

# Derivatization of heteroditopic cryptands: A new generation of amphiphiles

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**Multi-gram scale synthesis of a few heteroditopic cryptands have been achieved. These cryptands have three derivatizable secondary amino groups which could be derivatized with acid chlorides to form a new generation of amphiphiles. These amphiphiles readily form vesicular structures and monolayers as well.**

BIOMEMBRANES<sup>1</sup> provide one of the most important structural units in the organization of the biological cells. Synthetic molecules containing a hydrophilic headgroup and one or more tails (amphiphiles) are known to form a great variety of supramolecular structures such as micelles, monolayer, bilayer, multilayer rods and vesicles. Surfactant monolayers, bilayers and phospholipid vesicles have been used extensively as membrane models. In addition, such systems are useful in drug delivery and targeting<sup>2</sup>, medical imaging<sup>3</sup>, catalysis<sup>4</sup>, energy conversion<sup>5</sup> and separation<sup>6</sup>. Furthermore, highly charged synthetic bilayers offer a challenge to colloidal chemists. They are useful to test models for colloidal stability, electrical double layer and amphiphilic self-assembly.

In 1976, Kunitake *et al.* reported<sup>7</sup> for the first time a totally synthetic vesicular structure. Since then a large number of synthetic vesicles have been reported with different chemical structures and composition of hydrophilic headgroup(s) and hydrophobic tail(s). The examples include single tail surfactants with rigid segments<sup>8</sup>, a surfactant with a hyperextended chain<sup>9</sup>, a two-headed single-chain surfactant<sup>10</sup>, two-headed two-tail surfactants<sup>11</sup>, surfactants with identical hydrophobic chains and two hydrophilic headgroups connected through a spacer<sup>12</sup> and double-chain double-headgroup surfactants containing one cationic and one anionic headgroups<sup>13</sup>.

Formation of monolayer and multilayer films by the Langmuir-Blodgett technique has assumed greater importance in recent times with the current demand for materials with tailored interfacial properties. Langmuir monolayers incorporating different types of monocyclic compounds<sup>14-17</sup> have been reported in the literature. Fullerenes<sup>18,19</sup> have been studied in Langmuir troughs as such, or mixed with other molecules for the possible formation of monolayers at the air-water interface. The macrobicyclic benzo[2.2.2] Na-cryptate with covalently

linked fullerene (C<sub>60</sub>) as the hydrophobic moiety is also available in the literature<sup>20</sup>.

Cationic surfactants have a spectrum of biological activity, including antibacterial and immunosuppressant properties<sup>21</sup>. Synthesis of analogous molecules with higher charges on the head group is important as these synthetic amphiphiles can be used as anti-parasitic agents and finally as anthelmintic agents<sup>22</sup> owing to their detergent actions.

