

SELECTIVE IONOPHORIC PROPERTIES OF ANACARDIC ACID

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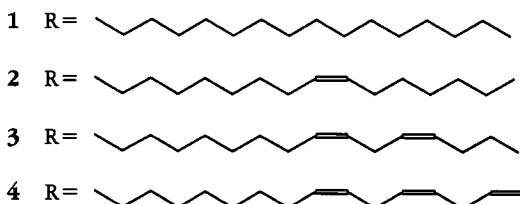
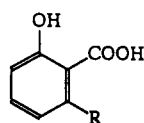
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ABSTRACT.—Anacardic acid, **1**, has been shown to form lipophilic metal derivatives with an unusually high degree of selectivity. Anacardic acid-metal derivatives in ratios of both 1:1 and 2:1 have been prepared and characterized. The order among the first row of transition metals is: $\text{Fe}^{2+} > \text{Cu}^{2+} > \text{Zn}^{2+} > \text{Ni}^{2+} = \text{Co}^{2+} = \text{Mn}^{2+}$ for the 2:1 derivatives.

Lipophilic or organic solvent-soluble metal derivatives have a variety of applications in such diverse fields as hydrometallurgy, medicine, and synthetic organic chemistry. Metal salts and complexes with long lipophilic chains have recently attracted attention due, in part, to their propensity to form molecular laminates (1) and other organized structures (2). Naturally occurring ionophores are of particular interest in view of their possible role in metabolic processes of the organism, as well as in antibiotic activity against other organisms (3). Most of the selective ionophores are either cyclic compounds with appropriate cavities (e.g., valinomycin) or those capable of forming such cavities in the presence of the cation (e.g., lasalocid, see below). We now report our finding that anacardic acid (2-hydroxy-6-pentadecylbenzoic acid) [**1**], which is a salicylic acid derivative with a linear 15-carbon alkyl chain, forms highly lipophilic metal derivatives with interesting selectivity.

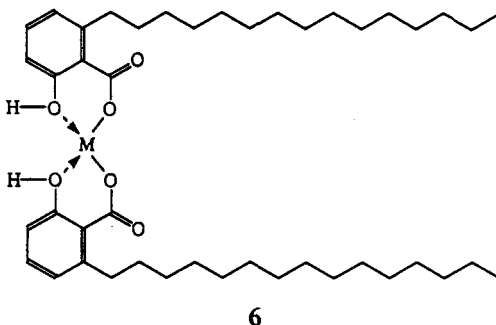
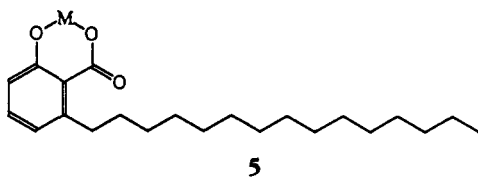
Anacardic acid [**1**] is the product of hydrogenation of the naturally occurring unsaturated anacardic acids, namely, the 8'Z-monoene, the 8'Z,11'Z-diene, and the 8'Z,11'Z,14'-triene (**2-4**, respectively). These compounds are the chief constituents (about 75%) of cashew nutshell liquid (CNSL), which is a byproduct of cashew (*Anacardium occidentale* L.) processing and is an abundantly available renewable resource (4). The anacardic acids are rapidly accumulated in the shell during the early part of the growth of the cashew nut (5) and may play an important role in the protection of the kernel and as well as affect the fecundity of the insect population living on the tree (6). The compounds have exhibited several other interesting biological properties including antitumor (7), antimicrobial (8,9), antiacne (10), and potent molluscicidal (11) activities. They also inhibit the activity of several important enzymes such as cyclooxygenases (6), lipoygenases (12), and tyrosinase (13). Compound **3** is a substrate for soybean lipoygenase L1 (14) and **2**, also known as ginkgoic acid, is a constituent of the Chinese drug, *Ginkgo biloba* L. Related phenolic compounds are present in poison ivy and Asian lacquer trees of the genus *Toxicodendron* (15).

Anacardic acid, **1**, with its phenolic and carboxylic acid groups, can form a monosodium as well as a disodium salt with one and two equivalents of NaOH. Both these H₂O-soluble compounds have now been found to react with a variety of metal halides, sulfates, and acetates in H₂O, yielding H₂O-insoluble derivatives. Divalent metals, such as Mg²⁺, Ca²⁺, Ba²⁺, Fe²⁺, Cu²⁺, Zn²⁺, Co²⁺, Mn²⁺, and Ni²⁺, were found



to form both 2:1 and 1:1 anacardic acid-metal derivatives on reaction with monosodium and disodium salts of **1**, respectively. Most of the compounds readily dissolved in organic solvents such as CH_2Cl_2 and EtOAc, and some even in pentane; all the compounds were insoluble in more polar hydroxylic solvents and H_2O . These compounds were also formed and extracted into organic media when **1** (e.g., in CH_2Cl_2) was stirred with an aqueous solution of H_2O -soluble metal carboxylates (e.g., acetates).

