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Amphiphiles I have known

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Abstract

This paper depicts twenty-five amphiphilic systems synthesized in our laboratory while reviewing the essential properties of ten of them. ***To cite this article: F. M. Menger, C. R. Chimie 12 (2009).***

Résumé

Cet article décrit vingt-cinq systèmes amphiphiles synthétisés dans notre laboratoire et reprend les propriétés majeures de dix d'entre eux. ***Pour citer cet article : F. M. Menger, C. R. Chimie 12 (2009).***

Keywords: Amphiphile; Micelle; Solubilization; Phase; Vesicle; Adhesion; Catalysis

Mots-clés : Amphiphile ; Micelle ; Solubilisation ; Phase ; Vésicules ; Adhésion ; Catalyse

"I am among those who think that science has great beauty" (a quote from Marie Curie to be followed by quotes from other great French intellectuals in tribute to Pierre-Gilles de Gennes who is commemorated in this issue). In concert with this sentiment, I regard amphiphiles, such as those listed in Scheme 1 [1–29], as quite beautiful. Amphiphiles refer to molecules that possess both polar and non-polar sections. There is no space here to describe the various reasons for our synthesizing all the amphiphiles in the scheme, but I will do so for a few of them. For the moment I only ask the reader to gaze at the scheme and reflect on the rich, almost limitless, array of structures available to the organic chemist. Although one might agree with Le Corbusier that "The greatest architect was the builder of the Dolomites", chemists have also been endowed by Nature with remarkable building skills, if on a more modest scale. No doubt the freedom of scientists to construct objects of their curiosity provides the profession with one of its greatest joys. As Jean Gabin said "Vive la liberté, surtout la mienne."

Compound **1** in Scheme 1 was important in developing our overall concept of micelles [1]. Micelles are roughly spherical structures containing about 50–100 single-chained amphiphiles (commonly called "surfactants" because they lower the surface tension of water). At the time of this work, most texts pictured micelles as having linear chains, arranged like the spokes of a wagon wheel, in what was termed the "Hartley model". The model was unproven but widely

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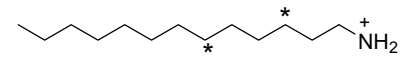

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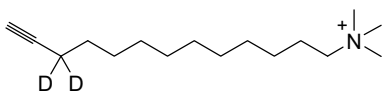

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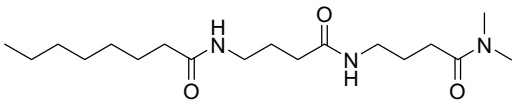

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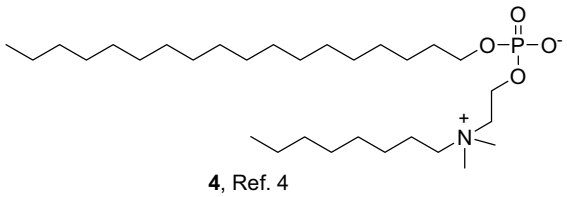

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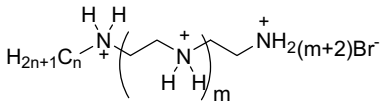

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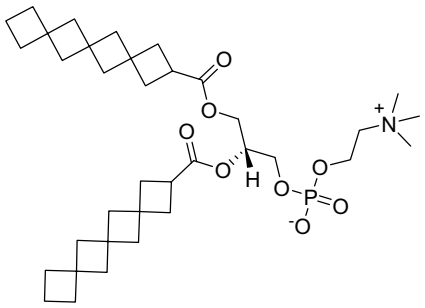

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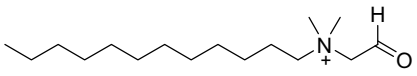

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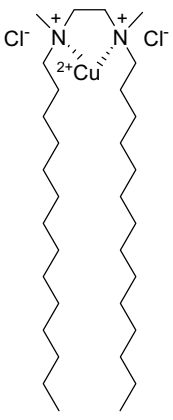

