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Importance of Interfacial Adsorption in the Biphasic Hydroformylation of Higher Olefins Promoted by Cyclodextrins: A Molecular Dynamics Study at the Decene/Water Interface

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Abstract: We report herein a molecular dynamics study of the main species involved in the hydroformylation of higher olefins promoted by cyclodextrins in 1-decene/water biphasic systems at a temperature of 350 K. The two liquids form a well-defined sharp interface of approximately 7 Å width in the absence of solute; the decene molecules are generally oriented "parallel" to the interface where they display transient contacts with water. We first focused on rhodium complexes bearing water-soluble $TPPTS^{3-}$ ligands (where $TPPTS^{3-}$ represents tris(*m*-sulfonatophenyl)phosphine) involved in the early steps of the reaction. The most important finding concerned the surface activity of the "active" form of the catalyst $[RhH(CO)(TPPTS)_2]^{6-}$, the $[RhH(CO)_2(TPPTS)_2]^{6-}$ complex, and the key reaction intermediate $[RhH(CO)(TPPTS)_2(decene)]^{6-}$ (with the olefin π-coordinated to the metal center) which are adsorbed at the water side of the interface in spite of their −6 charge. The free $TPPTS^{3-}$ ligands themselves are also surface-active, whereas the −9 charged catalyst precursor $[RhH(CO)(TPPTS)_3]^{9-}$ prefers to be solubilized in water. The role of cyclodextrins was then investigated by performing simulations on 2,6-dimethyl-β-cyclodextrin ("CD") and its inclusion complexes with the reactant (1-decene), a reaction product (undecanal), and the corresponding key reaction intermediate $[RhH(CO)(TPPTS)_2(decene)]^{6-}$ as guests; they were all shown to be surface-active and prefer the interface over the bulk aqueous phase. These results suggest that the biphasic hydroformylation of higher olefins takes place "right" at the interface and that the CDs promote the "meeting" of the olefin and the catalyst in this peculiar region of the solution by forming inclusion complexes "preorganized" for the reaction. Our results thus point to the importance of adsorption at the liquid/liquid interface in this important phase-transfer-catalyzed reaction.

Keywords: biphasic catalysis • hydroformylation • interfaces • molecular dynamics • olefins

Introduction

The immobilization of organometallic catalysts in the aqueous phase by choosing hydrophilic ligands is a well-established method for effective catalyst separation and recycling in two-phase catalytic systems.[1,2] This technique forms the basis of the Ruhr-Chemie/Rhône-Poulenc process involving water-soluble rhodium tris(*m*-sulfonatophenyl)phosphine (TPPTS) complexes, by which propene can be converted into butanal on a scale of 6×10^6 tons year^{-1}.[3,4] This reaction is generally believed to occur in the aqueous phase in which the gaseous reactants (CO, H_2, alkene) are somewhat solubilized, accounting for the lack of reactivity of water-insoluble high olefins under conditions in which smaller olefins (with two to about five carbon atoms) are transformed.[5]

This drawback can be circumvented by using, for example, surfactants,[6,7] co-solvents,[8] amphiphilic ligands,[9–11] or cyclodextrins[12] to promote the biphasic hydroformylation reaction. Cyclodextrins are cyclic oligosaccharides with six (α-), seven (β-), or eight (γ-)D-glucopyranose units that have a hydrophobic cavity in which hydrophobic guest molecules (e.g., an alkene substrate) can be complexed.[13] Native cyclodextrins with secondary 2-OH and 3-OH groups at the

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Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author. Neat decene/water interfaces obtained at 50 atm and with the TIP5P model for water (systems **A1**–**A3**) and simulations on the reaction intermediate using the TIP3P and TIP5P models for water (systems **B6** and **B6′**, respectively). Complexation of decene by CDs at the interface (system **C1′**) and results of the corresponding PMF calculations. Selected snapshots of complexes formed between CD and decene, undecanal and $[RhH(CO)_2(TPPTS)_2]^{6-}$.

wide rim and primary 6-CH_2OH groups at the narrow rim are water-soluble and their solubility in both organic and aqueous phases can be modified by functionalization of the hydroxy functions (Figure 1), thus modulating their complexation properties and, as a consequence, their efficiency as promoters in biphasic systems. For instance, methylated α-[12] or β-cyclodextrins[14] are more effective promoters than native cyclodextrins.[14]

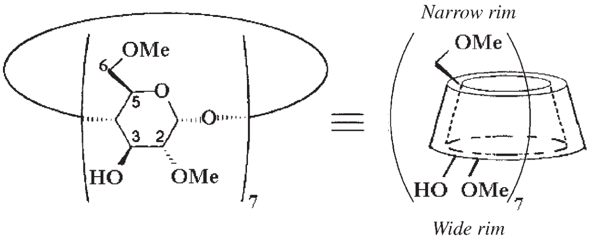

Figure 1. Schematic representation of the heptakis(2,6-di-*O*-methyl)-β-cyclodextrin (CD).

In phase-transfer-catalyzed reactions, the interface itself presumably plays a key role,[15–17] which is consistent with the increase in the catalytic rate observed on increasing the interfacial area (e.g., upon mechanical stirring[18] or by using aqueous catalysts immobilized on hydrophilic solid supports of high surface area like silica[19]). However, as pointed out by Cornils and co-workers "aqueous biphasic catalytic systems are still in the infancy of their significance" and, based on kinetic studies of the hydroformylation reaction of the propylene molecule, these authors proposed that the reaction in fact takes place at the interfacial layer between the gaseous and liquid phases instead of in the bulk water phase.[18] The microscopic nature of this interfacial layer has so far remained elusive and cannot be assessed by kinetic data. What happens with higher olefins has not been investigated so far and the role of promoters like cyclodextrins remains unclear. Do they act as "shuttles" transferring the hydrophobic olefin into the aqueous phase in which it reacts with the hydrophilic catalyst[20] or does the reaction also take place in the interfacial layer?

Experimentally, insights into the nature of liquid/gas or liquid/liquid interfaces and the interfacial distribution of solutes can be obtained by thermodynamic (surface tension) measurements,[21] interfacial electrochemistry,[22] as well as from surface spectroscopic studies.[23–25] Computer modeling studies, mainly molecular dynamics (MD), are also a valuable way of investigating liquid interfaces in their neat state (no solute)[26–30] as well as in the presence of all kinds of species like ions[31,32] and extractant molecules and their complexes,[33–35] mainly studied in the context of ion-partitioning by liquid/liquid extraction. Some papers are of more relevance to phase-transfer catalysis.[36,37] Concerning the hydroformylation of olefins, we recently reported an exploratory MD study of biphasic solutions of the main species of the reaction and these were found to be surface-active. Furthermore, a complex formed between a native cyclodextrin and the key reaction intermediate $[RhH(CO)(TPPTS)_2(decene)]^{6-}$ was also adsorbed at the interface.[38] In this study chloroform was used as a model of the organic phase and standard thermodynamic conditions were applied (a temperature T of 300 K and a pressure p of 1 atm). Experimentally, however, the reaction does not proceed under these conditions[39] and the relevance of these results for more realistic systems remains to be assessed.

This is why we decided to further investigate the interfacial behavior of the main species of the reaction by using more "realistic" conditions, that is, by using neat 1-decene both as the organic phase and as a reactant at a higher temperature ($T = 350$ K) and undecanal as the corresponding reaction product. We have considered typical rhodium complexes and other important species involved in the biphasic reaction, as described by Horváth et al.[40] and Monflier et al.[41] in reports of their high-pressure NMR studies in D_2O. These are sketched in Figure 2. They include the $[Rh(acac)(CO)_2]$ and $[Na_3TPPTS]$ species which react in water

