

Enantioselective Recognition of Phenylalanine by a Chiral Amphiphilic Macrocyclic at the Air–Water Interface: A Copper-Mediated Mechanism

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The synthesis of a new chiral amphiphilic calix[4]resorcinarene, tetrakis(*N*-methylpropyl)tetraundecylcalix[4]resorcinarene (L-RA-Pro), bearing four L-prolyl moieties at the macrocyclic upper rim and four undecyl chains at the lower rim is described. This synthesis has been carried out via a Mannich-type reaction of L-proline and formaldehyde. It has been shown by means of Langmuir balance technique that L-RA-Pro self-assemble as well-defined monomolecular layers at the air–water interface. The effect of various cations on the stability of these monolayers has been studied. The experiments reveal that while there is a slight stabilization effect of K⁺, Cd²⁺, Co²⁺, Mg²⁺, and Ni²⁺, there is a high decrease in the collapse pressure in the presence of Cu(II) cation, showing that monolayers of L-RA-Pro, formed at the air–water interface, have a certain selectivity for copper(II) ions with regard to other cations tested. This supramolecular complex exhibits enantioselective recognition properties vs phenylalanine; the mechanism of this interaction is discussed.

Introduction

Comprehension of molecular recognition processes^{1–3} is one of the most significant challenges to the understanding of (bio)chemical processes taking place in biological systems. They are governed by a set of weak forces (noncovalent interactions) ranging from hydrogen bonds to van der Waals interactions through ionic and dipole–dipole interactions. Because of the asymmetry of a large majority of biomolecules (proteins, peptides, nucleic acids, carbohydrates, hormones, etc.), these interactions take place in an asymmetric (i.e., chiral) fashion.⁴

Thus, most of the artificial drugs have to be chiral to be integrated in the vast and complex game of molecular interactions of living systems. In many cases, while one of the enantiomer (eutomer) shows the desired activity, the other one (distomer) may present some undesired side effects and even toxicity.⁵ In this context, reliable enantioselective chemical sensors appear to be of great interest to control the optical purity of synthetic drugs; it implies the rational design of synthetic receptors able to discriminate between two enantiomers of the same molecule.

In supramolecular chemistry, macrocyclic molecules such as cyclodextrins,⁶ crown ethers,⁷ calixarenes,⁸ and calixresorcinarenes^{9,10} have been widely used as organizing

platforms to build more complex structures possessing predefined complexation properties. The calixarenes and calixresorcinarenes represent a versatile class of macrocyclic molecules used for the design of specific host entities.⁸ Parent calixarenes are amphiphilic in essence because of their chemical structure,¹¹ while the amphiphilic character of calixresorcinarenes depends essentially on the aldehyde used for their synthesis.¹² The rational design of new systems, with these macrocycles as organizing platforms, has been shown to be successful in terms of modulation of self-assembly and complexation properties at interfaces. Numerous studies have shown that suitably modified calixarenes and calixresorcinarenes are able to self-assemble at the air–water interface as stable Langmuir monolayers.¹³ These systems have shown remarkable complexation properties of biomolecules (nucleosides,¹⁴ nucleotides,^{15,16} amino acids,¹⁷ and proteins¹⁸), small organic molecules,^{19,20} and ions.^{21–29} They have also

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been shown to self-assemble in water as stable micelles,³⁰ vesicles,³¹ or solid lipid nanoparticles (SLNs).^{29,32,33}

The morphology of monolayers containing chiral molecules has been broadly investigated³⁴ but the application of these systems for chiral recognition at the air–water interface is much less well developed. Nevertheless, Badis et al.³⁵ have recently reported on enantiomeric recognition properties of amino acids by a new class of amphiphilic crown ethers. Liu et al.¹⁷ have demonstrated that monolayers of amphiphilic calixarenes bearing bicyclic guanidinium groups enantioselectively interact with D- or L-phenylalanine.

