change of rate at low anodic potentials where Faradaic currents are negligible. At higher anodic potential there is a rise in rate caused by an increased adsorption of chloride accompanied by formation of the ion paired quaternary chloride. On the cathodic side there is also a rise which can be attributed to direct adsorption of the quaternary cation. Similar results have been obtained in other types of experiments.[11,12]

Acknowledgment. We thank the Robert A. Welch Foundation of Houston for their financial support of this work.

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Hexapus, a New Complexing Agent for Organic Molecules

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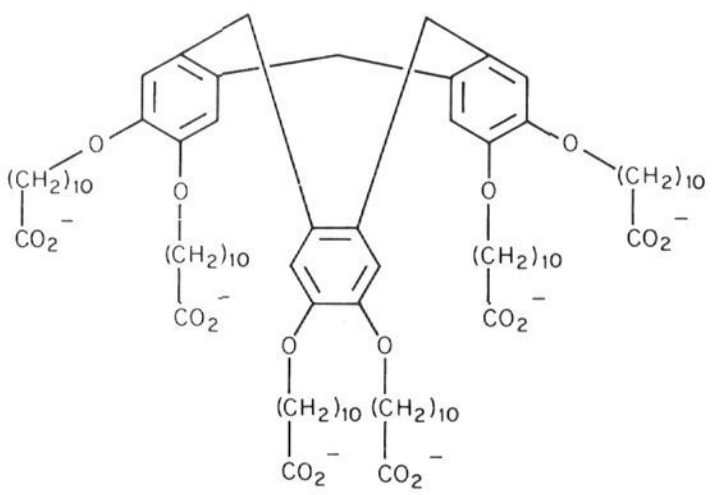
Received June 8, 1981

Enzymes function by assembling their catalytic groups and substrates in "cavities" or "grooves" located on the protein surface; proper orientation of the reactive functionalities within the small volumes of space greatly accelerates reaction rates. In an attempt to model enzyme action, chemists are synthesizing cavity-bearing compounds such as cyclodextrins,[1-3] crown ethers,[4-6] crosslinked polymers,[7,8] macrocycles,[9] and "tweezer" molecules.[10,11] We now report a new kind of space-encompassing compound, the hexa-10-carboxydecyl ether of 10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]-cyclononene-2,3,7,8,12,13-hexol, called "hexapus".[12] Six chains,



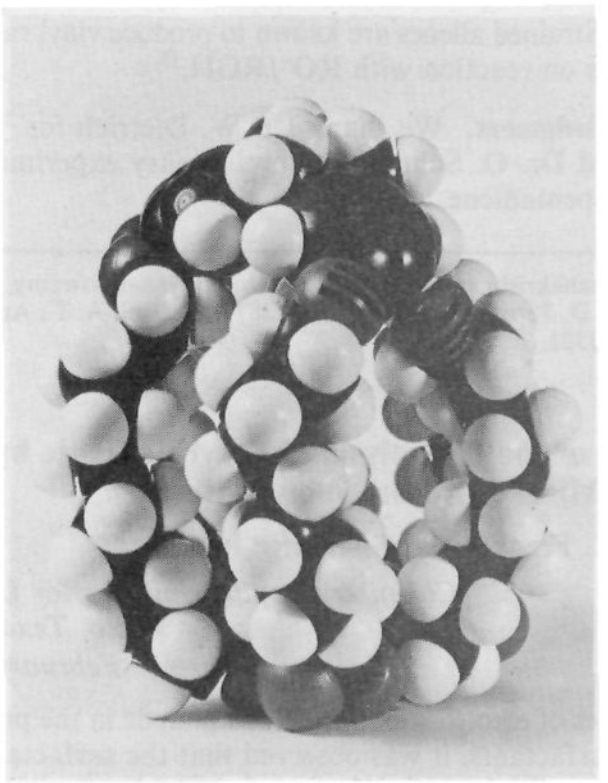


Figure 1. CPK model of hexapus having its six hydrophobic chains associated to minimize hydrocarbon–water contact.

projecting from a crescent-like cyclotriveratrylene framework, terminate with carboxylate groups that solubilize the compound in mildly basic water (solubility > 60 g/L or 0.04 M at pH 8.6, 25 °C). Hydrophobic association can gather together the six chains and create an adjustable "cavity" capable of incorporating small organic molecules (Figure 1). Hexapus thus resembles a micelle except that its six chains are covalently linked and prevented from participting in complex departure–entry equilibria found in micellar aggregates.[13]