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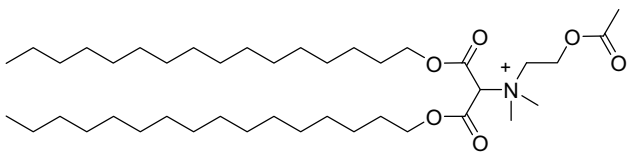

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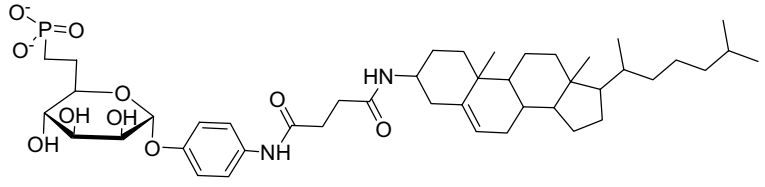
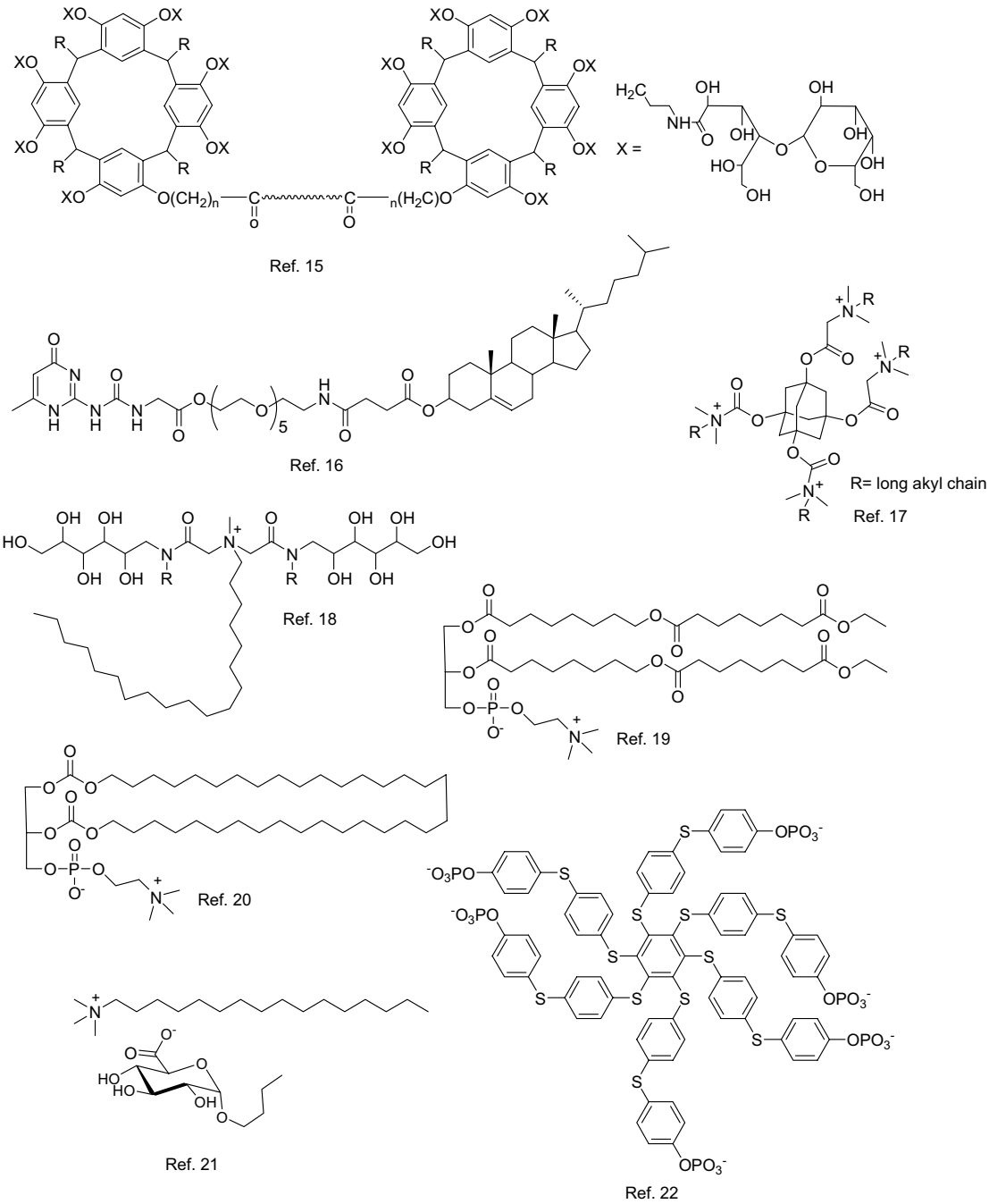


10, Ref. 14

Scheme 1.