Here we report on the synthesis and interfacial metal ion complexation properties of a novel amphiphilic calixresorcinarene bearing four proline moieties. It is demonstrated that this molecule can be produced in good yield and is capable of self-assembly at the air–water interface to form stable monomolecular layers. These monolayers present some specificity for copper ions in comparison to potassium, cobalt, nickel, magnesium, and cadmium. The supramolecular complex formed by this calixresorcinarene and Cu(II) possesses enantioselective recognition properties vs phenylalanine.

Experimental Section

Synthesis. Solvents (analytical grade) and chemicals were purchased from Fluka (Switzerland) and used without further purification. NMR experiments (¹H and ¹³C) were recorded on a Varian 400 MHz spectrometer. Electrospray mass spectrometry (ES-MS) was performed on a Perkin-Elmer Sciex API 165 system. Optical rotation was recorded on a Perkin-Elmer 241MC spectropolarimeter.

Compound **1** has been produced following the literature procedure.¹²

The synthesis of L-RA-Pro was adapted from the procedure described by Iwanek et al.³⁶ To a solution of **1** (5 g, 4.5 mmol) in ethanol (200 mL) were added 37% formaldehyde (18 mmol) and L-proline (18 mmol, 2.1 g). The solution was refluxed and a couple of minutes after the complete dissolution of proline a white precipitate appeared. To ensure completion of the reaction, the suspension was maintained under reflux during 8 h. The pale yellow solid obtained was consequently filtered, washed with ethanol, and dried under vacuum to afford L-RA-Pro in 85% yield.

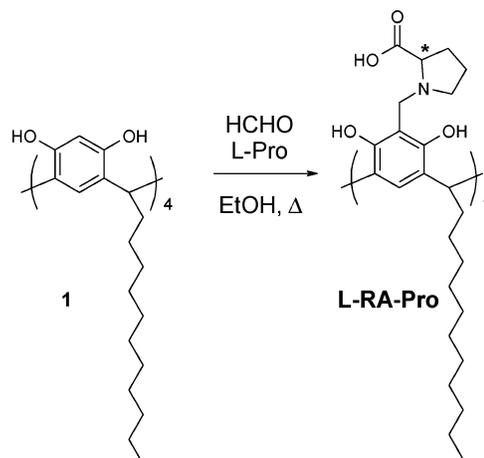


Figure 1. Synthetic route to L-RA-Pro.

¹H NMR (DMF-*d*₇): δ = 7.63 (s, 4H, Ar-H), 4.30 (t, 4H, Ar-CH-Ar), 4.04 (dd, 8H, Ar-CH₂), 3.56 (t, 4H, N-CH-CO₂), 2.52 (m, 8H, -N-CH₂-CH₂-), 2.33 (m, 8H, Ar-CH-CH₂), 1.93 (m, 8H, -N-CH₂-CH₂), 1.72 (m, 8H, -N-CH₂-CH₂-CH₂), 1.25 (s, 72H, (CH₂)₉), 0.85 (s, 12H, -CH₃).

¹³C NMR (DMF-*d*₇): 172.94, 151.15, 151.03, 124.55, 124.47, 108.36, 66.58, 35.74, 34.91, 34.49, 34.07, 33.66, 33.25, 30.62, 30.21, 29.80, 29.56, 29.38, 29.20, 28.96, 28.543, 28.12, 22.42, 13.58.

ES-MS (positive mode): 1615.1 [M + H]⁺, 1637.1 [M + Na]⁺, 1653.2 [M + K]⁺. [α]_{D578}²⁰ = -21 (c 0.1, CHCl₃).