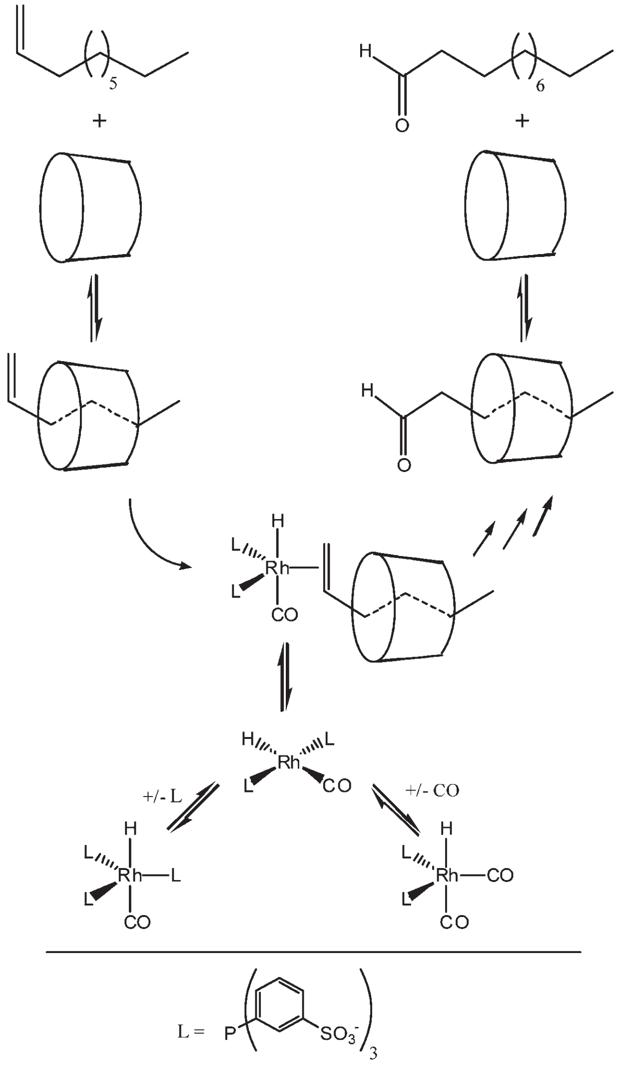

Figure 2. Rhodium-catalyzed hydroformylation of 1-decene to form undecanal in the presence of cyclodextrins (represented by a truncated cone).

to form the $[RhH(CO)(TPPTS)_3]^{9-}$ complex which is the precatalyst of the reaction. We then considered the active catalyst of the reaction, that is, the square-planar $[RhH(CO)(TPPTS)_2]^{6-}$ complex, as well as its adduct with the olefin, that is, the key intermediate $[RhH(CO)(TPPTS)_2(decene)]^{6-}$. The $[RhH(CO)_2(TPPTS)_2]^{6-}$ complex, which can also form in solution on addition of CO to $[RhH(CO)(TPPTS)_2]^{6-}$, has also been investigated. These rhodium complexes will first be considered "alone", that is, in the absence of promoters. In the next stage, we considered the effect of cyclodextrins, selecting the heptakis(2,6-di-*O*-methyl)-β-cyclodextrin (hereafter denoted CD; see Figure 1) derivative to model the experimentally used randomly methylated cyclodextrins. We wanted to see to what extent this water-soluble CD interacts with the interface in its uncomplexed state and how it can interact with the main species involved in the reaction, namely the reactant (decene), the key intermediate formed between decene and the catalyst (the $[RhH(CO)(TPPTS)_2(decene)]^{6-}$ intermediate), and the corresponding reaction product (undecanal). We will show in this report that most of these complexes adsorb at the interface, thereby demonstrating the importance of interfacial adsorption in the biphasic hydroformylation of higher olefins. Several arguments explaining the role of cyclodextrins will be presented.

Methods

Energy representation of the systems: The molecular dynamics (MD) simulations were performed using the modified AMBER 7.0 software[42] in which the potential energy *U* is described by the sum of the bond, angle, and dihedral deformation energies and pairwise additive 1-6-12 (electrostatic and van der Waals) interactions between nonbonded atoms [Eq. (1)].

$$U=\sum_{\text{bonds}}K_l(l-l_0)^2+\sum_{\text{angles}}K_\theta(\theta-\theta_0)^2+\sum_{\text{dihedrals}}\sum_n V_n[1+\cos(n\omega-\varphi)]+\sum_{i<j}\left[\frac{q_iq_j}{R_{ij}}-2\varepsilon_{ij}\left(\frac{R^*_{ij}}{R_{ij}}\right)^6+\varepsilon_{ij}\left(\frac{R^*_{ij}}{R_{ij}}\right)^{12}\right] \quad (1)$$

Cross terms in the van der Waals interactions were constructed by using the Lorentz–Berthelot rules. Water was described by using the TIP3P model[43] and, in test cases, by using the TIP5P model.[44] 1-Decene molecules in the liquid phase and complexed decene ligands were described by using the AMBER/PARM99 parameters[45] and their atomic charges (see Figure S1) were fitted by using electrostatic potentials (the ESP/Merz–Kollman–Singh procedure) calculated at the DFT (B3LYP) level of theory with the 6-31G* basis set. The intramolecular and van der Waals parameters of the solutes were also taken from the AMBER/PARM99 force field. The atomic charges on the CD were taken from reference [38]. The nonbonded parameters used for rhodium were those of Li^+.[46] The structures of the $[RhH(CO)(TPPTS)_3]^{9-}$ and $[RhH(CO)(TPPTS)_2]^{6-}$ complexes were derived from the X-ray structures of the $[RhH(CO)(PPh_3)_3]$ and $[RhCl(CO)(PPh_3)_2]$ complexes,[47,48] respectively, to which sulfonate groups were added to form the $TPPTS^{3-}$ ligands. The structure of $[RhH(CO)_2(TPPTS)_2]^{6-}$ was also derived from that of $[RhH(CO)(TPPTS)_3]^{9-}$, with one $TPPTS^{3-}$ ligand being replaced by CO. The $[RhH(CO)(TPPTS)_2(decene)]^{6-}$ complex was derived from $[RhH(CO)(TPPTS)_3]^{9-}$, substituting a $TPPTS^{3-}$ ligand by the alkene. The atomic charges of the complexes were fitted from electrostatic potentials calculated with the 6-31G* basis set for all the atoms except rhodium for which the LANL2DZ basis set was used (single-point calculations performed on the X-ray adapted structures). All quantum mechanics calculations were performed at the DFT (B3LYP functional) level of theory using the Gaussian03 software package.[49] The intramolecular parameters of the rhodium complexes were chosen to fit the X-ray structures, allowing for free rotation around the $P-C_{phenyl}$ and Rh−Ligand bonds. The latter were represented by a harmonic potential and 1-decene was π-coordinated via its two sp^2 carbon atoms. The 1-4 electrostatic and van der Waals interactions were scaled down by 1.2 and 2.0, respectively, as recommended by Cornell et al.[50] All MD simulations were performed using 3D periodic boundary conditions, thus the solutions were represented as alternating slabs of water and decene. Nonbonding interactions were calculated using a 12 Å atom-based cutoff, correcting for long-range electrostatics by the Ewald summation method (particle mesh Ewald approximation).[51,52]

Molecular dynamics: The MD simulations were performed at 350 K starting from random velocities. The temperature was controlled by coupling the system to a thermal bath using the Berendsen algorithm[53] with a relaxation time of 0.2 ps. All C−H, O−H, and H···H "bonds" were constrained with SHAKE and the Verlet leapfrog algorithm implemented in AMBER[42] with a time step of 2 fs being used to integrate the equations of motion.

The biphasic systems were prepared by using adjacent cubic boxes with sides of 40 Å containing 160 decene and 2316 water molecules into which the solutes were immersed (Figure 3). After performing 1000 energy minimization steps, the systems were simulated by MD for 5 ps at a constant volume with frozen solutes (BELLY option of AMBER), followed by a MD simulation for 500 ps at a constant pressure of 1 atm with the freed solutes. Tests were also performed at 50 atm. All systems were then simulated at a constant volume for 2–10 ns. Their characteristics are given in Table 1.

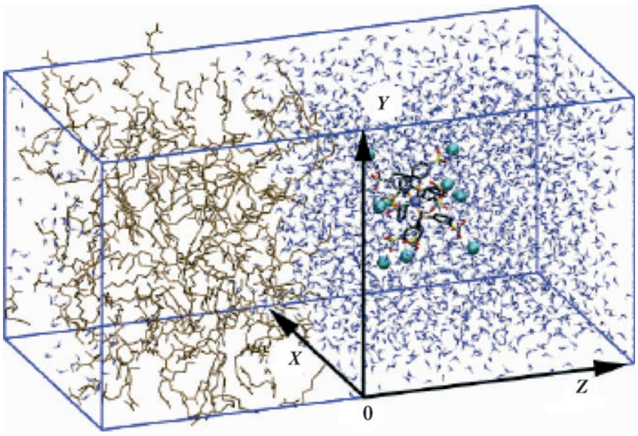

Figure 3. Simulation box containing one $[RhH(CO)(TPPTS_3)]^{9-}$ complex immersed in the aqueous phase with Na^+ as counterions (system **B3**) and definition of the *x*, *y*, and *z* axes.

Analysis of the trajectories: The MD trajectories were saved every 1 ps and analyzed using our DRAW software.[54] Typical snapshots were redrawn with the VMD software.[55] Insights into the energy components were obtained by group analysis using a cut-off distance of 17 Å and a reaction field correction for the electrostatics.[56] The solvent and solute densities were calculated as a function of the *z* coordinate in slices of $\Delta z = 0.5$ Å (the axes are defined in Figure 3) and the position of the interface (Gibbs dividing surface at $z=0$) was dynamically defined as the intersection of the water and 1-decene density curves. The positions of the solutes with respect to the interface were monitored by using the *z* position of the rhodium center for complexes or the *z* position of the center of mass for the other solutes.