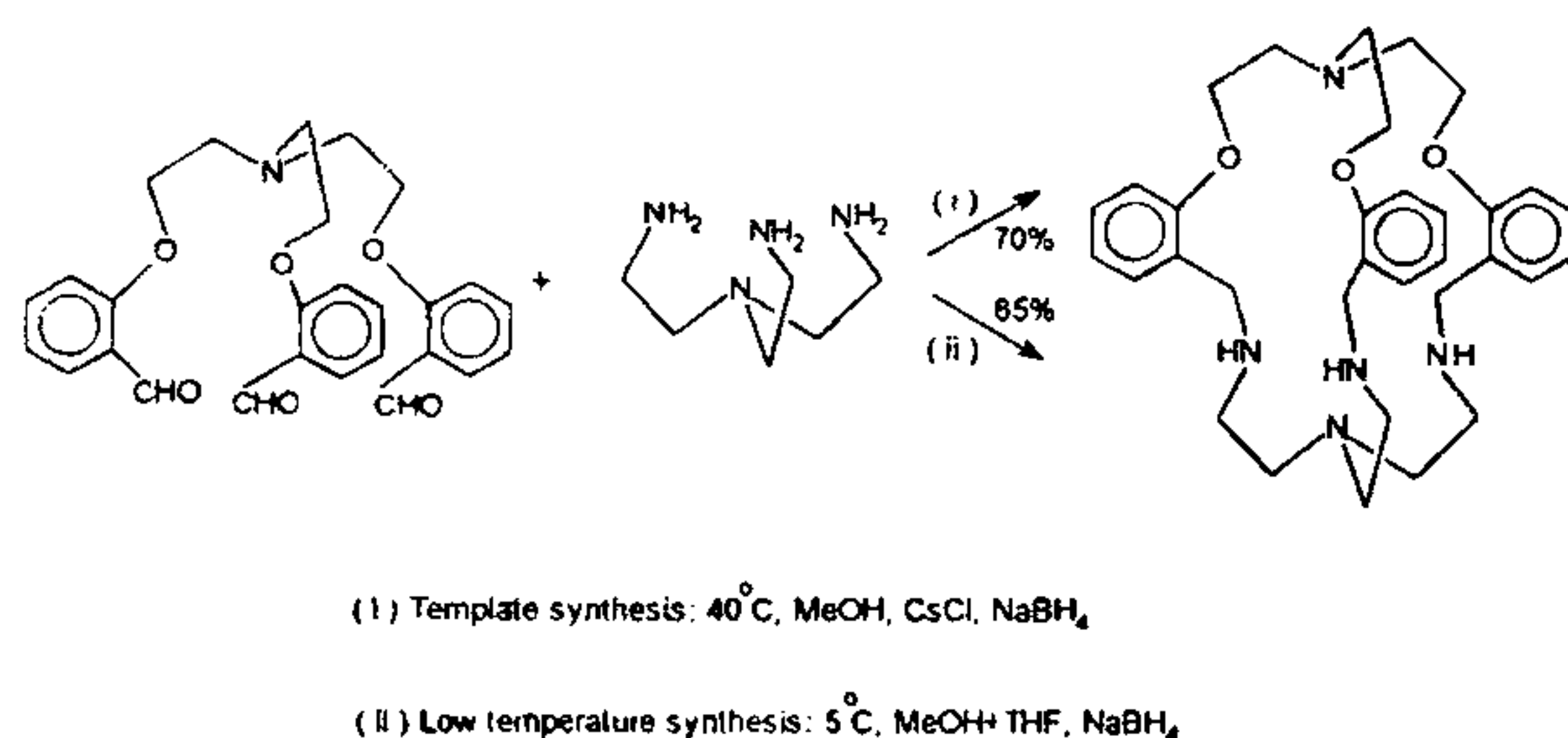
We became interested in synthesizing cryptand, with long alkyl chains attached as side-groups, for having new generation amphiphiles which would lead to yet another class of vesicular structures and mono- and multi-layer films. Cryptands<sup>23</sup> have proved their usefulness in many areas of chemistry and biochemistry such as molecular recognition, catalysis, transport and molecular devices. In a cryptand, the donor atom's topology can be varied through ligand design. The information thus stored in the form of three-dimensional disposition of donor atoms can be read out by a specific metal ion or a molecular guest. This phenomenon of molecular recognition has become a prominent field of research. It not only serves in the understanding of biological functions but also offers a key in the development of new types of functionalized materials. Cryptand-based amphiphiles can form organized molecular assemblies, incorporating metal ion/molecular recognition sites. Such systems are expected to have characteristics quite different from homogeneous media. They are expected to be useful in understanding biological membranes, in the development of novel two-dimensional molecular assemblies, in fabricating new generation molecular devices<sup>24</sup> etc. Furthermore, when a metal ion is included inside the cavity, the resulting charged cationic surfactant can have a spectrum of biological activity which includes antibacterial and immunosuppressing properties.