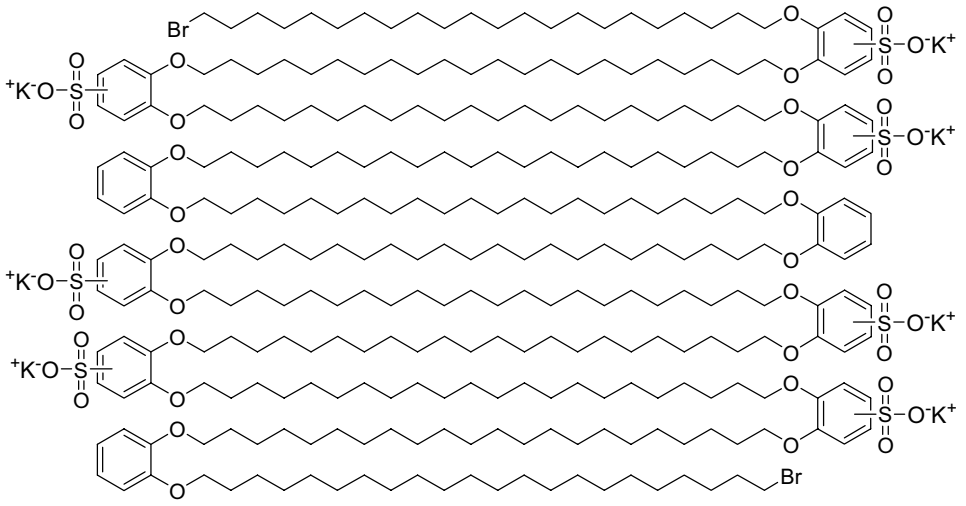
accepted. As Pierre Lecomte du Noüy said, ‘‘Whenever there is no objective confirmation, our attitude toward certain theories depends, in the last resort, on aesthetic considerations, disturbing as this may seem’’. In the case of micelles, ‘‘aesthetic considerations’’ seemingly refer to the Hartley model’s appealing, easy-to-draw radial symmetry. To test the model, we endowed compound **1** with two C-13 atoms placed four carbons apart (at various locations along the chain, only one of which is shown in Scheme 1 [1]). The dihedral angle between the isotopic carbons, obtained from the C-13/C-13 long-range NMR splitting, proved



Scheme 1 (*continued*).

that the chains are highly bent. Thus, ''objective confirmation'' was provided that chains within a micelle, engaged in a brush-heap of disorganization, are not as ''aesthetic'' as originally assumed.

Jean-Baptiste Dumas said, ''A theory established with the help of twenty facts must explain thirty, and lead to the discovery of ten more.'' In concert with this philosophy, and with our ^{13}C NMR results in mind, we were able to explain both kinetic and spectroscopic properties of chain termini that are situated within micellar aggregates. For example, the terminal triple bond of micellized compound **2** in Scheme 1 displays an ^{1}H-chemical shift of 2.2 ppm, consistent with a polar medium but far downfield from 1.6 to 1.8 ppm



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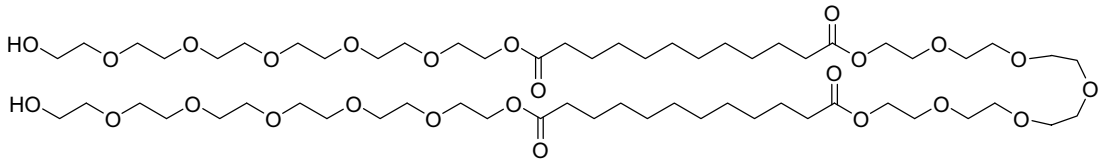

