_4SO_3Na)_2(p\text{-}tBu\text{-}C_6H_5)$, TPPbiSptBu) in β-CD (Figure 1) and compare the results with those obtained for the TPPmSptBu [7]. In our theoretical study, the inclusion of the TPPbiSptBu is first considered as an isolated molecular system in different conformations. In a second step, we investigate the inclusion pathway in order to describe the host–guest potential energy profile and the corresponding structures of the complexes obtained at different penetration levels. To achieve such investigations, the insertion pathway is described as a function of the distance between two dummy atoms Du_y–Du_z, as sketched in Figure 1. We shall focus on the electronic properties of the complex and its components (i.e. the host and the guest molecule taken separately). These investigations are carried out both with semi-empirical quantum calculations with the AM1 Hamiltonian [30] and ab-inito quantum calculation methods at the Hartree-Fock level part of the Gaussian 98, Revision A [30]. The first method is a prerequisite to any full optimizations of points, which will be performed at a higher level of theory. The host–guest inclusion process is investigated starting from optimized structures. In order to examine in detail the insertion pathways and seek for possible global minima, we proceeded as described earlier [7]. Electronic properties of the inclusion complex and its components taken separately are worked out using both semi empirical and ab-inito calculations at the Hartree-Fock level with a 3-21G basis set.

Results of the inclusion process of the TPPbiSptBu in the β-CD.

The penetration of the bi(3-sulfonatophenyl) (4-tert-butylphenyl) phosphine ($P(m\text{-}C_6H_4SO_3Na)_2(p\text{-}tBu\text{-}C_6H_5)$) named (TPPbiSptBu) in the β-CD is investigated first. Since the inclusion process may take place on either side of the β-CD, a potential energy scan of the inclusion process is carried out through both sides of the guest molecule. Several mechanisms and orientation of the guest molecule may occur theoretically; either the SO_3^- or the tBu group may be oriented towards the hydrophobic cavity of the β-CD. The hydrophilic character of the SO_3 group is not favorable for its penetration on either side of the β-CD. Therefore, for the remaining group (i.e. the tBu), the inclusion may occur either from the primary hydroxyl group or from the secondary hydroxyl groups.

According to the methodology described earlier [7], we undertake the inclusion process of the guest molecule presenting the tBu group through either the primary or the secondary face. The potential energy profile of the inclusion process is reported in Figure 2. The well depth in the potential energy profile for a free inclusion gives

evidence, as reported in Figure 2 (Curve 'a'), of an inclusion process of the tBu group occurring preferentially from the primary face and leading to a 1:1 inclusion complex. Theoretical results do not eliminate any possible penetration of the tBu group from the secondary face as reported in Figure 2 (Curve 'b').

The potential energy profile gives evidence of the differences of energies involved between the two processes. Such results suggest that the penetration from the secondary face probably needs more energy to overcome the energy barrier. Through the first profile in the most favorable penetration path way (i.e. curve "a"), one can predict two insertion levels called points P_{1a} and P_{2a} in Figure 2. Such results suggest that the inclusion process of TPPbiSptBu in the β-CD occur through the primary face with the insertion of the tBu group into the hydrophobic cavity of the β-CD. A calculation performed with the PM3 Hamiltonian leads to a similar penetration pathway (inset in Figure 2). The differences arise from the method used, since the PM3 method is much more sensitive to the hydrogen bond network of the β-CD.

Two minima P_{1a} and P_{2a} are observed in the insertion through the primary face, Figure 2 (Curve "a"). The following results are obtained from a full optimization of these points (i.e. P_{0a}, P_{1a} and P_{2a}) performed with the AM1 Hamiltonian, and at the Hartree-Fock level with a 3-21G basis set. The optimized structures obtained at the Hartree-Fock level of calculation and corresponding to the lowest energy P_{2a} is pictured in Figure 3. An analysis of the structures of the obtained complexes is carried out. First, we have worked out the mean distance between hydrogen atoms of the tBu group (H-tBu) with surrounding hydrogen atom neighbors of type H3, H5 and H6 (see Figure 1) in the β-CD. These results, reported in Table 1, clearly show that the tBu group penetrates deep inside the host molecule and is close to hydrogen atoms of type H5 and H3. Similar calculations of the mean distance of hydrogens of the phenyl group (H–Ph) of the TPPbiSptBu to hydrogen atoms of type H6 of the β-CD indicate that primary 6-CH_2OH groups surround the phenyl group. These results are consistent with NMR data published elsewhere [5–7, 10, 38]. The insertion level is deeper when compared to the inclusion complex of the TPPmSptBu in β-CD, as reported in our previous calculations [7]. This result suggests a possible substituant and electronic effect upon the host–guest inclusion processes.