Table 1. Characteristics of the MD simulations performed on the systems under study at constant volume.[a]

	Solute	Starting position	Time [ns]
	neat interface		
A1	no solute	–	2.0
	rhodium complexes and free ligands		
B1	$[Rh(acac)(CO)_2]$	9-9-9	5.0
B2	$[Na_3L]$	4-4-4	8.0
B3	$[Na_9RhH(CO)L_3]$	in water	8.0
B4	$[Na_6RhH(CO)_2L_2]$	in water	8.0
B5	$[Na_6RhH(CO)L_2]$	in water	8.0
B6	$[Na_6RhH(CO)L_2(\text{decene})]$	in water	8.0
	free CDs		
C1	8 CDs	in water	10.0
	CD complexes		
D1	decene$\subset$CD	in water	5.0
D2	undecanal$\subset$CD	in water	5.0
D3	$[Na_6RhH(CO)_2L_2]\subset$CD	in water	5.0
D4	$[Na_6RhH(CO)L_2(\text{decene})]\subset$CD	in water	5.0

[a] CD represents the heptakis(2,6-di-*O*-methyl)-β-cyclodextrin and L = $TPPTS^{3-}$.

PMF (potential of mean force) calculations: We calculated the potential of mean force (PMF),[57] which corresponds to the free energy profile for the dissociation of the decene$\subset$CD complex at the decene/water interface (with 160 decene molecules and 1715 water molecules) at 350 K. The reaction coordinate is the distance *d* between the terminal C_{methyl} atom of decene and a glycosidic O_g oxygen atom of the CD (linking two glucopyranose units). The *d* distance was increased stepwise from $\lambda = 1$ (associated decene$\subset$CD complex at the interface; $d = 7.6$ Å) to $\lambda = 0$ (free decene in the organic phase + free CD at the interface; $d = 15.0$ Å). The change in free energy ΔG was obtained by using the free energy perturbation technique (FEP)[57] based on Equation (2).

$$\Delta G_\lambda = RT\ln\langle \exp\frac{U_\lambda - U_{\lambda+\delta\lambda}}{RT}\rangle_\lambda \text{ and } \Delta G = \sum \Delta G_\lambda \quad (2)$$

The transformation from state 1 to 0 was achieved in 100 steps, that is, in increments $\Delta\lambda$ of 0.01, corresponding to 0.0735 Å each. At each step λ, 20 ps of equilibration were performed, followed by 20 ps of data collection to calculate the contribution from ΔG_λ.

Results

We will first describe the characteristics of the neat decene/water interface and then analyze the interfacial behavior of the main rhodium complexes involved in the early steps of the hydroformylation reaction. We also consider the free ligands ($TPPTS^{3-}$) and the $[Rh(acac)(CO)_2]$ complexes which are in situ precursors of the catalyst. The last part of this paper deals with the interfacial behavior of CD and its inclusion complexes with the reactant, the product, and the key intermediate ($[RhH(CO)(TPPTS)_2(\text{decene})]^{6-}$) of the hydroformylation reaction.

Characteristics of the neat decene/water interface: The neat decene/water interface (no solutes; system **A1**; see Figure 4) is molecularly sharp, in keeping with the low miscibility of these liquids, with no intersolvent mixing in the bulk phases. The interfacial width (defined as the *z* portion of the solution in which the solvent densities are less than 90 % of the bulk densities) is about 7.5 Å, which is comparable to that of the chloroform/water interface.[58] At the interface each molecule of a given solvent retains direct contact with the molecules of the corresponding bulk solvent. Furthermore, the orientation of the solvent molecules at the interface is anisotropic, as indicated by the order parameter $<S> = 0.5(3\cos^2\theta - 1)$, where θ is the angle between the *z* axis and either the Me···=CH_2 vector of the olefin or the H···H vector of water. *S* was averaged over time (0.5 ns) and over all the molecules present in dynamically defined slabs of $\Delta z = 1$ Å

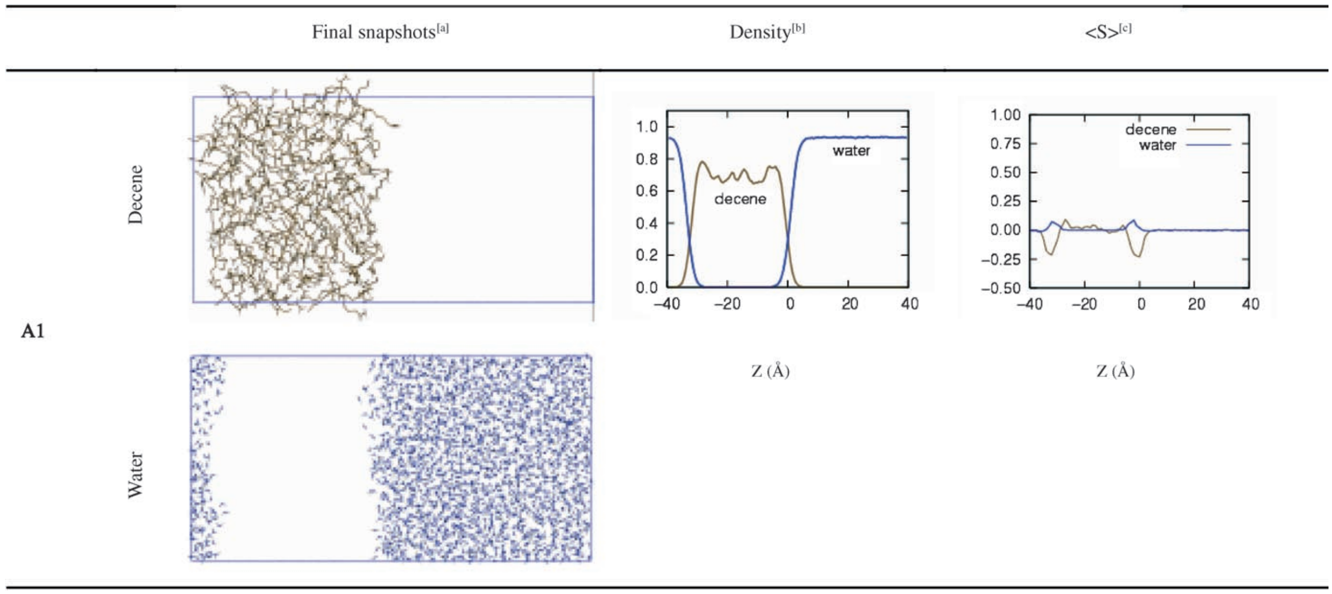

Figure 4. Neat decene/water interface (the two solvents are shown separately for clarity): [a] after 2 ns of MD. [b] Density [kg dm^{-3}] of the decene/water system as a function of the *z* direction [Å] of the box and averaged over the last 0.5 ns of the MD. [c] Order parameter < S > of decene and water as a function of the *z* position [Å] (see text for definition).

parallel to the interface. The results indicate that both decene and water molecules are isotropically oriented in their bulk domains ($<S>\approx 0$), but not at the interface(s), especially in the case of decene ($<S>\approx -0.23$). For water, $<S>$ is closer to zero ($\approx +0.09$). In fact, decene molecules tend to be oriented parallel to the interface, as observed with decane at the interface with water.[26] Generally, decene molecules are not linear, but undergo conformational exchange between *gauche* and *trans* C−C bonds. Visual inspection of the trajectories reveals that the decene C=C bond displays transient contacts with water (the lifetime at the interface is represented in the histogram shown in Figure S2 in the Supporting Information and typical snapshots in Figure 5 and Figure S3 in the Supporting Information), in keeping with its somewhat polar character. However, the lifetime of such contacts is quite short (ca. 50–200 ps, depending on the width of the selected interfacial slab) and each decene molecule rapidly exchanges between the bulk and interfacial domains (in less than 0.5 ns), as illustrated by the cumulated positions represented in Figure S4 in the Supporting Information.