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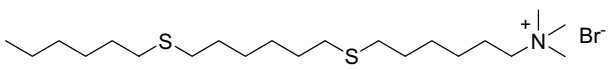

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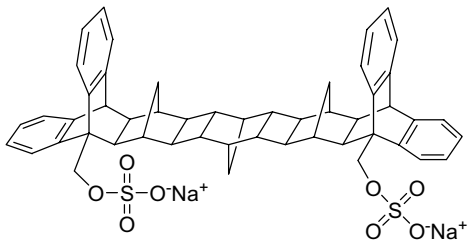

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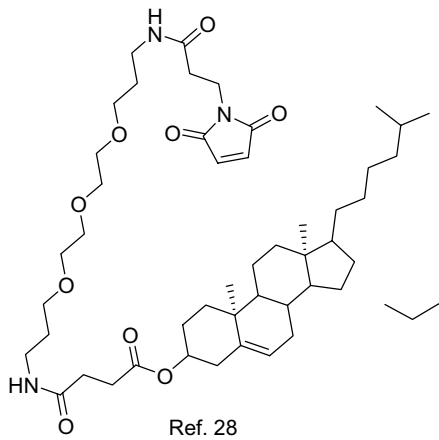

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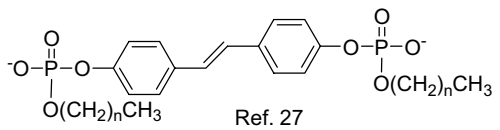

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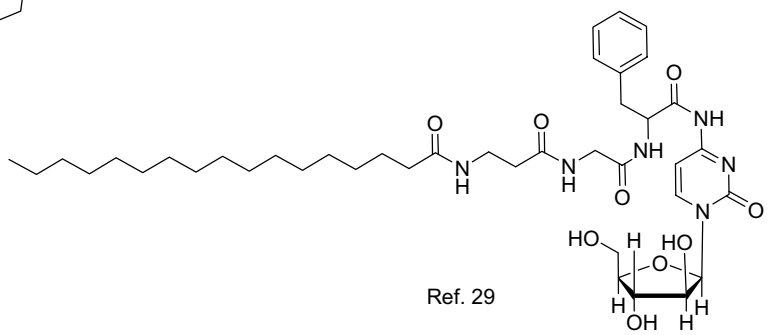

Ref. 29

Scheme 1 (*continued*).

expected for a hydrocarbon environment [2]. This is best explained by chain bending within the micelles so as to transiently expose the chain termini to external water.

C. Bachelard in his ''La Formation de l'Esprit Scientifique'' (an activity in which de Gennes excelled throughout his career) wrote the following: ''Le monde de la Science est beau avant d'être vrai. Ce monde est admiré avant d'être vérifié.'' As applied to amphiphiles, it might be mentioned that soaps have been used, and I presume appreciated if not admired, centuries before micelles were ever shown to exist. One important amphiphile property, which is still not fully understood, relates to an ability to solubilize compounds, including drugs, into water. Consider paclitaxel (Taxol), a widely used but highly water-insoluble anti-cancer drug (Fig. 1). This drug is administered to patients after it is first solubilized into water using a commercial amphiphilic material prepared from caster oil. Unfortunately, the additive itself has caused all sorts of health problems. We have found that compound **3** in Scheme 1, consisting of a long hydrocarbon chain joined to three hydrophilic amide groups (called a ''peptoad''), effectively solubilizes Taxol in water [3]. The question arose as to how the peptoad accomplishes this feat, and to answer the question we resorted to molecular dynamics calculations described in the next paragraph.

Peptoads in water were shown to form ''clumps'' of about 97 molecules with amide groups residing on the external surface and with the chains projecting inwardly toward the center. During the assembly process, the amide groups engage in intermolecular hydrogen bonding, ultimately reaching equilibrium in 2 ns. The interior of the assemblies is water-free. When Taxol is solubilized into the interior of a clump, 2–6 peptoad molecules hydrogen-bond to sites on the Taxol, thereby encasing the drug in a mobile sheath of hydrocarbon chains. These chains are compatible with the hydrophobic clump interior, and they serve to retain the drug within the clump, i.e. to solubilize the drug. Since this mechanism for Taxol solubilization may not necessarily apply to other drugs, each drug must be investigated on a case-by-case basis. We take seriously the words of A. Dumas, fils, who said ''All generalizations are dangerous…even this one.''