## Synthesis of cryptands and their derivatization

Since the first synthesis of cryptands by Lehn<sup>25</sup>, various procedures have been adopted to synthesize these molecules. Stepwise synthesis is one of the most commonly used methods and involves the generation of an inter-



mediate macrocycle followed by bridging with another chain to yield the macrobicyclic. However, more often than not the yields of the desired products are quite poor. The principal problem encountered during the synthesis has been the oligomerization of the reactants leading to lower yields. Besides, the desired products are often mixed with impurities from which the pure product cannot be isolated easily. We have adopted a new strategy<sup>26,27</sup> in synthesizing these molecules. The method involves coupling of two tripodal units by [1 + 1] Schiff base condensation which is the more direct route and involves the formation of three bonds in one pot synthesis. The logistics behind our synthetic approach has been to use a large alkali metal ion like  $\text{Rb}^+$  or  $\text{Cs}^+$  as a template (Scheme 1) where the two tripodal



Scheme 1. Synthetic strategy for the heteroditopic cryptands.

units can converge. The usual high-dilution condition is thus not necessary. Moreover, to expedite the condensation reaction, expecting that the side products will be minimized, the temperature of the medium was elevated to  $-40^\circ\text{C}$ . These reaction conditions lead to high yields of the desired cryptand in pure form. Subsequently, another strategy<sup>28-30</sup> has been adopted for the synthesis of these molecules that affords comparable yields. This strategy involves low temperature condensation (Scheme 1) of the two tripodal units under moderate dilution without using any templating metal ion. Following the lead by Smith and coworkers<sup>31</sup>, we have found that if the two tripodal units are allowed to react at  $5^\circ\text{C}$ , the reaction proceeds smoothly without a templating metal ion. However, the solvent system for the condensation reactions is quite crucial in that only a particular solvent system gives better yields. In our case, MeOH:THF (40:1 v/v) is found empirically to be the solvent of choice. This method works well with a number of different tripodal units. We believe that at low temperature, the tripodal units have significantly less movement of the tripods and can converge to give the product in high yields. The rate of Schiff base condensation reaction is not adversely affected due to lowering of the temperature. Figure 1 shows three X-ray crystallographically