Langmuir Film Experiments. Langmuir film experiments were performed on a Nima (Coventry, U.K.) 112D Langmuir–Blodgett system. A Teflon trough (100 cm², 50 mL) equipped with two hydrophobic barriers was used to compress symmetrically monolayers from 100 to 20 cm². The trough and the barriers were cleaned with analytical-grade dichloromethane, ethanol, and purified water (deionized water purified with a Millipore Milli-Q water system, resistivity ≥ 18 MΩ·cm). Surface tension was monitored by use of a Wilhelmy plate system. Compressions were performed continuously at a speed rate of 20 cm² min⁻¹. Spreading solutions were prepared by dissolving L-RA-Pro (24 mg) in 4 mL of hot DMF. After the complete dissolution of L-RA-Pro, the solution was cooled to room temperature and chloroform (16 mL) was added. To prevent solvent evaporation, the solution was stored at 0 °C and changed daily. This solution (8 μL) was spread on the aqueous subphase with a Hamilton gastight microsyringe; 30 min was allowed for total evaporation of the chloroform and equilibration of the amphiphiles on the surface.

Subphases were freshly prepared by dissolving the appropriate quantity of the relevant salt in pure water. The absence of surface-active molecules in subphases was checked by performing compression without amphiphiles spread on the surface; in no case was a change in surface tension observed. All the subphases were adjusted to pH 3 (±0.1) with hydrochloric acid. This pH was chosen because it is commonly accepted that, in chiral ligand exchange separation methods with proline–copper complexes, the best enantioselectivity is obtained for pH value ranging from 3–4.³⁷ Each sample was run at least three times to ensure reproducibility of results.

Results and Discussion

The synthetic route to tetrakis(*N*-methyl-prolyl)-tetraundecylcalix[4]resorcinarene (L-RA-Pro) is given in Figure 1. Tetraundecylcalix[4]resorcinarene, **1**, has been produced following the literature procedure.¹² The synthesis of L-RA-Pro has been carried out by a Mannich-type reaction of tetraundecylcalix[4]resorcinarene, **1**, L-proline, and formaldehyde in ethanol (yield 85%).

The behavior of L-RA-Pro has been studied at the air–water interface by the Langmuir balance technique; the

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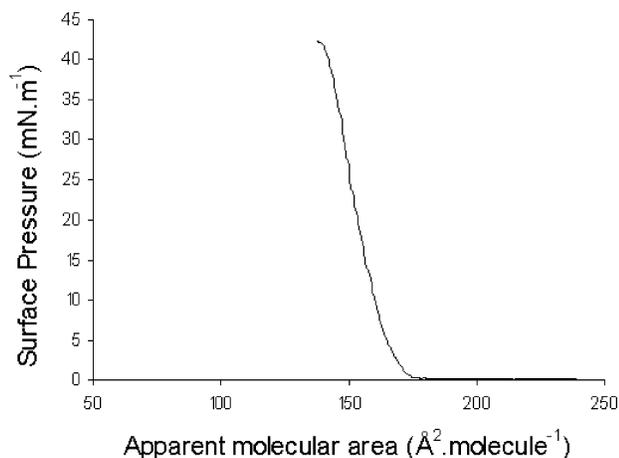


Figure 2. Π/A isotherm of L-RA-Pro on pure water subphase at pH 3.

Π/A isotherm measured at room temperature on a water subphase at pH 3 is given in Figure 2.

Considering the amphiphilic character of L-RA-Pro, it can form insoluble monolayers at the air–water interface. The isotherm measured shows an apparent molecular area (calculated by extrapolation of the linear part of the isotherm on the x -axis) of $160 \text{ \AA}^2/\text{molecule}$. This value is in perfect agreement with that published for the parent molecule **1** in a flattened cone conformation.²⁶ This result shows that there is no significant effect of prolyl moieties on the area occupied at the interface by L-RA-Pro, suggesting that these moieties are “immersed” in the water subphase and do not affect either the conformation or the packing of L-RA-Pro; the limiting area is due to the macrocycle itself. A schematic representation is given in Figure 3.