The characteristics of the interface are weakly sensitive to the thermodynamic conditions or the water model. This was tested by running a simulation under a pressure of 50 atm (the **A2** system) instead of 1 atm (the **A1** system) with the TIP3P model for water and a simulation under 50 atm with the more demanding TIP5P model for water (system **A3**), which better solvates hydrophobic solutes and may be more suitable for the study of interfaces.[30,59] The thickness of the interface is similar (ca. 6.5 Å for **A2** and 7.0 Å for **A3**; see Figure S5 in the Supporting Information) as are the order parameters of the decene and water molecules ($<S>=-0.24$ and $+0.09$, respectively, for **A2** and $<S>=-0.24$ and $+0.06$ for the **A3** system). The lifetimes of the decene molecules within ±2, ±4, or ±8 Å of the interface are also similar for the three models (see Figure S2 in the Supporting Information). The important feature, in the context of the studied reaction, is that even at 50 atm no intersolvent mixing occurs, thus precluding any further reaction of decene in the aqueous phase.

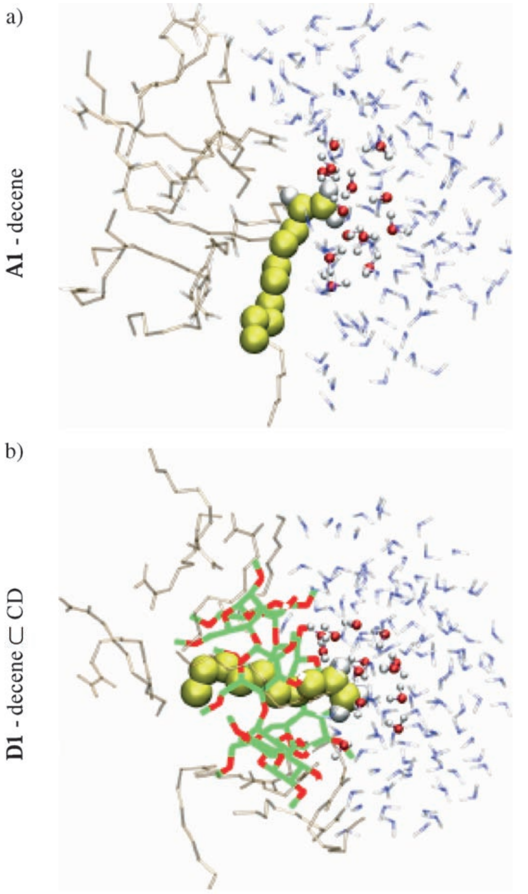

Figure 5. Zoom view of a) an uncomplexed decene molecule (system **A1**) and b) a decene molecule complexed to CD (system **D1**) with selected surrounding solvent molecules (a full version of this figure is given in Figure S3).

Rhodium complexes at the decene/water interface: In this section we first consider the $[Rh(acac)(CO)_2]$ precursor, the free ligands ($TPPTS^{3-}$), and the precatalyst $[RhH(CO)(TPPTS)_3]^{9-}$ at the interface. We then consider the key rhodium complexes involved in the hydroformylation reaction, that is, $[RhH(CO)(TPPTS)_2]^{6-}$, $[RhH(CO)_2(TPPTS)_2]^{6-}$, and $[RhH(CO)(TPPTS)_2(decene)]^{6-}$, investigated through independent simulations. All negatively charged species were simulated with Na^+ as the counterions, which, in all cases, remained solubilized in the aqueous phase, as expected.

The precatalyst, its precursor, and the free $TPPTS^{3-}$ ligands: Experimentally, the $[Rh(acac)(CO)_2]$ precursor reacts in an aqueous solution with the $TPPTS^{3-}$ ligand to form the water-soluble rhodium catalyst. However, we decided to simulate the $[Rh(acac)(CO)_2]$ complex in the biphasic system as a computational test to see where it would partition. We started with a concentrated solution of 27 complexes dispersed in the simulation box (nine in decene, nine at the interface, and nine in water; system **B1**; Figure 6); by the end of the simulation, all the complexes were dissolved in the organic phase with a slight peak of concentration at the interface (see Figure 6).

On the other hand, a similar simulation performed with three "layers" of four $TPPTS^{3-}$ anions (system **B2**; Figure 6) shows that these ligands are hydrophilic but also surface-active. The ligands initially in the organic phase are expelled towards the water in the early stages of the simulation, whereas the others are distributed between the interface and the bulk water (see the density plots in Figure 6). At the end of the simulation, one finds seven anions at the interface(s) and five in the bulk water. At the interface, they adopt two orientations; the phosphorus atom points towards either the aqueous phase or the decene phase. In both cases, their position and conformation are amphiphilic, that is, with the aromatic rings in contact with the decene phase and the sulfonate groups solvated by water.

The −9 charged $[RhH(CO)(TPPTS)_3]^{9-}$ complex is very hydrophilic and remains solubilized in the aqueous phase

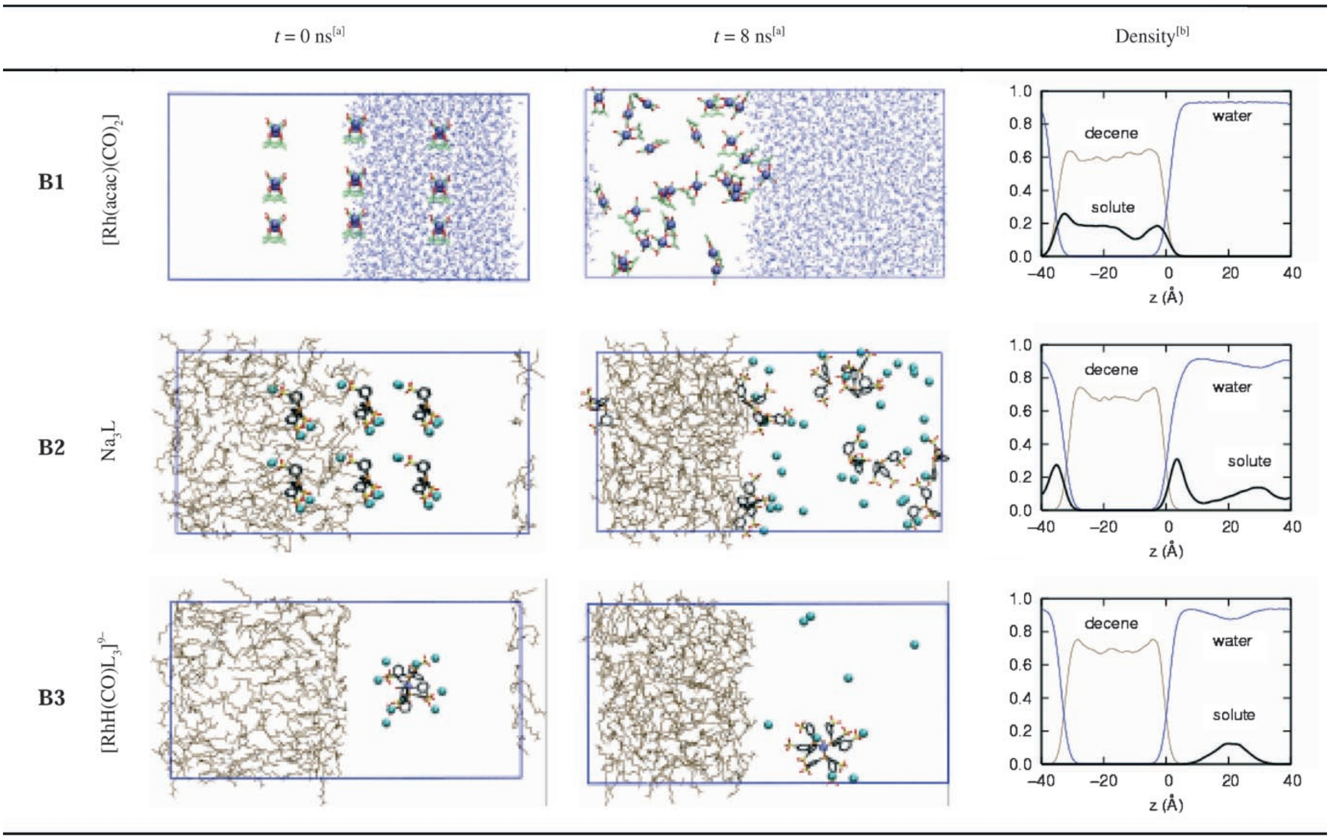

Figure 6. $[Rh(acac)(CO)_2]$ complexes (system **B1**), $TPPTS^{3-}$ ligands L (system **B2**), and the $[RhH(CO)(TPPTS)_3]^{9-}$ precatalyst (system **B3**) at the decene/water interface. [a] Initial and final snapshots (only one solvent is represented for clarity). [b] Density curves [$kg\,dm^{-3}$] of the solvents and the solute (without Na^+ counterions) as a function of the z position [Å] measured over the last 3 ns of the MD simulation.

with its Na^+ counterions during the whole simulation without forming any contacts with the decene phase or the interface (system **B3**; Figure 6). It thus cannot react with decene.