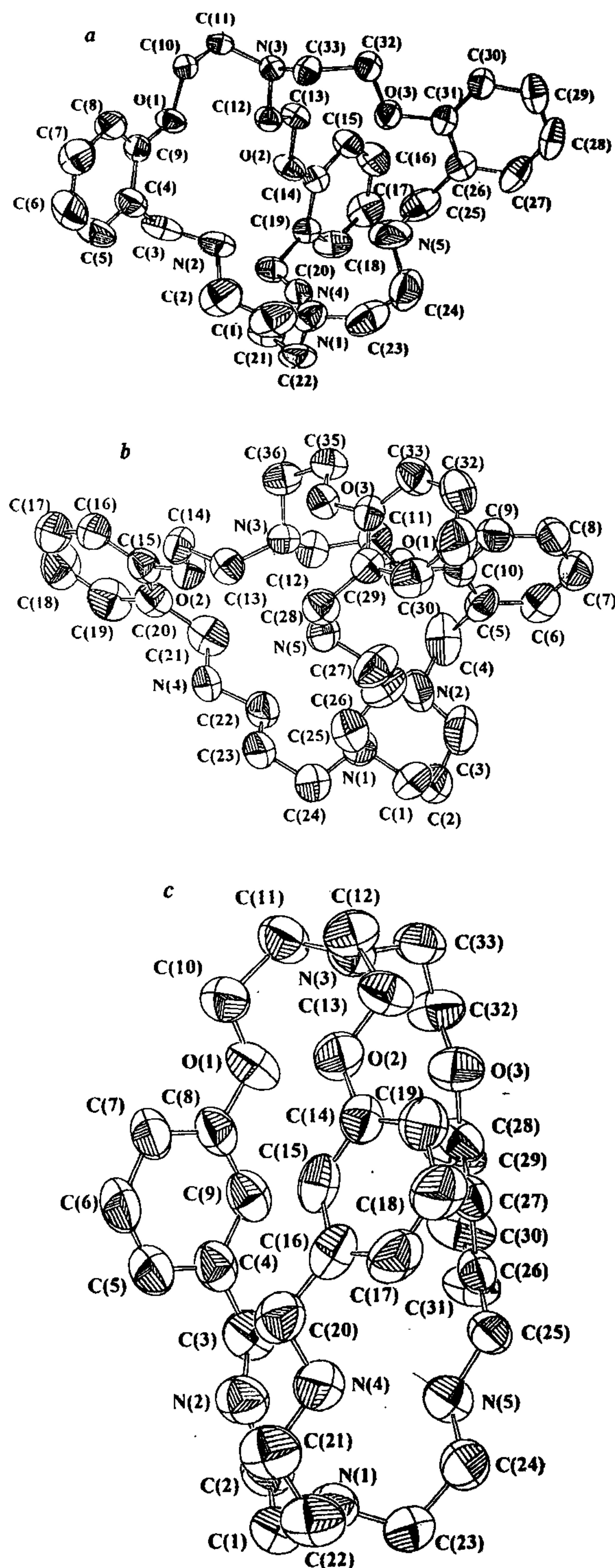


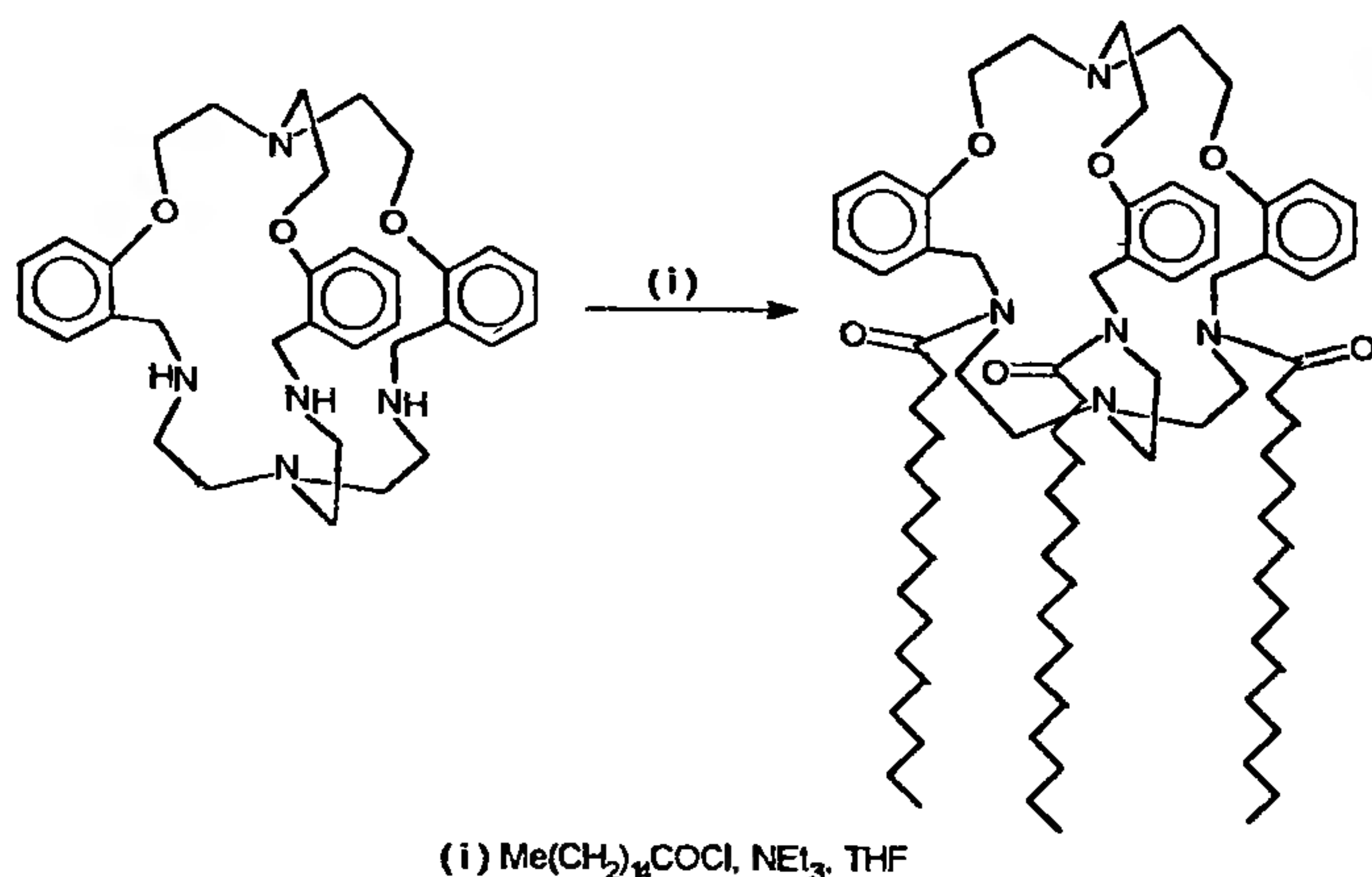
Figure 1 a-c. An ORTEP drawing of heteroditopic cryptands showing the thermal ellipsoids and the atomic numbering scheme. Hydrogen atoms are omitted for clarity.