When comparing hydrogen atoms of the tBu group with their neighbors in the β-CD (i.e. H3, H5 and H6) in this case with the previous complex [7] at the minimum in the of the potential energy profile, several comments can be made. The penetration level at points P_{1a} and P_{2a} is different to the inclusion complex obtained with the mono sulfonated phosphine [27] (Table 1). This remark stands also for hydrogen atoms of the phenyl with respect to hydrogen atoms of type H3, H5 and H6. Consequently, this suggests that the orientation of the two types of phosphines in the cavity is completely different. The evidence of the substituant effect upon the inclusion process appears at this point to be crucial, since in the present case the bi sulfonated phosphine undergoes a further penetration when compared to the mono sulfonated phosphine. The supramolecular system at point P_{1a} should be favorable for an insertion process of a second phosphine from the other side (i.e. the

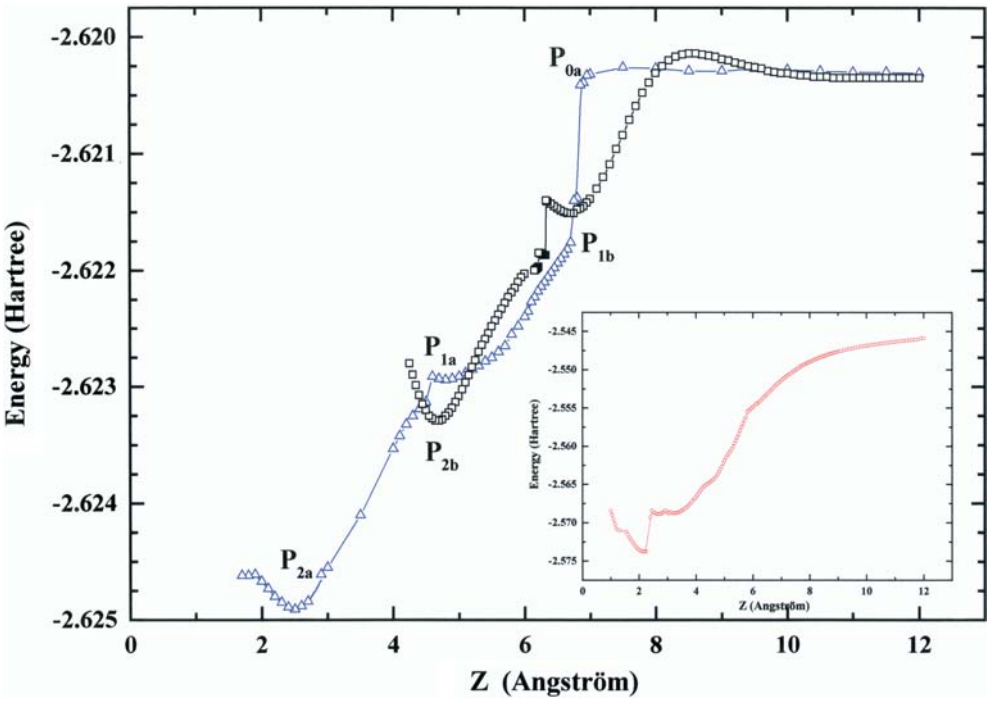

Figure 2. Potential energy profile of the inclusion process of the tBu group of the TPPbiSptBu through the primary face (open triangles 'curve (a)') and the insertion through the secondary face (open squares 'curve (b)'). The inset in figure reports the potential energy profile of the insertion process worked out with the PM3 Hamiltonian.