Taken together, these results are consistent with the relative solubility data of the different species. The $[Rh(acac)(CO)_2]$ complex is quite hydrophobic and would react with the olefin in the organic phase if no hydrophilic phosphine ligands were added. Upon coordination of $TPPTS^{3-}$ ligands to form $[RhH(CO)(TPPTS)_3]^{9-}$, the rhodium complexes clearly become hydrophilic, therefore preventing catalyst lost and facilitating its recyclability. Simulations also show that $TPPTS^{3-}$ ligands are surface-active, which is consistent with experimental observations on these ligands[9] and on their less charged $Ph_2P(C_6H_4SO_3)^-$ analogues[60] and has important implications for the interfacial behavior of the −6 charged rhodium complexes (see below).

The reactive rhodium complexes and the key reaction intermediate: In the early stages of the hydroformylation reaction, the active form of the catalyst $[RhH(CO)(TPPTS)_2]^{6-}$ can be formed either from the precatalyst $[RhH(CO)(TPPTS)_3]^{9-}$ or from the $[RhH(CO)_2(TPPTS)_2]^{6-}$ complex by the loss of one equatorial $TPPTS^{3-}$ or of one CO ligand, respectively. Figure 7 shows the results of the simulations obtained with these −6 charged complexes (systems **B4** and **B5**, respectively) and with the $[RhH(CO)(TPPTS)_2(decene)]^{6-}$ reaction intermediate (system **B6**). The simulation started with solutes positioned where they were expected to be, that is, in the water phase. During the simulations, however, all three complexes migrated to the water side of the interface and remained there until the end, in an amphiphilic conformation and orientation. The phenyl moieties of the $TPPTS^{3-}$ ligands are in contact with the decene molecules, while the sulfonate groups point towards the water. The interface therefore induces a conformational change of the ligands through rotation of the phenyl rings around the $P-C_{phenyl}$ bonds. A more detailed examination of the distances between rhodium and the plane of the interface (Figure 7) shows that for the $[RhH(CO)(TPPTS)_2]^{6-}$ complex, the rhodium atom remains separated from the interface by approximately 5.5 Å owing to the presence of phenyl groups that are in contact with the decene phase. In the case of the $[RhH(CO)_2(TPPTS)_2]^{6-}$ complex, the adsorption occurs stepwise during the simulation. First, between 1–5 ns only one $TPPTS^{3-}$ ligand is in contact with the decene phase and rhodium is separated from the interface by around 6.5 Å. After 5 ns of MD the complex reorients itself in such a way that the second $TPPTS^{3-}$ ligand forms contacts with the decene phase, bringing the rhodium center closer (at ca. 3.0 Å) to the interface. The complex therefore

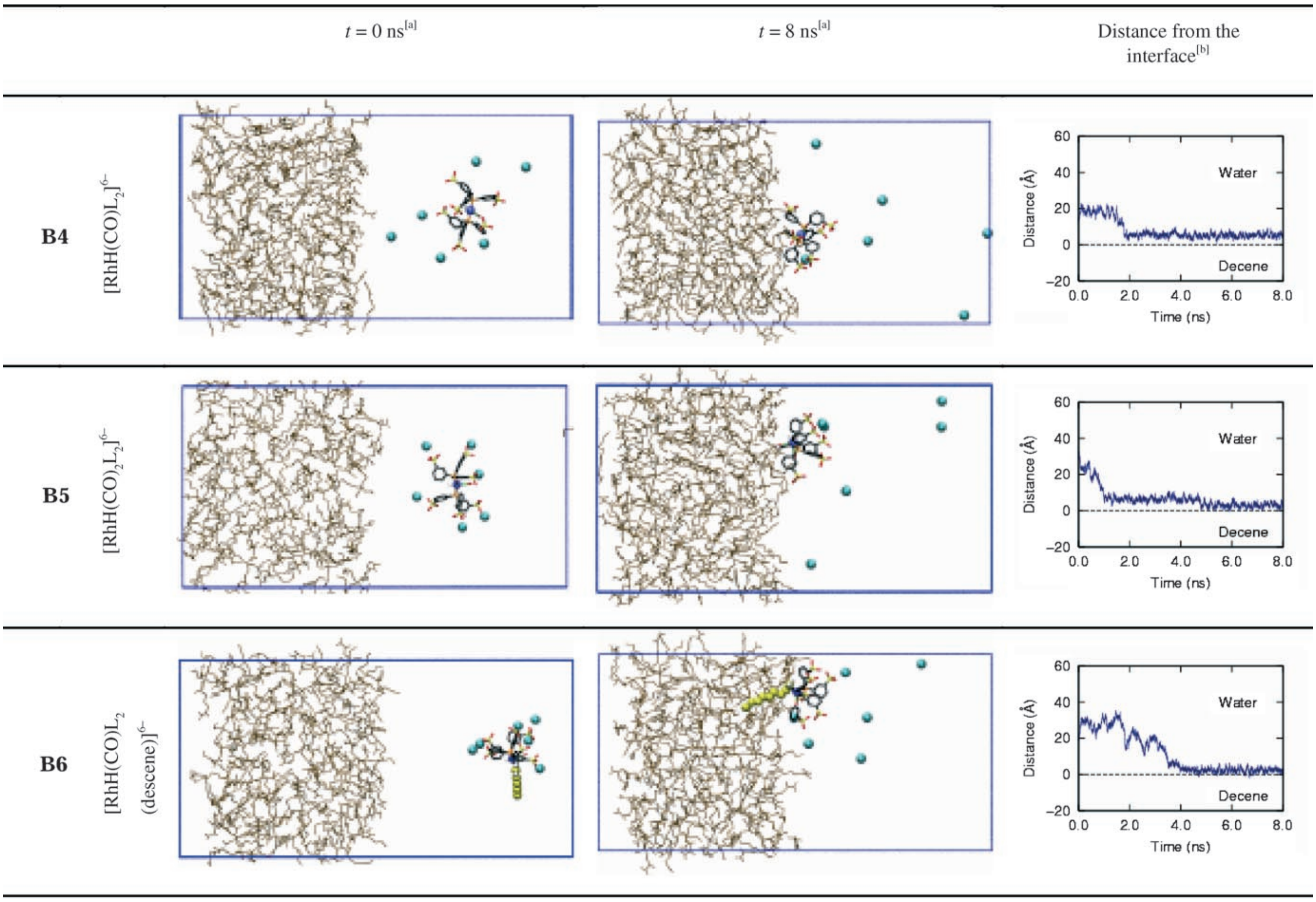

Figure 7. Rhodium complexes at the decene/water interface. [a] Initial and final snapshots (water is hidden for clarity). [b] Distance [Å] between the rhodium atom and the interface as a function of time [ns].

adopts an amphiphilic orientation at the interface with its equatorial CO and axial hydrogen ligands pointing towards the decene phase and its $TPPTS^{3-}$ ligands towards the water (Figure 8). The $[RhH(CO)(TPPTS)_2(decene)]^{6-}$ intermediate also adopts a well-defined amphiphilic orientation at the interface, its decene and CO ligands pointing towards the decene phase and its $TPPTS^{3-}$ ligands towards the water; its solvation behavior at the interface is similar to that of $[RhH(CO)_2(TPPTS)_2]^{6-}$.

The interfacial adsorption of the $[RhH(CO)(TPPTS)_2(decene)]^{6-}$ reaction intermediate obtained with the TIP3P water model was confirmed by another simulation using the TIP5P model (system **B6′**; see Figure S6 in the Supporting Information). Although diffusion is generally slower with TIP5P than with the TIP3P model,[61] the complex was again "attracted" from the bulk water to the aqueous side of the interface, adopting an amphiphilic conformation and orientation as was the case with the TIP3P model for water.

Free β-cyclodextrins and their inclusion complexes at the interface

Free cyclodextrin hosts at the interface: Free cyclodextrins, although readily soluble in water, prefer to adsorb at the interface, as observed in the simulation of eight CDs initially positioned in the bulk water (system **C1**; see Figure 9). The CDs adsorb at the decene side of the interface and form oligomers via intermolecular hydrogen bonds. Some of them are oriented with the wide rim "parallel" (in fact, slightly tilted) to the interface in an amphiphilic manner: the wide rim (possessing hydroxy functions) points towards the water phase while the fully methylated narrow rim points towards the decene phase. Other CDs adopt a more perpendicular orientation to the interface, forming intermolecular hydrogen bonds with the other CDs. This distribution is reminiscent of the one observed at the chloroform/water interface,[38] the "parallel" orientation being the preferred one for monomers, whereas the perpendicular orientation is observed only in concentrated systems. The density curves of the solvents and the solute (Figure 9) indicate that the interface is broadened, from around 8 Å in the absence of CDs to around 20 Å in the presence of CDs.