characterized<sup>28-30</sup> cryptands, synthesized at low temperature in multi-gram scale quantities. This method has also been used successfully for the [2+3] condensation reactions<sup>32</sup> as well where two tripods and three spacer units are involved. When the two tripodal units have different sizes, they undergo [2+2] Schiff base condensation to generate macrotricycles<sup>33</sup>. However, it is now realized that not only the size mismatch but the conformational rigidity of the tripodal units is also important to drive the reaction to a particular product<sup>34</sup>. It is of relevance to mention here that low-temperature synthetic strategy is superior to that of the high-temperature one for multi-gram scale synthesis of the cryptands.

Each of the cryptands synthesized has at least three secondary amino groups in their framework which can be functionalized. To have amphiphiles<sup>35</sup>, each cryptand is treated with an acid chloride (Scheme 2) in 1:3

also readily forms vesicular structures<sup>35</sup>. Average diameter of the vesicles (Figure 2) ranges between 350 and 450 nm. Since the first report, a number of new amphiphiles have been found to be able to form vesicular structures. However, the stability of the structures depends upon the alkyl chain length<sup>36</sup>; the stability of



Scheme 2. Synthetic strategy for the amphiphile.

molar ratio in dry THF medium under an Argon blanket. The reaction goes cleanly and almost quantitatively. The <sup>1</sup>H-NMR spectra of the amphiphiles are consistent with their structures and the FAB-mass spectra exhibit the molecular ion peak (100%) in all cases. These cryptand-based triple-tailed triple-head amphiphiles represent a new generation of surfactants.

### Formation of vesicles by cryptand-based metal-free or complexed amphiphiles

We have reported that a cryptand based triple-head triple-tailed amphiphile, where the alkyl chain has fifteen carbon atoms, readily forms stable vesicles<sup>35</sup>. When copper(II) perchlorate hexahydrate salt is added to a methanolic solution of the amphiphile, the Cu(II) complex is formed. The coordination of Cu(II) within the cryptand cavity can be established by its EPR and electronic spectral signatures. The amphiphile with Cu(II) inside