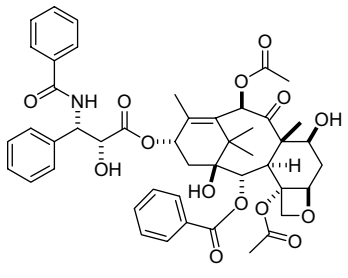

Fig. 1. Structure of paclitaxel (Taxol).

I suppose that every scientist at some time or the other is sympathetic to the words of Coluche: ''I understand nothing, but I speak about everything; this is what counts''. I feel this way about those triangular phase diagrams, sometimes encompassing a dozen or more distinct regions, that have been constructed for amphiphilic compounds in aqueous systems. Although complicated and unpredictable interconversions among a host of morphologically different phases may not be fully understood, this did not stop us from expounding on phase changes in a study of zwitterionic gemini surfactants such as compound **4** in Scheme 1 [4]. Owing to our proclivity for making new compounds, we had on hand 42 such surfactants whose chains varied between 6 and 18 carbons for both the P and N sides of the molecules. This allowed us to study phase-state as a function of structure for an unusually large family of surfactants, and thus to construct a ''structural phase diagram'' with 42 points. Long-long geminis (e.g. 14,16) formed vesicles; short-short geminis (e.g. 8,8) formed micelles; long-short or short-long geminis (e.g. 18,8 or 8,18) formed gels; and (most interesting) geminis of intermediate length (e.g. 8,10 or 10,10) formed an esoteric phase called a coacervate (i.e. a phase that is water-immiscible despite being composed of more than 90% water). Subsequent cryo-high-resolution-scanning-electron-microscopy on a coacervate particle showed a porous structure resembling the honeycomb of bees [5]. Owing to walled cells enclosing small regions of water, the coacervate is no more soluble in water than is a water-saturated sponge.

Lavoisier wrote, ''When we begin the study of any science, we are in a situation, respecting that science, similar to that of children''. How true! Just as children build a sand castle with no clear plan in mind, we had no particular expectations as we synthesized compound **5** in Scheme 1 with its ''hyperextended'' chain fully 35 carbons in length [6]. Along the way we discovered that 3–5 ammonium groups are required to render such a long-chained compound soluble in water. And the amphiphile assembles into vesicles as opposed to micelles normally expected for single-chained surfactants. Apparently, the long chain folds back on itself, like a hairpin, and then self-assembles into a bilayer. Similarly, the spiro-phospholipid, compound **6** in Scheme 1, was made with a child-like curiosity as to

the thermotropic behavior of a lipid whose chains are totally rigidified [7]. It turned out that the gel-to-liquid-crystal transition temperature of the spiro-phospholipid was too high to measure in our calorimeter…the ultimate in ''saturated fat''.

Upon reading Rousseau's poem entitled ''To Posterity'', Voltaire wrote, ''This poem will never reach its destination.'' There is no fear that the science of Pierre-Gilles de Gennes will be forgotten by posterity! Although scientists may wish for everlasting impact, a more earthly (and reliable) reward comes from the pleasure of a successful experiment such as carried out with compound **7** in Scheme 1 [8]. Compound **7** forms micelles with its aldehyde group hydrated into a $RCH(OH)_2$ functionality. When a hydrophobic ester substrate binds to the micelle, one of the two hydroxyls of the aldehyde-hydrate becomes acylated. Thereupon the second hydroxyl participates in the elimination of a carboxylate so as to regenerate the aldehyde. After the aldehyde spontaneously rehydrates, the catalytic mechanism can begin all over again. In other words, compound **7** serves as an ''esterse'' model with enzyme-like turnover capabilities. A subsequent study of compound **8** in Scheme 1 found that the amphiphile forms a ''metallomicelle'' that can hydrolyze phosphate esters with a 10^5 rate enhancement [9].