We note that in the simulations the CDs do not spontaneously complex decene molecules at the interface as a result of conformational changes of the CD, such as rotation of one or two glucopyranose units, allowing the methyl groups of the narrow rim to "fill" the cavity. Such "deformations" can be observed in X-ray structures[62–64] and are more pro-

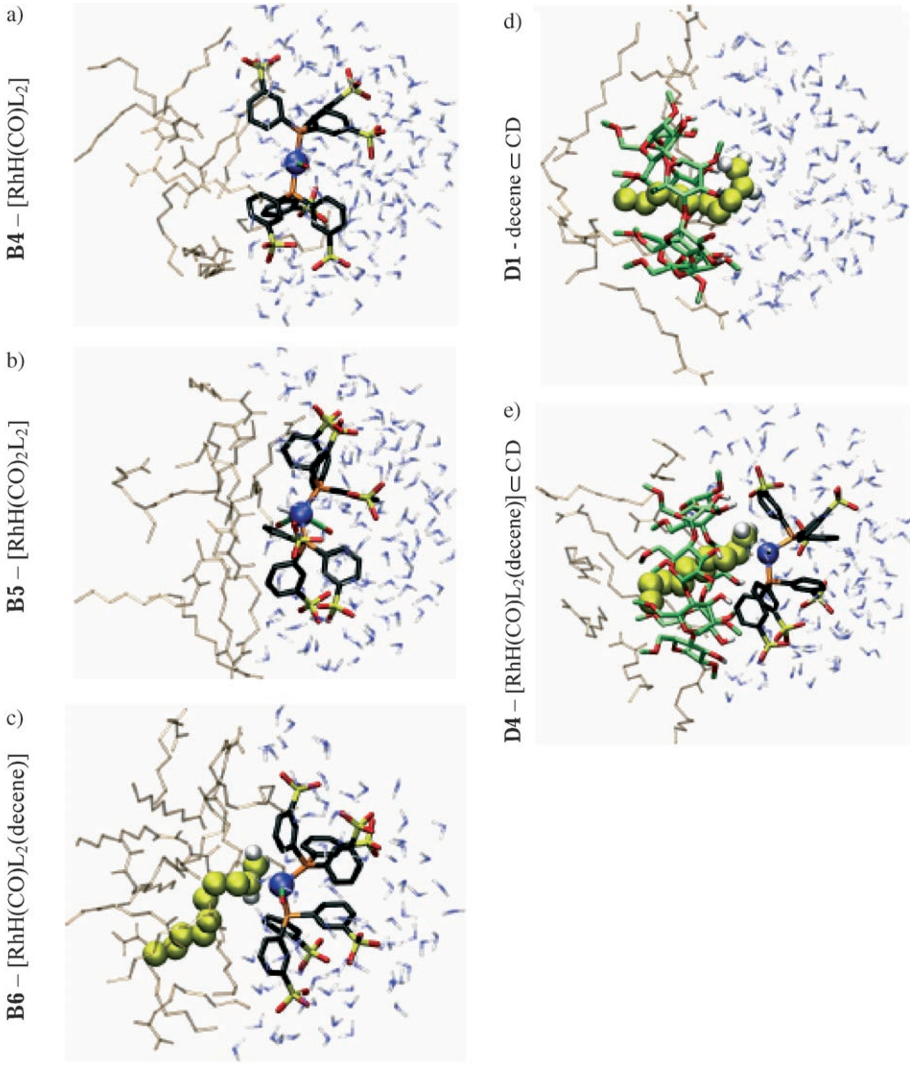

Figure 8. The a) [RhH(CO)(TPPTS)$_2$]$^{6-}$, b) [RhH(CO)$_2$(TPPTS)$_2$]$^{6-}$, c) [RhH(CO)(TPPTS)$_2$(decene)]$^{6-}$, d) decene$\subset$CD, and e) [RhH(CO)(TPPTS)$_2$(decene)]$^{6-}$$\subset$CD complexes adsorbed at the decene/water interface (systems **B4**, **B5**, **B6**, **D1**, and **D4**, respectively).

nounced in methylated cyclodextrins than in the unmethylated (native) one[38] for two main reasons. First, methylation reduces the number of intramolecular hydrogen bonds which rigidify the "symmetrical" structure of the cyclodextrin. Second, the cavity of the CD is hydrophobic and tends to be filled by the methyl groups, thereby releasing water, which is favorable from an entropic point of view. However, repeating this MD simulation, again starting with eight CDs in water, but constraining their cavity so that they remain open,[65] produced a different picture (see system **C1′** in Figure S7 in the Supporting Information): all the CDs moved to the interface where seven of them spontaneously complexed a decene molecule indicating that this is a rapid process. The C=C bond of the complexed decene pointed either towards the water phase (in five complexes) or towards the organic phase (in two complexes). Note that the former type of complex can be considered to be "reactive" (since the reactive C=C bond points towards the phase that contains the catalyst), whereas the latter type of complex would be "unreactive". This simulation clearly demonstrates the affinity of the CD for the interface and for the reaction substrate (decene).

Further computational proof for the stability of the decene$\subset$CD complex stems from free energy calculations on the decomplexation process, conducted at the interface. This was obtained by increasing stepwise the distance between the C_{methyl} terminal atom of decene and a glycosidic oxygen atom of the CD, retaining all other degrees of freedom. Ultimately the complex dissociated; while the CD remained anchored at the interface, the decene substrate was immersed in the decene phase. The results (see Figure S8 in the Supporting Information) confirm that the decomplexation is an uphill process ($\Delta G = 17.7\,\mathrm{kJ\,mol^{-1}}$) without an energy barrier, which is fully consistent with the spontaneous complexation of decene when the CD's cavity is open. They are also consistent with the high stability of analogous cyclodextrin complexes with decane[66,67] or decene[39] substrates observed experimentally in solution.

Inclusion complexes at the interface: The behavior of guest$\subset$CD inclusion complexes was also investigated by starting the simulations with the preformed complex positioned in the water phase, in which case the CDs would react through a "shuttle" mechanism if the reaction with the alkene and the rhodium catalyst was to take place in "bulk" water.

First, we consider the substrate of the reaction (decene) as the guest (system **D1**; see Figure 10) complexed in a "reactive mode", that is, with the -CH=CH$_2$ function pointing towards the wide rim of the CD and the terminal methyl group pointing towards the narrow rim. The simulation shows that the complex prefers the interface over the bulk phase and that it is quite stable as it remained associated during the 5 ns of the simulation (i.e., when solubilized in water as well as at the interface). This is consistent with the PMF results and contrasts with the behavior at the chloro-

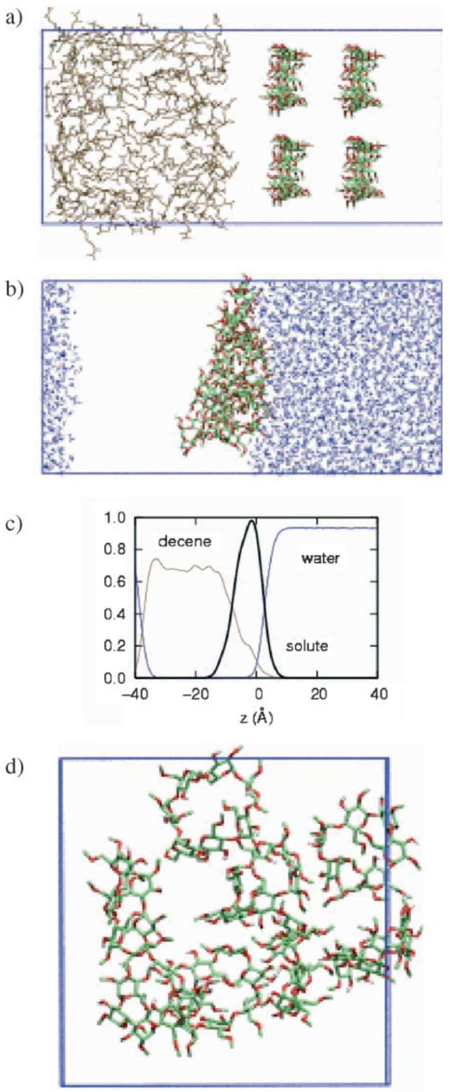

Figure 9. Eight free CDs at the interface (system **C1**). a) Initial ($t=0$ ns) and b) final snapshots ($t=10$ ns). Only decene (a) or water (b) is represented for clarity. c) Density curves [kg dm^{-3}] of the solvents and the solute calculated during the last 3 ns of the MD simulation. d) *xy* view of the simulation box (solvents hidden for clarity).

form/water interface where the complex dissociated once it had been adsorbed at the interface owing to the substitution of decene by a chloroform molecule inside the cavity of the cyclodextrin.[38] At the interface with decene, the CD is oriented in an amphiphilic manner and, as a result, the -CH=CH$_2$ function of the complexed substrate points towards the aqueous phase, which is quite favorable for further reaction with the catalyst by a least-motion pathway (Figure 8). The decene molecule is quite mobile in the CD cavity and oscillates between an "internal" binding mode (with -CH=CH$_2$ deeply included inside the cavity) and a more "external" binding mode (with -CH=CH$_2$ attracted outside by water; see Figure S9 for zoom views of the adsorbed complexes). It is hydrated by around seven H$_2$O molecules within 5 Å (see the time evolution in Figure S3 and the RDFs in Figure S10 in the Supporting Information). Note, the reversed binding mode, with the -CH=CH$_2$ group of the decene molecule pointing towards the narrow rim of the CD, was not simulated because it would turn the C=C bond away from the water phase (and therefore away from the rhodium catalyst).