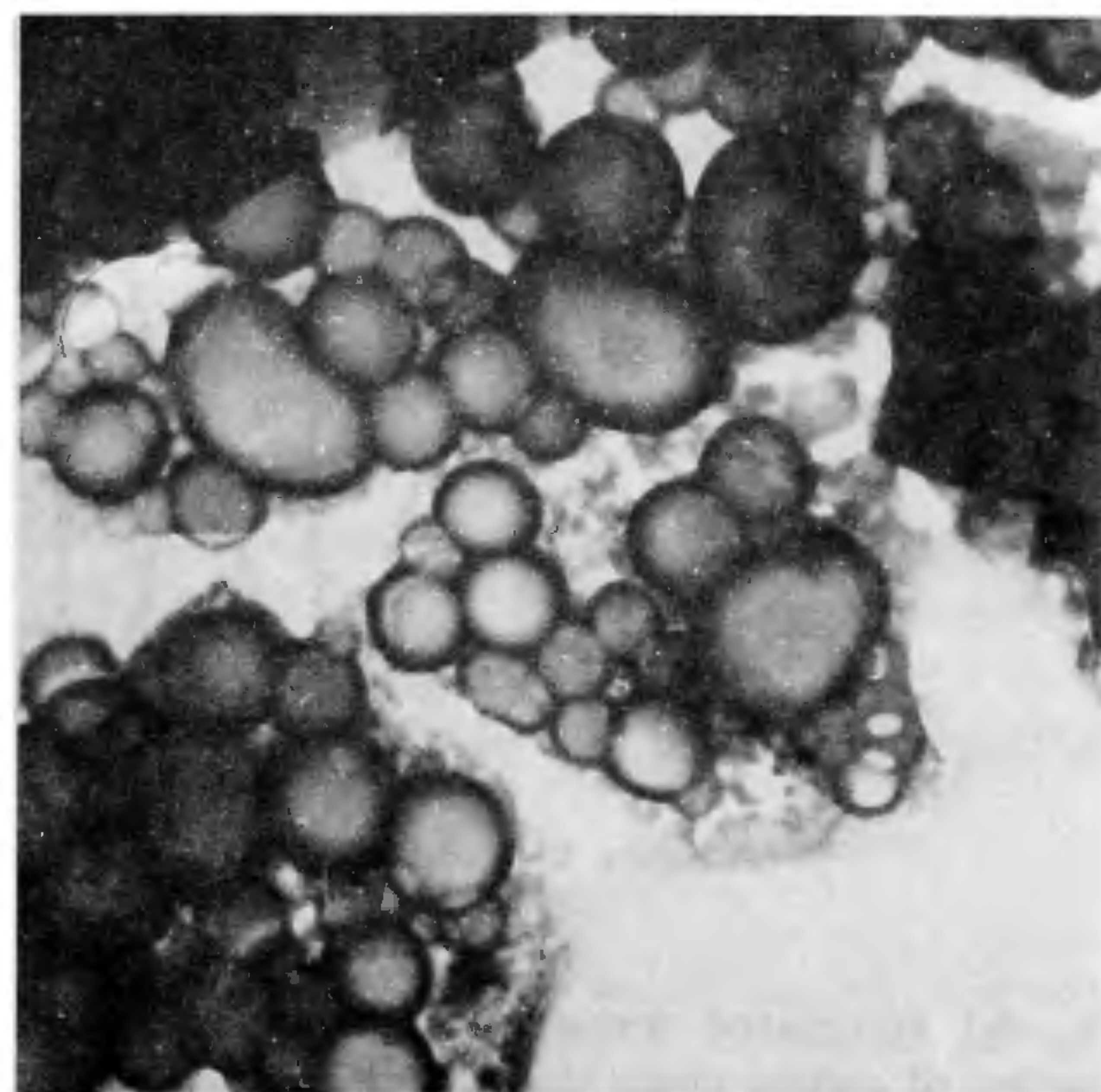


Figure 2. Negative-stain transmission electron micrographs of vesicles of a new generation amphiphiles ( $\times 20000$ ).