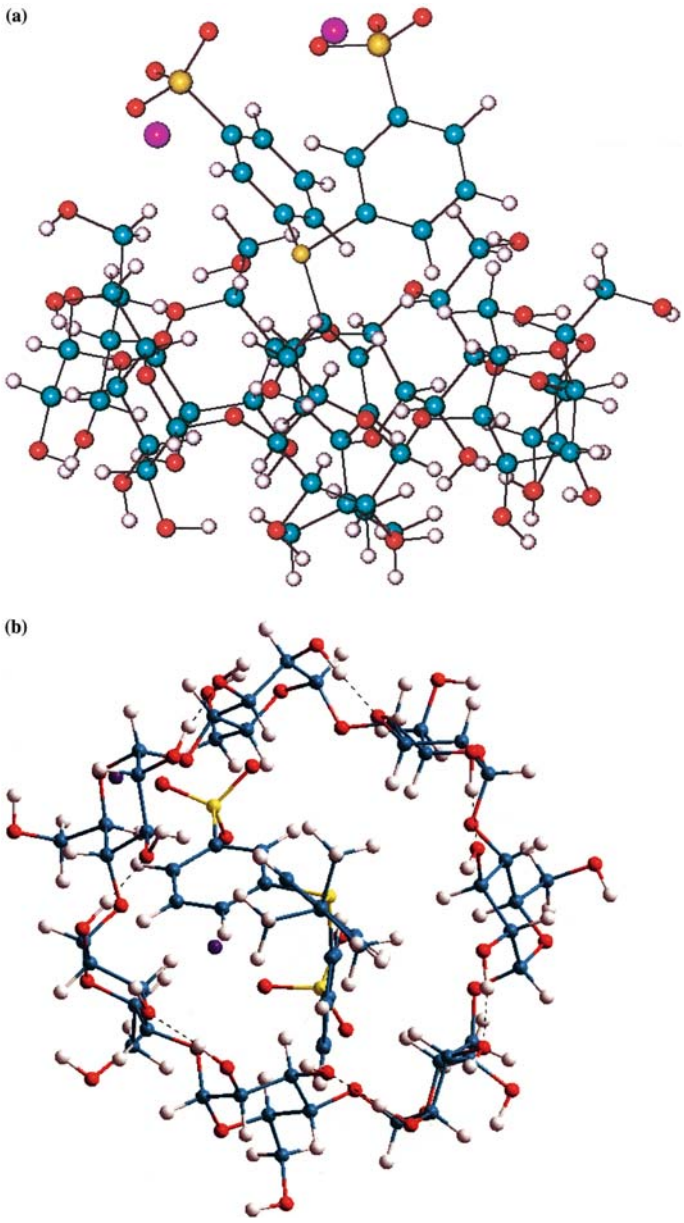

Figure 3. Snapshots of the complex at the second minimum P_{2a} of Figure 2, all structures are obtained from a full optimization at the HF level with a 3-21G basis set.

secondary face), leading to a 1:2 stochiometry association, and may therefore be seen as a non-concerted insertion mechanism. Indeed, for the formation of the 1:2 complex, from recent calculations that we will publish soon, all attempts made when including both guests at the same time in a concerted way in the β-CD have failed. The 1:2 association can only be formed when the 1:1 association has been saturated, this result first being observed from experimental and theoretical studies by Lino *et al.* [39–41].

All calculated data of interest are reported in Table 2. The interaction energy within the supramolecular approach for the highest level of theory is calculated from the expression:

$$\Delta E = E_{AB} - (E_A + E_B) \qquad (1)$$

where E_{AB} is the energy of the complex, and E_A and E_B are energies of monomers A and B. The deformation energy of a component X of the complex DE_X^{PTi} at point i, is calculated from the expression,

$$DE_X^{PTi} = E_X^{PT0} - E_X^{PTi} \qquad (2)$$

which corresponds to the energy difference between a given points and the starting point (i.e. P_{0a}). The full counterpoise method of Boys and Bernardi [42] was used to avoid the appearance of the basis set superposition error. The reported data describe the binding energy of the host–guest supramolecular system as a function of the penetration depth. The host–guest association is thermodynamically stable when compared to the separate state and the binding energy is about 40.6 kcal $mole^{-1}$. The calculated deformation energy for each component

Table 1. Calculated mean distance between hydrogens (H -tBu) and (H-Phi) of the tBu and the phenyl group respectively in the TPPbiSptBu and hydrogens of type H3, H5 and H6 (see figure 1b) in the β-CD

	Host Hydrogen type		
	H3	H5	H6
Guest (H-tBu)HF/3-21G	[a]5.92 Å	[a]4.31 Å	[a]5.21 Å
	[1a]7.00 Å	[1a]6.33 Å	[1a]7.15 Å
	[2a]4.26 Å	[2a]5.02 Å	[2a]7.05 Å
Guest (H-Phi)HF/3-21G	[a]14.175 Å	[a]11.815 Å	[a]10.881 Å
	[1a]4.71 Å	[1a]4.90 Å	[1a]6.85 Å
	[2a]6.24 Å	[2a]4.85 Å	[2a]5.67 Å

Table 2. Calculated properties of the inclusion complex and its components at different state points of the association process (P_{0a}, P_{1a}, P_{2a})