Hexapus was synthesized by first reacting veratrole and formaldehyde in aq. HCl to form cyclotriveratrylene. This was demethylated with BBr_3 according to a literature procedure.[14] The resulting hexahydroxy compound (5.0 g, 0.014 mol) in DMF under N_2 was converted into its salt with NaH (2.5 g, 0.10 mol); the salt was then heated with ethyl 11-bromoundecanoate (33 g, 0.11 mol) at 90–100 °C for 3 h and 70 °C for 16 h. Removal of the solvent under reduced pressure, addition of CH_2Cl_2, filtration through Celite, and flash evaporation of the filtrate gave hexaester which was purified by column chromatography (SilicAR CC-7 Special/heptane–benzene eluant). Purified material (a light yellow syrup) weighed 10.6 g (46%). Hexaester (10.6 g, 0.0065 mol) in 50 mL of THF was added to 50 mL of 30% aqueous NaOH and boiled under reflux for 18 h. Standard workup produced yellowish crystals that were crystallized once from ether/benzene and four times from ether/hexane to yield 4.2 g (44%) of hexapus (colorless crystals, mp 99–100 °C). Structure proof consisted of the usual spectral and chemical analyses. In particular, the ^{13}C NMR spectrum showed only three aromatic carbons (two quaternary and one tertiary); the neutral equivalent was 245 (calc. 245); a correct molecular weight was obtained by field desorption mass spectrometry.[15] Thus the key alkylation step provides a satisfactory yield of product free from impurities with fewer than six chains.

Hexapus exhibits much less surface activity than single-chained fatty acid salts. Solutions do not foam even at 0.02 M hexapus. The surface tension of water mainfests a constant 61.0 ± 0.4 dyn/cm (pH 9.5 at 24 °C) in the presence of 4.0×10^{-4} – 1.0×10^{-2} M hexapus. In contrast, 1.0×10^{-2} M potassium laurate at pH 10.0 lowers the surface tension of water to 34 dyn/cm[16] Apparently, the tendency of hexapus to absorb at the air–water

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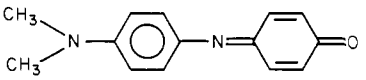
interface is impaired by the difficulty of placing above the water phase *both* the hydrocarbon portion of the tails and the aromatic "cap". Hexapus and fatty acids are similar, on the other hand, in that they aggregate in aqueous solutions as shown by light scattering experiments.[17] A plot of Rayleigh ratios for a 90° scattering vs. hexapus concentration ($4.1 \times 10^{-4} - 1.0 \times 10^{-2}$ M at pH 9.5) curves downward and corresponds (when coupled with differential refractometry data) to an aggregation number of 9 ± 1. Since there are 6 chains per hexapus, each aggregate contains 54 chains which equals, perhaps coincidentally, a typical aggregation number for a single-chained surfactant. The Rayleigh plot shows no break indicative of a CMC; thus if hexapus has a CMC, it must be smaller than 4×10^{-4} M. This point was investigated further by using pinacyanol chloride as a spectrophotometric probe for aggregation; the dye is known to change from pink to blue in the presence of anionic mielles. We found that the absorbance of 5.5×10^{-6} M dye at 610 nm remains essentially constant from 1.6×10^{-5} to 1.0×10^{-2} M hexapus at pH 9.5. Below 1.0×10^{-5} M hexapus, where its concentration approximates that of the probe, the absorbance decreases precipitously. It can be concluded that the CMC of hexapus, if one exists, must be less than 1×10^{-5} M (compared to 1×10^{-2} M for a 12-carbon surfactant).

Addition of 0.010 M hexapus to an aqueous solution of 4.2×10^{-5} M phenol blue (pH 9.50) induces a 67% hyperchromic shift in the visible spectrum as well as a peak narrowing. From



absorptivity vs. [hexapus] data plus the Ketelaar equation,[18] we calculated an association constant of 1.0×10^4 M^{-1} between phenol blue and hexapus. Since phenol blue has a solvent-sensitive λ_{max} (e.g., 575, 605, and 658 in benzene, ethanol, and water),[19] we could also assess the environment of the dye when fully bound to hexapus (or hexapus aggregates). This environment is highly polar (λ_{max} = 657 mm in 0.010 M hexapus), suggesting that water is plentiful at the host–guest binding sites.