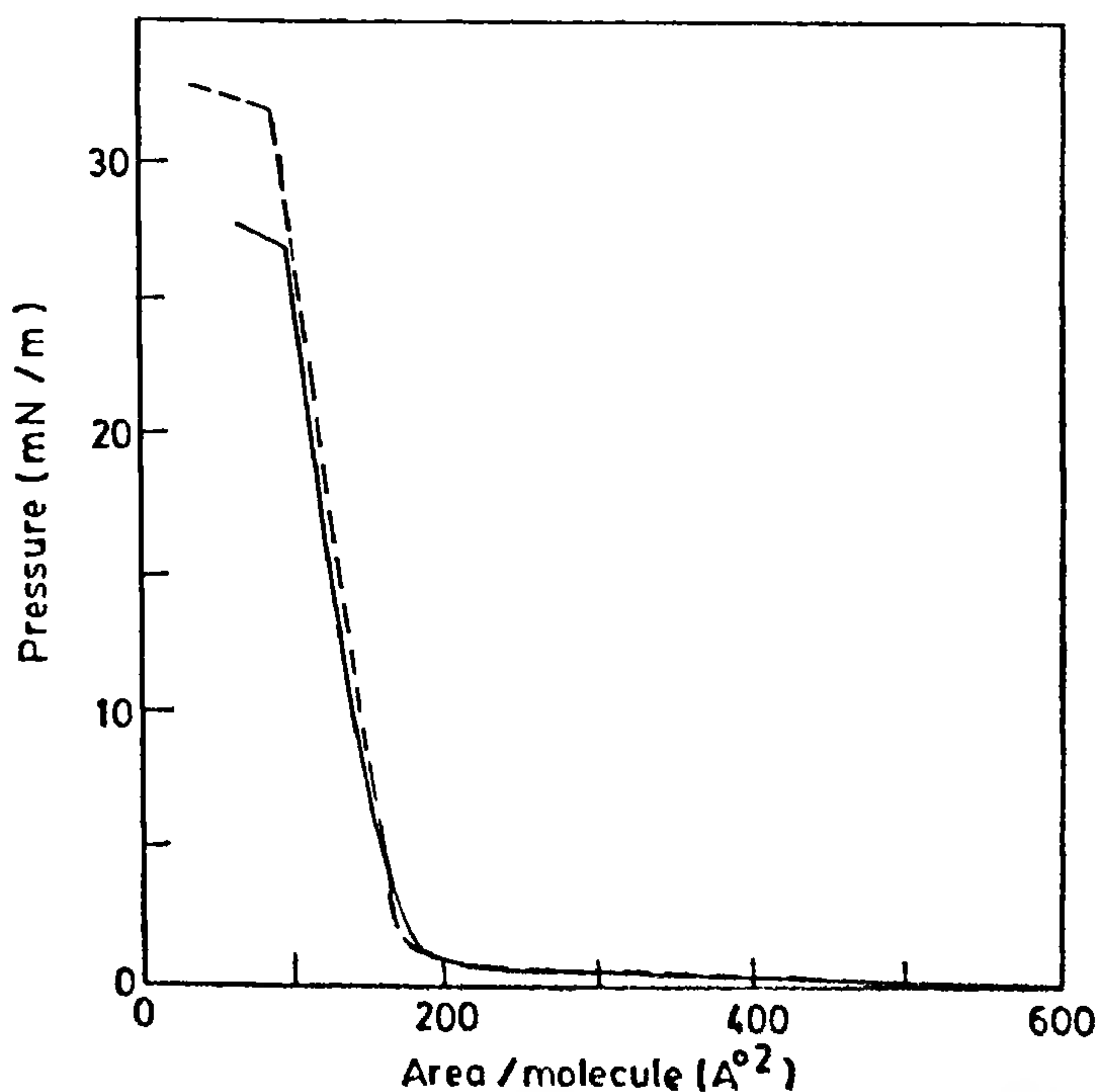


Figure 3. Pressure-area ( $\Pi$ -A) isotherm of a metal free amphiphile (solid line) and complexed amphiphile (broken line), at 298 K.