The undecanal⊂CD inclusion complex formed with the reaction product (system **D2**; see Figure 10) also migrates from the "bulk" water domain to the interface during the simulation, to finally be adsorbed at the decene side of the interface. It also remains associated in the bulk water as well as at the interface. Note that the undecanal molecule is longer than decene and only about half of the molecule can be included in the CD cavity. Its carbonyl group oscillates between being in an "internal" position (anchored by hydrogen-bonding interactions with the hydroxy groups of the CD) and an "external" position (where it is hydrated by two interfacial H$_2$O molecules). Typical snapshots are shown in Figure S11 in the Supporting Information.

We also considered the $[RhH(CO)(TPPTS)_2(decene)]^{6-}$ reaction intermediate as a guest with the decene ligand included inside the cavity of the CD (system **D4** ; see Figure 10). Such a complex would form from the reaction between the decene⊂CD complex and the catalyst in a least-motion pathway in the early stages of the reaction catalyzed by CDs (Figure 2). Its initial structure was prepared by a MD simulation in the gas phase in the absence of Na$^+$ counterions. In this structure, three of the catalyst's sulfonate groups (two from one TPPTS ligand and one from the other) point towards the wide rim, forming hydrogen bonds with the hydroxy groups of the CD (see Figure S12 in the Supporting Information). The resulting host–guest interaction energy is quite high, around −660 kJ mol^{-1}. This "supermolecule" was initially positioned in water, but, as seen with the other CD complexes, it migrated to the decene side of the interface where it remained adsorbed. We note that this complex is highly dynamic as the decene moiety oscillates between more or less deep positions in the CD cavity, while the remaining ligands adjust accordingly. Sometimes an aryl(TPPTS) group interacts "facially" with the CD, forming -SO_3^-···H−O(CD) hydrogen bonds, as observed by NMR spectroscopy of the sulfonated ligands/cyclodextrin adducts in D$_2$O.[68] The resulting host–guest interaction energy at the interface, although weaker than in the gas phase, remains quite high, around −225 kJ mol^{-1} (involving a contribution of −100 kJ mol^{-1} from decene itself and of −125 kJ mol^{-1} from the remaining parts of the catalyst).

The CDs may display "facial" interactions with the rhodium complexes and these were investigated by simulating the $[RhH(CO)_2(TPPTS)_2]^{6-}$⊂CD species (system **D3**; see Figure 10) starting with the guest perched over the host, its equatorial CO ligand pointing towards the CD cavity, perpendicular to the upper rim (see Figure S13 in the Supporting Information). The simulation was again started with the complex in the bulk water phase. Such a configuration is not optimal and, at an early stage in the simulation (while the solute is still in water), the rhodium catalyst repositioned itself to "complex" one aryl(TPPTS) ligand inside the CD

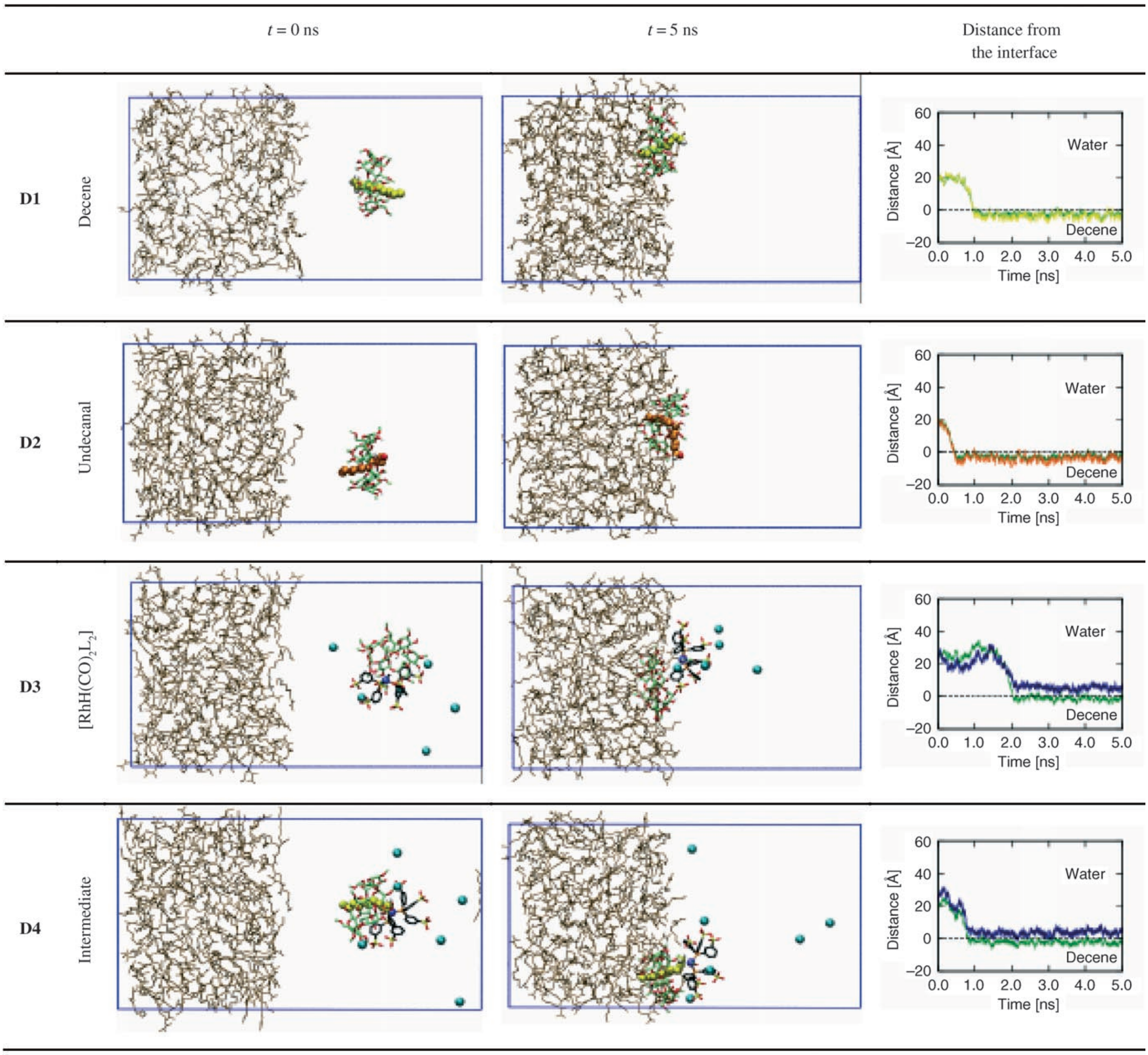

Figure 10. Cyclodextrin complexes at the decene/water interface. a) Initial and final snapshots. Water is hidden for clarity. b) Distances [Å] between the interface and solutes as a function of time [ns] (decene yellow; undecanal orange; cyclodextrin green; Rh complexes blue).

cavity, anchoring its sulfonate group onto hydroxy groups on the wide rim of the CD (see Figure S13 in the Supporting Information). The resulting host–guest interaction energy is attractive (-120 ± 35 kJ mol^{-1} on average), but less than that of the $[RhH(CO)(TPPTS)_2(decene)]^{6-} \subset CD$ complex intermediate with decene complexed by the CD. During the simulation, the complex remains associated and migrates to the interface, showing that it is surface-active, as are its molecular components. Note that the $[RhH(CO)(TPPTS)_2(decene)]^{6-}$ intermediate might, in principle, form a complex with CD in a similar fashion, with one of the aromatic group of $TPPTS^{3-}$ complexed to the CD instead of the alkene moiety, but this should be less favorable owing to the loss of CD/decene attractions and to the exposure of the hydrophobic decene moiety to water.