The collapse pressure of 42.4 mN/m (at an area of $135 \text{ \AA}^2/\text{molecule}$) is consistent with the formation of a stable monomolecular layer at the air–water interface. This value is lower than that published for **1** (50 mN/m),²⁶ showing that the presence of prolyl moieties affects the stability of the monolayer; in view of the drastic changes in the structural properties of the macrocycle, this variation could not be clearly attributed to a decrease in the amphiphilic properties of L-RA-Pro. The determination of the compressibility modulus (C_S^{-1}) shows that the monolayer is macroscopically in a liquid-condensed state ($C_S^{-1} = 180 \text{ mN/m}$);³⁸ the rapid takeoff observed at 180

Table 1. Characteristic Values Extracted from Isotherms of L-RA-Pro on Salt Subphases at 0.1 M Concentration^a

cation	Π_{coll} (mN/m)	areas ($\text{\AA}^2/\text{molecule}$)					C_S^{-1} (mN/m)
		A_{coll}	A_{10}	A_1	A_0	A_{lim}	
K^+	42.4	135	160	175	180	160	180
Cd^{2+}	44.0	131	162	180	185	163	190
Cu^{2+}	44.5	130	167	182	187	165	180
Cu^{2+}	36.0	143	165	180	185	159	200
Co^{2+}	43.6	133	168	177	180	158	190
Mg^{2+}	43.6	136	170	180	188	165	200
Ni^{2+}	45.0	138	162	170	183	158	185

^a Π_{coll} and A_{coll} represent the surface pressure and the surface area at the collapse of the monolayer; A_{10} , A_1 and A_0 represent apparent molecular areas for surface tensions of 10, 1, and 0 mN/m, respectively; A_{lim} is the extrapolation of the linear part of the isotherm on the x axis; and C_S^{-1} is the compressibility modulus.

$\text{\AA}^2/\text{molecule}$ reports on the relative rigidity of the monolayer even at low surface pressure values.

$$C_S^{-1} = -A(\partial\pi/\partial A)$$

The effect of the presence of various cations (K^+ , Cd^{2+} , Cu^{2+} , Co^{2+} , Mg^{2+} , Ni^{2+}) at concentrations ranging from 10^{-5} to 10^{-1} M has been studied, while the anion is kept constant (Cl^-). The need to keep the counterion constant is mandatory and should be carefully respected for the reason that, even when it is not expected, it could have significant effects. For example, it has been shown that, in the case of *p*-dodecanoylcalix[4]arene, the effect of stabilization/destabilization of the monolayer may arise under the influence of both the cation and the anion.²¹ Characteristic values for isotherms measured at a salt concentration of 0.1 M are given in Table 1. In Figure 4 the variations of the collapse pressures (Π_{coll}) are presented as a function of the concentration of each salt (for clarity and comparability, variations are expressed as absolute values; numerical values are given as Supporting Information).

From Table 1 it could be clearly seen that, except for Cu^{2+} , there is no significant variation in isotherm characteristic values in terms of area measured; the slight variations observed for A_0 and A_{lim} could not be considered as relevant. The only significant change in terms of area is observed for the collapse area in the presence of Cu^{2+} . This increase in the collapse area to a value of $143 \text{ \AA}^2/\text{molecule}$ could be explained by the decrease of the collapse pressure (i.e., the stability of the monolayer); indeed, during the compression process, the monolayer collapses earlier (i.e., at a higher area). Values of the compressibility moduli show that in all cases, monolayers are macro-