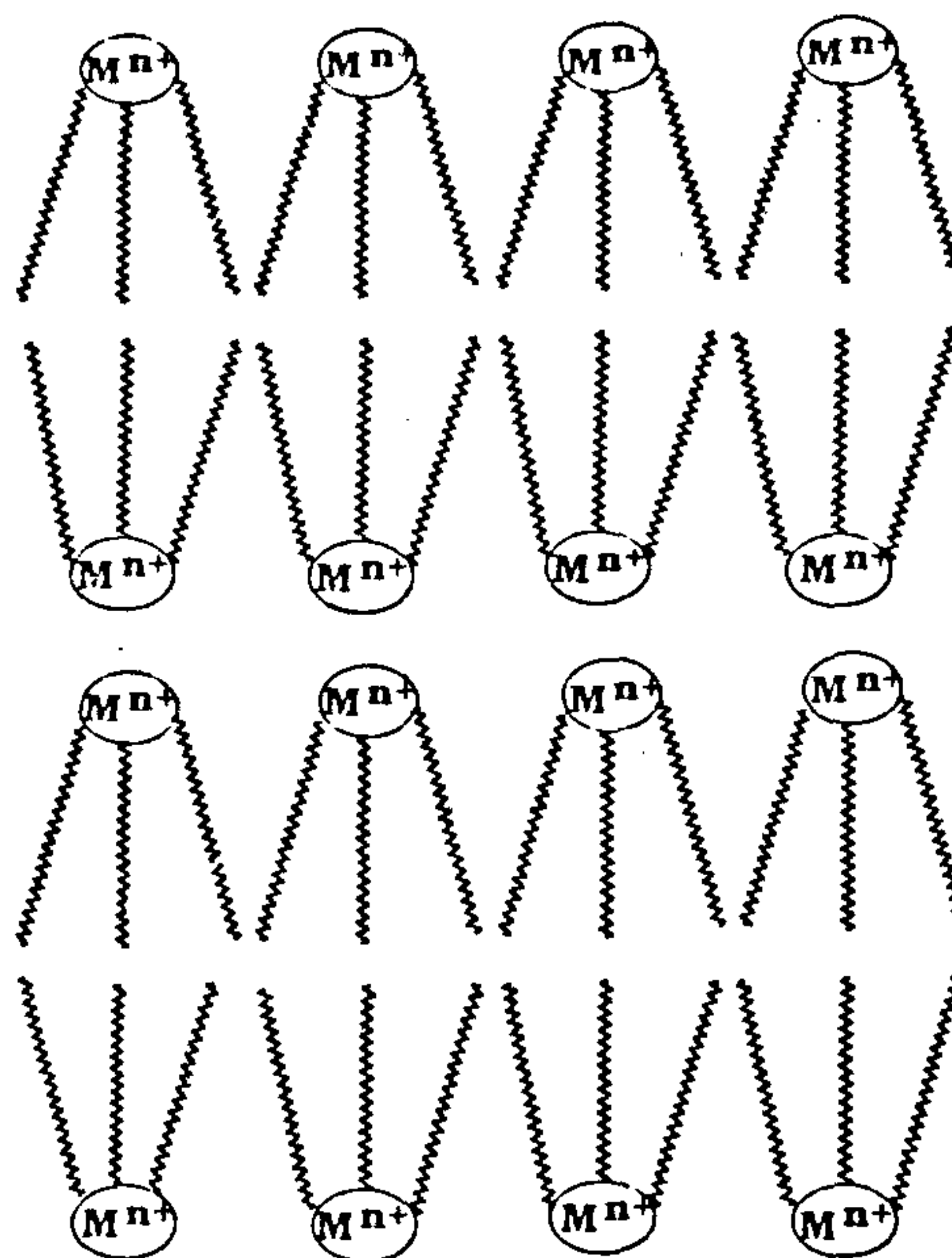


Figure 4. An illustration of a multilayer LB-film with metal ions included in the cavities.

free and complexed amphiphiles decreases with the lowering of carbon chain length. No correlation can be made, however, regarding the vesicular size and alkyl chain lengths from the electron micrographs.

### Formation of monolayer by cryptand-based metal-free or complexed amphiphiles

It is of interest to see whether cryptand-based amphiphiles can form stable monolayers at the air-water interface. When probed with the tris-palmitoyl derivative<sup>35</sup> of the cryptand as illustrated in Scheme 2, in a Langmuir trough at 298 K, a well-defined isotherm<sup>37</sup> (Figure 3) is obtained. Subsequently, a number of amphiphiles with varying chain lengths as free or metal complexed are found to exhibit isotherm as in Figure 3. The stability of the films are found to be dependent on the length of the alkyl chain. As the chain length increases, the monolayer becomes more stable whether free- or metal-complexed. However, it was not possible to transfer any of the monolayer films by vertical dipping onto a variety of substrates, e.g. glass, polycrystalline Pt or Au, glassy carbon, etc.

### Conclusion and future scope

It is now realized that cryptand-based amphiphiles form stable vesicular structures as free- or as metal-complexed

states. It is to be probed whether they can form vesicular structures spontaneously. This would be an important study as suitably designed cryptand-based amphiphiles can be potentially useful in catalysis and in charge separation to harvest solar energy. Preliminary studies in our laboratory show that the metallo-amphiphiles can cause death to certain parasites and ultimate disintegration of their cell-wall. A likely mechanism<sup>22</sup> for this type of effect is the destabilization of the tegumental membrane bilayer due to detergent action of metallo-amphiphiles.

The propensity with which these amphiphiles form Langmuir monolayers can be made use of to have new materials. If it is possible to get stable LB-films with paramagnetic metal ion(s) inside the cavity, it will lead to a structure where we can have two-dimensional paramagnetic layer followed by diamagnetic spacers (Figure 4). Such magnetically anisotropic systems are of enormous importance in materials research. Some of these potential uses of cryptand-based amphiphiles are being probed in our laboratory.

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