Discussion and Conclusions

We have reported herein a molecular dynamics study of the interfacial behavior of the main species involved in the biphasic hydroformylation of olefins. The catalytic process is a complex multistep reaction and we selected rhodium complexes that are generally assumed to be involved in the reaction[40,41,69,70] and analyzed their distribution in an "oil"/water biphasic system, where "oil" molecules are potential substrates of the reaction. It is clear from experiment,[18] as well as from this study, that in the case of high olefins like decene the reaction cannot proceed in the aqueous phase and an insight into the role of cyclodextrins as promoters of the reaction can be obtained from our MD simulations. In all the simulated systems, the organic and water phases are separated by a molecularly sharp interface, with no intersolvent mixing. The interface, with an area of around 16 nm^2, may in fact model the surface of liquids at rest or the surface of droplets of a few nanometers radius that would form under stirring conditions. Thus, the gradient concentration at the "interfacial layer", if any, more likely corresponds to microdroplets or microemulsions than to locally homogeneous mixtures. Like classical amphiphiles, surface-active solutes such as solvent modifiers, alcohols, or cyclodextrins promote the formation of such "droplets". Also note that, generally speaking, adsorption at the liquid interface reduces the interfacial pressure, thereby facilitating the transfer of solutes from one phase to the other, and such should be the case for most of the molecules simulated here (see below).

Surface activity of the main species of the biphasic hydroformylation of olefins: The most important finding concerns the surface activity of the main species of the reaction. The rhodium complexes with hydrophilic $TPPTS^{3-}$ ligands are water-soluble, but those of moderate charge (a charge of −6 with two $TPPTS^{3-}$ ligands) are surface-active. This is the case for the "active" form of the catalyst ($[RhH(CO)(TPPTS)_2]^{6-}$), for the $[RhH(CO)_2(TPPTS)_2]^{6-}$ complex, and for the key reaction intermediate $[RhH(CO)(TPPTS)_2(decene)]^{6-}$ which prefers to adsorb at the water side of the interface instead of being solubilized in the bulk water. The free $TPPTS^{3-}$ ligands also adsorb at the interface, which is consistent with surface tension measurements of these ligands themselves and of their less hydrophilic analogues.[9,60] Concerning the rhodium complexes, we note that our finding is consistent with the report of Borowski et al. on the surface activity of rhodium complexes with $Ph_2P(C_6H_4SO_3)^-$ ligands.[60] As the ligands are generally used in large excess over the rhodium catalyst, they lower the interfacial pressure and increase the interface area, possibly leading to the formation of supramolecular assemblies that may range from small aggregates to micro-micelles or emulsions in the aqueous phase. This feature might explain the experimentally observed increase in reaction activity with the increase in $TPPTS^{3-}$ concentration.[10,11] On the other hand, the addition of nonamphiphilic salts to the aqueous phase reduces the reaction activity,[11,71–73] a feature that has been attributed to the decrease in the (already limited) solubility of the olefin in the aqueous phase (salting-out effect) under the hypothesis that the reaction would take place in water. By focusing on the interface properties, we propose that increasing the ionic strength of the aqueous phase also increases the interfacial pressure, thereby increasing the barrier to interface crossing and preventing the interfacial reaction between the substrate and the catalyst.

The role of cyclodextrins: Based on the fact that the $[RhH(CO)(TPPTS)_2]^{6-}$ active catalyst and the $[RhH(CO)(TPPTS)_2(decene)]^{6-}$ reaction intermediate are surface-active and therefore close to molecules of decene at the interface, one might argue that they can react without further assistance and wonder why the addition of cyclodextrins is necessary to promote the reaction. In fact, an analysis of the distribution of the -CH=CH_2 groups of decene around the rhodium center of $[RhH(CO)(TPPTS)_2]^{6-}$ at the interface indicates that one never finds any =$C(H_2)$ atom within 3 Å of rhodium during the whole simulation. Looking further away, that is, up to 4 and 5 Å, one finds one =$C(H_2)$ atom in only 1.5 and 11.5%, respectively, of the configurations (Figure S14). These distances are clearly too long and the probability of the rhodium and -CH=CH_2 centers meeting is very low. Also note the very short lifetime of the decene molecules at the interface, which also reduces the probability of meeting the catalyst.

When CDs are present in the biphasic system, they should partition to the phase in which they are most soluble, that is, water in the studied case. Our simulations reveal, however, that the CDs are surface-active and prefer the decene interface over the bulk aqueous phase. Their inclusion complexes with the reactant (decene) and reaction product (undecanal) are also surface-active. This finding is consistent with surface tension measurements of the cyclodextrins themselves[74] and of their complexes with lipophilic neutral guests[75] as well as with their stabilizing effect on the formation of oil/water emulsions of, for example, fatty acids and glycerides.[76,77] At the decene interface, the CDs and their complexes are found to adopt an amphiphilic orientation, with the hydrophilic wide rim directed towards the water phase. As a result, the C=C bond of the reactant and the C=O bond of the product also point towards the water, that is, towards the catalyst, at the interface. Less expected is the surface activity of the CD complexes with highly charged hydrophilic rhodium complexes and, among these, the key reaction intermediate $[RhH(CO)(TPPTS)_2(decene)]^{6-}$. Taken together these results strongly suggest that the sequence of catalytic reactions mainly takes place at the interface and are facilitated by cyclodextrins. As a consequence, increasing the interfacial area should also increase the catalytic efficiency.

There are a number of arguments concerning the role of cyclodextrins as "promoter" at the interface. 1) The reaction is favored by the locally enhanced concentration of the different species. In particular, the concentration of the rhodium catalyst at the interface should be increased upon its complexation with cyclodextrins. 2) With regards to the reaction substrate, the decene molecules are found to penetrate more deeply into the aqueous phase when they are included in the cyclodextrin cavity than in the absence of the CD (Figure 5). They can, in principle, adopt two different inclusion modes in the CD cavity: a "reactive" one, in which the -CH=CH_2 group points towards water, and an "unreactive" one, in which it points towards the organic phase. The former should be preferred because of the attractions between -CH=CH_2 and water. An analogous "reactive" inclusion mode should be a fortiori preferred for the reaction product (undecanal) whose -CH=O group is more hydrophilic than the -CH=CH_2 group of the reactant. Once complexed, the alkene has restricted conformational freedom and is more "linear", while it is generally folded and conformationally labile at the interface. Also, the lifetime of the properly oriented complexed olefin is quite high at the interface (here, several nanoseconds, but more if the simulation was pursued further), which contrasts with the short lifetime of uncomplexed -CH=CH_2 groups at the interface. The CDs thus preorganize the olefinic substrate at the interface (Figure 8) and this is favorable from the structural and entropic points of view. 3) The rhodium complexes (the catalyst as well as the $[RhH(CO)(TPPTS)_2(decene)]^{6-}$ reaction intermediate) are found to be surface-active and this feature should be enhanced upon complexation with CD. 4) The reaction product (undecanal) can also be complexed by the CD at the interface. 5) As a result of the surfactant behavior of CDs and of their complexes, the interfacial pressure should decrease and the interface broaden, thereby facilitating the transfer from one phase to the other. In practice, there is thus a complex interplay between the water solubility of the ligands, of the catalyst, and of the CDs, their surface activity, and their mutual interactions, which also likely determine the precise nanoscopic and microscopic nature of the biphasic solution. Any modulation of the CDs (size, functionalization),[12] or of the rhodium ligands (see, for example, refs. [20,68]) also modulates their surface activity.

To summarize, MD simulations of "nanobiphasic solutions" using decene as the organic phase support the view that the hydroformylation of higher olefins promoted by cyclodextrins takes place "right" at the interface and that cyclodextrins act as surfactants and receptors "catalyzing" the meeting of the catalyst and the olefin. The CDs also interact with the key reaction intermediate better than with the reactant, in analogy with enzymatic catalysis in which the enzyme interacts better with the transition state of the reaction than with the Michaelis precursor.[78] The explicit use of decene as the organic phase instead of models like chloroform[38] allows us to better understand the specific interactions between the decene molecule both as reactant and ligand of the rhodium catalyst and CDs at the interface. In this context, one advantage of using methylated CDs instead of native cyclodextrins is that the former adopts specific amphiphilic orientations at the interface, with the wide rim pointing towards the water phase, and this orientation is suitable for the formation of inclusion complexes with the reactant, the key reaction intermediate, and the reaction product. These results point more generally to the importance of interfacial phenomena in biphasic reactions and we hope that they will stimulate further experimental and theoretical investigations on "what happens at the interface" in biphasic hydroformylation reactions and related processes like phase-transfer catalysis,[8,15,17,79] supported aqueous-phase catalysis,[19] interfacial electrochemistry,[22,80] and extraction processes.[81]

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