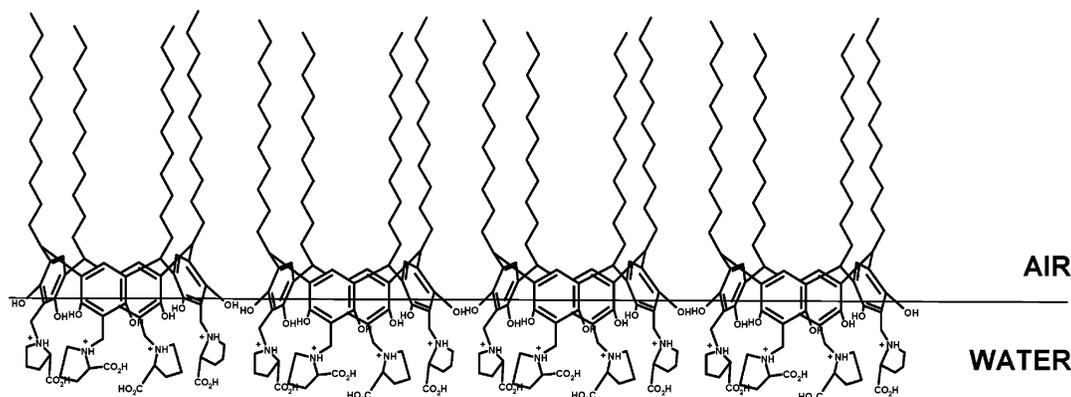


Figure 3. Schematic representation of a compressed monolayer of L-RA-Pro at the air–water interface.

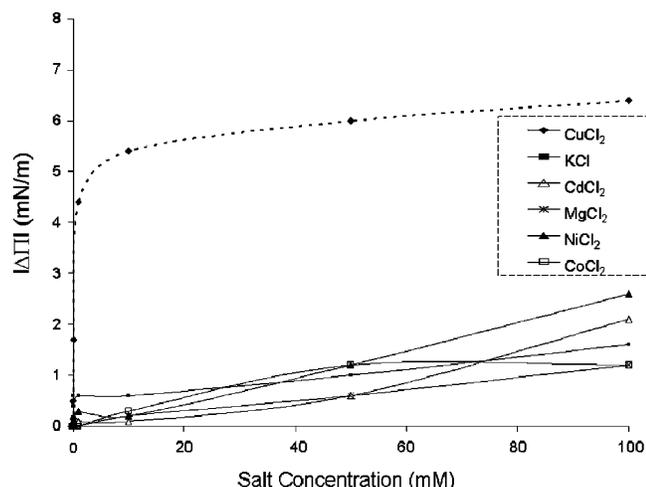


Figure 4. Effect on the collapse pressure of monolayers of L-RA-Pro of the presence of salts (KCl, CdCl₂, CuCl₂, CoCl₂, MgCl₂, and NiCl₂) at concentrations of 10⁻¹, 5 × 10⁻², 10⁻², 10⁻³, 10⁻⁴, and 10⁻⁵ M in the subphase. (Variations are expressed as $|\Delta\Pi| = |\Pi_{\text{H}_2\text{O}} - \Pi_{\text{salt}}|$; negative variations are represented by a dashed line).

scopically in a liquid-condensed phase and are not affected significantly by the presence in the subphase of ions. From the above, we conclude that no drastic molecular rearrangement take place in L-RA-Pro-based monolayers when the composition of the subphase is modified with the ions tested (K⁺, Cd²⁺, Cu²⁺, Co²⁺, Mg²⁺, and Ni²⁺).