Compound **9** in Scheme 1 illustrates our interest in developing an enzyme-triggered liposomal drug-release mechanism [10]. Thus, the goal was to design liposomes that are destroyed by a specific enzyme, causing the release of the liposome contents. Since compound **9** possesses two long chains, it forms liposomes upon sonication in water. These liposomes are stable until they are exposed to acetylcholine esterase. The enzyme hydrolyzes the acetate ester, producing a terminal hydroxyl that, in turn, rapidly forms a 6-membered lactone ring by reacting intramolecularly with one of the remaining ester groups. The combination of enzymatic and organic reactions serves to eliminate one of the amphiphile's two 16-carbon chains. But a single-chained amphiphile forms micelles, not liposomes, so that the liposome disintegrates and releases its contents as per our original objective.

The preceding paragraph brings up (somewhat peripherally to our amphiphile chemistry) a long-standing side-interest in the theory of enzyme catalysis. Certain past attempts to explain the source of 10^8–10^{10} enzymatic rate accelerations are reminiscent of Proust's incisive comment: ''People regard as clear that which measures up to the degree of confusion they are used to.'' For example, there is an important school of thought advocating favorable entropic effects as the main source of enzyme catalysis. But entropic effects in enzyme chemistry are an intractable mixture of changes in solvation, conformation, translation, etc. Indeed, even the definition of an ''entropy of an active site'' is not at all obvious. Valid or not, the entropy theory of enzyme action is devoid of information at the molecular level, predictive value, and falsifiability. Imposition of short distances (obvious in most X-ray pictures of enzyme/inhibitor complexes) is much preferred by us as the key factor in explaining the speed of enzymatic reactions [11]. Our own organic models (including micellar systems) along with theoretical computations all point in that direction [12]. Although our ''spatio-temporal model'' (or a subsequently proposed mechanistic offshoot [13]) has not been universally adopted, we are nonetheless comfortable with its basic tenets. The fact of the matter is that enzyme action still remains today a difficult and unresolved problem reflecting the words of Claude Bernard: ''The science of life is a superb and dazzling lighted hall which may be reached only by passing through a long and ghastly kitchen''.

Returning to the matter of amphiphiles, it is especially appropriate here, in an issue commemorating French science, to describe compound **10** in Scheme 1 that was synthesized in my department by Dr. Veronique Barragan, now on the faculty of the University of Montpellier [14]. Compound **10** consists of a steroidal unit coupled to a mannose phosphonate. The hydrophobic steroid can bind to a liposome's bilayer, whereas the mannose phosphonate can bind to a receptor for this sugar that happens to be over-expressed in breast cancer cells. There exists, therefore, the medically important potential of using the mannose phosphonate to specifically link a particular cancer cell to a liposome containing an anti-cancer drug. Evidence for such cell/liposome adhesion is two-fold: (a) When a giant liposome (visible under the microscope) containing a few percent of compound **10** is brought into contact with a breast cancer cell, the liposome cannot be easily pulled away from the cell with a micropipet. This ''stickiness'' was not observed in the absence of compound **10**. (b) Submicroscopic fluorescent liposomes will bind to the cancer cells and cause them to fluoresce, but only if compound **10** is present within the liposome bilayers as an adhesive.

Anatole France wrote the following: ''Do not try to satisfy your vanity by teaching a great many things. Awaken people's curiosity. It is enough to open minds; do not overload them. Put there just a spark. If there is some good inflammable stuff, it will catch fire''. And Voltaire wrote: ''The secret of being tiresome is to tell

everything''. Time for me to stop! Details of the compounds of Scheme 1 not discussed herein can be found in the cited references.

Since I began with a quote from Madame Curie, I will end with one as well: ''It is hard to think that after so many centuries of development, the human race still doesn't know how to resolve difficulties in any way except by violence.''

Acknowledgment

Jean Cocteau wrote: ''As a young man, I was forever being told, 'One day you will see.' I am fifty years old, and I have yet to see a thing.'' Although I commiserate with the sentiment, I do see one thing clearly: I owe an incalculable debt to the many fine students who synthesized and studied the amphiphiles in Scheme 1 as well as many other compounds not mentioned here.

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