	AM1 hamiltonian	HF/3-21G
Starting Point P_{0a}		
Energy of the complex (Hartree)	−2.807484	−6967.038114
Energy of isolated β-CD (Hartree)	−2.652958	−4227.694236
Energy of isolated TPPbiSptBu (Hartree)	−0.154588	−2739.343930
Interaction energy (kcal/mole)	0.04	0.03
1st minimum P_{1a}		
Energy of the complex (Hartree)	−2.808837	−6966.685584
Energy of isolated β-CD (Hartree)	−2.651225	−4227.751259
Energy of isolated TPPbiSptBu (Hartree)	−0.154384	−2738.925300
Interaction energy (without BSSE) (kcal/mole)	−2.02	−6.46
Interaction energy (CP-corrected) (kcal/mole)	–	−11.31
Deformation energy of the β-CD (kcal/mode)	1.09	35.75
Deformation energy of the TPPbiSptBu (kcal/mole)	0.13	262.48
2nd minimum P_{2a} (Hartree)		
Energy of the complex (Hartree)	−2.811594	−6966.724529
Energy of isolated β-CD (Hartree)	−2.6519294	−4227.741104
Energy of isolated TPPbiSptBu (Hartree)	−0.154018	−2738.918676
Interaction energy (without BSSE) (kcal/mole)	−3.54	−40.6
Interaction energy (CP-corrected) (kcal/mole)		−32.22
Deformation energy of the β-CD (kcal/mole)	0.65	29.38
Deformation energy of the TPPbiSptBu (kcal/mole)	0.36	266.64

[a] are calculated data for the TPPmSptBu-β-CD complex [7], [1a] and [2a] are calculated data for the TPPbiSptBu-β-CD complexes corresponding respectively to points P_{1a} and P_{2a} in the potential energy profile of the inclusion process (Figure 2).

shows a more important value for the guest molecule, suggesting an important rearrangement of the molecule to accommodate in the cavity of the host molecule.

The analysis of the molecular orbital energies at different steps of the association process, as shown in Figure 4, clearly indicates the narrow gap between the HOMO of the host molecule and the LUMO of the guest, suggesting a possible charge transfer interaction, a mechanism in favor of the data observed by Lino *et al.* [41]. Such a mechanism suggests an influence of the solvent, the pH of the medium and a substituant effect on both species upon the association process. No global shift towards lower energies of the binding molecular orbitals is observed at any of the state points in the potential energy surface. An attempt to perform the Morokuma's decomposition [43], not reported in this paper, led two major components in the interaction energy. The first component is the polarization interaction (i.e. the effect of the distortion of the electron distribution of the host and guest molecules and reciprocally); the second is the charge transfer (or electron delocalization interaction); both interactions are attractive and the most important term corresponds to the charge transfer.

Conclusion

This work has shown that the accurate search for global minima through the inclusion process pathway may lead to complete mechanisms and illustrates in more details all possible orientations or regioselective penetrations involved in host–guest interactions. The penetration process of the tBu group of the guest molecule occurs from the primary side of the β-CD. There is strong theoretical evidence of the substituant effect upon the

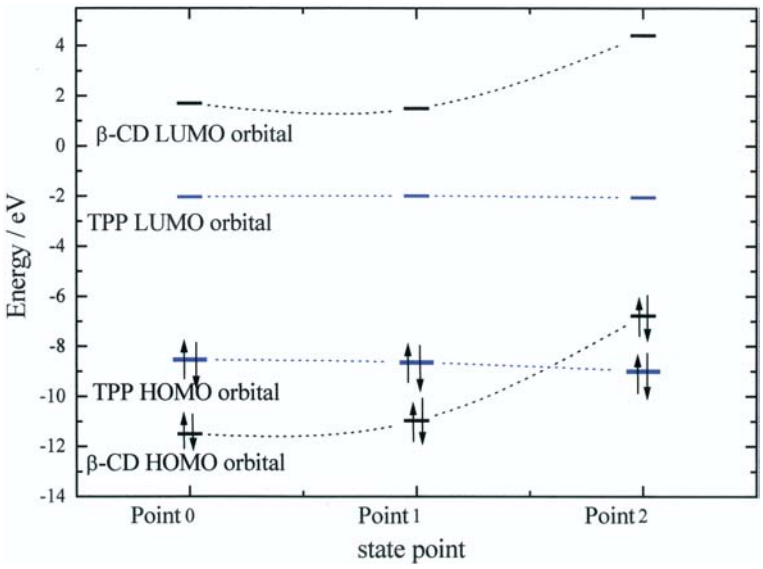

Figure 4. HOMO–LUMO molecular orbital levels of the two separated species at different state points of the association process (P_{0a}, P_{1a}, P_{2a}).

penetration level, but not the orientation of the guest with respect to the host molecule. A complete description of the host–guest inclusion complex may be obtained through the electronic properties of the two species within the supramolecular system.

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