The study of variations of collapse pressure as a function of the concentration in salt shows a number of interesting points. While there is a slight stabilizing effect in the presence of Mg²⁺ and Co²⁺, with an increase in collapse pressure values of 1.2 mN/m, this effect is more important in the presence of K⁺ and Cd²⁺ with values, respectively, of 1.6 and 2.1 mN/m. The highest stabilizing effect is observed for Ni²⁺ with an increase in the collapse pressure value of 2.6 mN/m. In the case of Cu²⁺ ion, there is a drastic destabilization of L-RA-Pro-based monolayers with a decrease of the collapse pressure value of 6.4 mN/m. This destabilizing effect is much more important than stabilizing effects observed for other cations. When variations of collapse pressure with concentration of Cu²⁺ are considered, it can be seen that the value decreases significantly, from 41.9 mN/m at 10⁻⁵ M, 40.7 at 10⁻⁴ M, 38.0 at 10⁻³ M, 37.0 at 10⁻² M, 36.4 at 5 × 10⁻² M, to 36.0 at 10⁻¹ M. The stability of Langmuir monolayers is due to van der Waals interactions between hydrophobic chains and interactions of polar headgroups with the subphase. Here, a change in the stability of these monolayers could be attributed to a change in interactions between polar headgroups of the calixresorcinarene and the water subphase. From these results, we expect that there is a specific interaction taking place between L-RA-Pro-based monolayers and Cu²⁺. In a recent paper,²⁸ Turshatov et al. reported on the interfacial behavior of three amphiphilic calix[4]resorcinarenes. It has been shown that a calixresorcinarene, bearing ternary amine groups, does interact strongly with Cu²⁺ and this interaction causes rearrangements in the packing of the amphiphiles at the interface, demonstrated by variations of molecular area values. Here, even if there is evidence of an interaction with Cu²⁺ cation, no significant variations in characteristic area values are measurable on compression isotherms (the mechanism of the molecular interaction is discussed below). From this, we can postulate that one copper ion interacts only with one L-RA-Pro and does not form any bridge between these amphiphiles at the interface, as has been described for

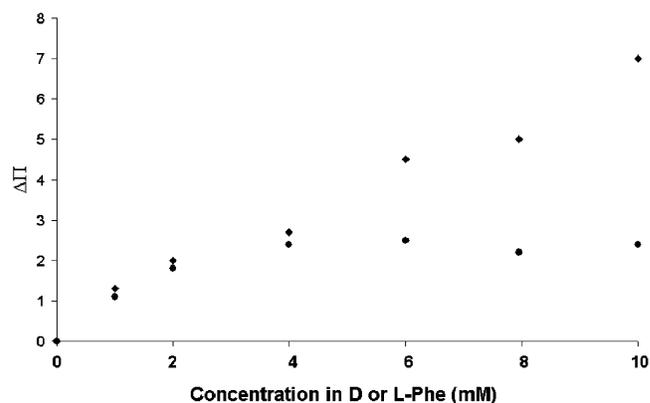


Figure 5. Effect of the concentration of L- (●) or D-Phe (◆) (in subphases containing 10⁻³ M CuCl₂) on the collapse pressure of monolayers of L-RA-Pro. Values are normalized as follows: $\Delta\Pi = \Pi_c - \Pi_{\text{CuCl}_2}$, where Π_c is the collapse pressure measured and Π_{CuCl_2} is the value measured on a subphase of 10⁻³ M CuCl₂.

Table 2. Characteristic Values Extracted from Π/A Isotherms of L-RA-Pro Measured on Subphases Containing 10⁻² M D- or L-Phe^a

L-Phe (M)	D-Phe (M)	Cu ²⁺ (M)	π_{coll} (mN/m)	areas (Å ² /molecule)					C_S^{-1} (mN/m)
				A_{coll}	A_{10}	A_1	A_0	A_{lim}	
	10 ⁻²	0	42.5	131	155	171	180	159	190
10 ⁻²		0	42.4	129	149	166	175	157	200

^a Cf. Table 1.

phosphonate-bearing calix[4]arene.²⁹ Similarly, interactions of *p*-dodecanoylcalix[4]arene with anions and cations at the air–water interface have been shown to affect the stability of the monolayers without influencing the molecular arrangement of the amphiphiles at the interface.²¹

The second part of this paper concerns the study of the interactions between L-RA-Pro with an amino acid, phenylalanine, in the presence of copper(II) in the subphase. Copper binding receptors have been widely used as a stationary phase in chiral separation techniques and have been shown to form a ternary complex with copper and amino acids.³⁹ Here, we have chosen phenylalanine (Phe) as a model molecule to study the formation of this kind of complex at the air–water interface. Varying concentrations of D- or L-Phe dissolved in water subphases containing CuCl₂ (10⁻³ M) have been investigated. Characteristic values extracted from isotherms of L-RA-Pro measured on water subphases containing 10⁻² M D- or L-Phe are presented in Table 2. In Figure 5 we report on the variations of the collapse pressure of monolayers of L-RA-Pro on subphases containing 10⁻³ M CuCl₂ and concentrations of L- and D-Phe varying from 10⁻³ to 10⁻² M. (Other characteristic values of these isotherms are given as Supporting Information.)