An aqueous hexapus solution (0.011 M, pH 9.50) was sonicated with excess naphthalene at 55 °C, cooled, filtered through UF sintered glass, and spectrophotometrically assayed for naphthalene (λ = 312 nm, ϵ 136). It was found that hexapus solubilizes 1 naphthalene for every 2.5 hexapus molecules. Almost 40% ethanol is required to achieve an equivalent concentration of naphthalene in water without hexapus. A similar experiment showed that hexapus binds *p*-nitroaniline with 1:1 stoichiometry. Hexapus (0.010 M) also enhances the solubility of cholesterol in water although to a relatively small extent (3×10^{-4} M). Finally, hexapus binds *p*-nitrophenyl butyrate and inhibits its base-catalyzed hydrolysis. For example, the observed rate constant decreases from 20.1×10^{-3} to 1.86×10^{-3} min^{-1} when 0.0106 M hexapus is added to a borate buffer (pH 9.50, 25.0 °C). Inclusion of the ester among the carboxylate-terminated chains protects the ester from hydroxide attack. Rate data from several hexapus concentrations (treated by means a scheme commonly applied to micellar kinetics of simple surfactants[20]) yielded an association constant of 9.9×10^3 M^{-1} for the ester. This compares with, for example, a K_{assoc} = 2.9×10^2 M^{-1} for complexation of *m*-chlorophenyl acetate with β-cyclodextrin[2].

In summary, hexapus was found to be an effective new complexing agent for a variety of organic molecules. The nonspecificity no doubt relates to the flexible nature of the six chains. In the future we plan to convert the terminal carboxylates into catalytically active groups and thus create an enzyme simulant; the anticipated universal binding will be both an advantage and disadvantage. Future work will also center on locating the binding sites of hexapus. At present we do not know whether guests associate near the carboxylates or near the aromatic cap; nor do we know whether the binding takes place inside the hexapus cavity or external to the cavity but within the aggregate. Nonetheless, the hexapus system seems in concert with Lord Todd's recent dictum that "the organic chemist must turn his attention seriously to the study of large molecules where conformations or, if you will, tertiary structures can be adopted which permit the specific inclusion of other smaller molecules which can then react with one another".[21]

Acknowledgment. We are grateful to the National Science Foundation, the National Institutes of Health, and the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

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Chemical Model Studies for the Mechanism of Vitamin K Epoxide Reductase

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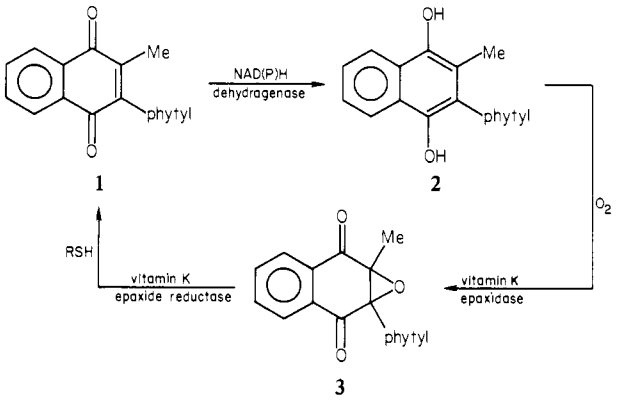
Received June 5, 1981

Vitamin K (**1**), which is essential for blood coagulation,[1] is converted into vitamin K 2,3-epoxide (**3**) by a coupled two-enzyme system. NADPH dehydrogenase catalyzes the reduction of vitamin K to its hydroquinone (**2**),[2] and vitamin K epoxidase catalyzes the monooxygenation of **2** to give **3**.[3] The epoxide of



vitamin K is not active in coagulation but is readily converted back to vitamin K by the enzyme vitamin K epoxide reductase[4] in a reaction which has been shown to require exogenous thiols in vitro.[5] It has been found that NADPH cannot be substituted for thiol.[5] Compounds that inhibit this reductase possess anticoagulant activity.[6] Recently I proposed[7] a molecular mechanism for this enzyme which is shown in Scheme I. Results of chemical model studies supporting that mechanistic proposal are communicated here.

The mechanism shown in Scheme I depicts *simultaneous* acid and base catalysis. While such a process is reasonable for an

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