From Table 2, we can conclude that there is no significant effect of D- or L-Phe on the stability of monolayers of L-RA-Pro at concentrations up to 10⁻² M in the absence of copper. In the presence of CuCl₂, considering the effect of L-Phe, there are no substantial variations in terms or area measured (cf. Supporting Information) while there is a slight increase in the stability of the monolayer (with regard to the value obtained at a concentration of CuCl₂ of 10⁻³ M without Phe). It increases by 0.1 and 0.8 mN/m for concentrations of L-Phe of, respectively, 10⁻³ and 2 × 10⁻³ M. For concentrations above, the value of the collapse pressure stays almost

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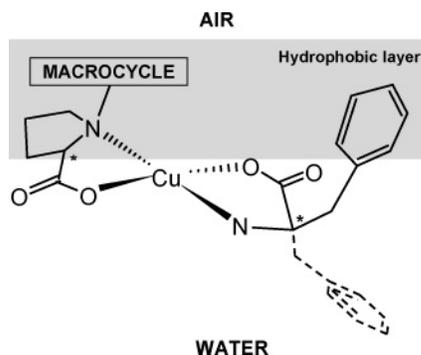


Figure 6. Schematic representation of the proposed interaction mechanism, the lateral chain of Phe is represented by a dashed line for the L-enantiomer (For clarity, only the prolyl moiety of L-RA-Pro is represented).

constant with an increase of 1.3 ± 0.2 mN/m. In the case of D-Phe, the increase in collapse pressure is much more significant with values of 0.3, 1.0, 1.7, 3.5, 4.0, and 6.0 mN/m for respective values of (1, 2, 4, 6, 8, and 10) $\times 10^{-3}$ M. From this, we can conclude that there is differential binding of D- and L-Phe to monolayers of L-RA-Pro in the presence of Cu^{2+} . We can postulate that the recognition process takes place via the formation of a ternary complex composed of L-RA-Pro, Cu^{2+} , and Phe as proposed in Figure 6.

In the molecular structure proposed for the ternary complex, the copper ion is chelated by the carboxylate oxygen atoms of the prolyl moiety of L-RA-Pro and that of phenylalanine and by the two nitrogen molecules of these amino acids, forming a planar square.⁴¹ The enantioselectivity of this interaction may arise from favorable–unfavorable interactions of the side chain of the amino

acid with the hydrophobic layer formed by aromatic functions of the calixresorcinarene with a possible inclusion of the aromatic side chain in the macrocyclic cavity.

Conclusion

The synthesis of a new chiral amphiphilic calix[4]-resorcinarene, L-RA-Pro, bearing four L-prolyl moieties at the wide rim and four undecyl chains at the narrow rim has been described. This molecule has been shown to self-assemble at the air–water interface as stable Langmuir monolayers.

The study of the effect of various cations has shown a selectivity of these monolayers for copper(II) ions. The supramolecular complex formed by L-RA-Pro and $\text{Cu}(\text{II})$ exhibits enantioselective recognition properties vs Phe with a greater affinity for D-Phe. Work is in progress to use these macrocyclic receptors as active layers for building enantioselective sensors.

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Supporting Information Available: Variations of collapse pressure in the presence of K^+ , Cd^{2+} , Cu^{2+} , Co^{2+} , Mg^{2+} , and Ni^{2+} at concentrations of 10^{-5} , 10^{-4} , 10^{-3} , 10^{-2} , 5×10^{-2} , and 10^{-1} and isotherm characteristic values obtained with subphases containing 10^{-3} M CuCl_2 and concentrations of D- or L-Phe ranging from 10^{-3} to 10^{-2} (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>

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