The uv spectra of the complexes were similar to those of **1** (λ max 250 and 310 nm), except for weak bands of some colored compounds in the visible region. In the ir spectrum, the carbonyl absorption of anacardic acid (1657 cm^{-1}) generally shifted to $1587\text{--}1599\text{ cm}^{-1}$, indicating the carboxylate nature in both 2:1 and 1:1 derivatives; in the case of the 1:1 derivatives, the ir spectrum also showed the absence of the phenolic hydroxyl function. The compounds readily decomposed in acid media, yielding free **1**. In solution, at low temperatures, the 2:1 anacardic acid-metal compounds slowly disproportionated to free **1** and 1:1 derivatives, and the 1:1 compounds yielded the 2:1 derivatives in the presence of excess **1**. The 1:1 and 2:1 derivatives could, therefore, be represented as in **5** and **6**, respectively. The alternative representation for the 2:1 complexes (with the alkyl chains extending in opposite directions) was not preferred as they did not show liquid crystalline properties expected of such structures.



The solubility properties of anacardic acid metal derivatives were not entirely surprising considering the presence of the long alkyl chains. However, anacardic acid showed very interesting selectivity, which could not be explained simply in terms of relative solubility. Among the first row of transition metals, it showed high selectivity toward Fe^{2+} and Cu^{2+} , followed by Zn^{2+} , in preference to Co^{2+} , Mn^{2+} , and Ni^{2+} .

Addition of two molar equivalents of an aqueous solution of monosodium anacardate to a mixture of one equivalent of each of Cu^{2+} , Zn^{2+} , Co^{2+} , Ni^{2+} , and Mn^{2+} salts in H_2O precipitated the copper anacardate selectively (about 82% with the zinc compound largely accounting for the remainder); the metal ions were determined by conventional wet analytical methods (16). On the other hand, addition of excess (five or six equivalents) of monosodium anacardate to the above mixtures did not precipitate the other metal salts but caused redissolution of the precipitated copper derivative; the copper complex was then non-extractable into CH_2Cl_2 . The non-formation of the other metal derivatives in the presence of the metal ion to which **1** has high relative affinity

and redissolution of the precipitated metal derivative in the presence of excess sodium anacardate, as well as the non-extractability of the new species into organic solvents, suggested the possible formation of vesicles or similar organized structures (e.g., micelles) containing the metal and **1**. Zinc anacardate was preferentially precipitated from an equimolar mixture of Zn^{2+} , Co^{2+} , Ni^{2+} , and Mn^{2+} salts; analysis of the precipitate gave Zn, 47.4% and Co, Ni, Mn, 16–18% of each.

Cu^{2+} and Zn^{2+} were preferentially extracted from an aqueous mixture of acetates of the above five or four metals, respectively, into CH_2Cl_2 containing **1**. Thus, when **1** (25 mM) in CH_2Cl_2 (10 ml) was shaken with a mixture of Cu^{2+} , Zn^{2+} , Co^{2+} , Ni^{2+} , Mn^{2+} acetates (12.5 mM each) in H_2O (10 ml), the organic phase contained mainly Cu^{2+} and Zn^{2+} in the ratio 7:3. When the experiment was repeated without copper, an analysis of the organic phase gave: Zn (48.7%), Co (21.4%), Ni (18.9%), and Mn (11.0%).

Cu^{2+} in H_2O displaced Zn^{2+} from zinc anacardate in CH_2Cl_2 . When 5 mM solutions of copper acetate in H_2O (10 ml) and zinc anacardate (2:1) in CH_2Cl_2 were stirred together for 0.5 h and the organic phase analyzed for Zn^{2+} and Cu^{2+} , they were found in the ratio 26:74. Repetition of the experiment for 3 h extracted 88% of Cu^{2+} into the organic phase and when the concentration of zinc in CH_2Cl_2 was increased to 7.5 mM (Zn:Cu ratio 1.5:1), 97% of Cu^{2+} was found in the organic phase in 0.5 h. Fe^{2+} and Cu^{2+} appeared to have nearly the same affinity as Fe^{2+} could partially displace Cu^{2+} from copper anacardate in CH_2Cl_2 (53%). However, ready oxidation of Fe^{2+} to Fe^{3+} in H_2O was a source of complication in quantitation experiments.

The selectivity and permeability of the metal ions across a liquid membrane could also be demonstrated in a familiar U-tube experiment with a mixture of metal acetates (25 mM; 10 ml) in H_2O in one arm and an aqueous solution of H_2SO_4 or glycine (50 mM; 10 ml) in the other, separated by CH_2Cl_2 containing **1** (25 mM; 20 ml). From an equimolar mixture of Cu^{2+} , Zn^{2+} , Ni^{2+} , Co^{2+} , and Mn^{2+} salts, Cu^{2+} (72%) and Zn^{2+} (22%), along with Ni^{2+} (6%) were transported across the liquid membrane in 24 h. When the mixture contained Zn^{2+} , Ni^{2+} , Co^{2+} , and Mn^{2+} salts, all the metal ions were transported across the organic layer, with Zn^{2+} forming 57% of the mixture. No selectivity could be observed among Mn^{2+} , Co^{2+} , and Ni^{2+} . As expected, minimal transport (<1% in 24 h) and no selectivity was seen when anacardic acid was replaced by oleic acid.

Attempts are under way to explain the observed selectivity by molecular modeling and determination of stability constants and other thermodynamic parameters. Lasalocid, a salicylic acid-containing ionophore, has been known to possess moderate selectivity towards certain alkaline earth metal ions and this has been explained in terms of both calculated and observed thermodynamic parameters such as entropy, enthalpy, and heat of formation; the values correlate well with those calculated for salicylic acid itself, indicating that the salicylic acid moiety has a major role in the complexation (17). The present findings of the formation of linear, lipophilic metal derivatives with a high degree of selectivity (particularly to the important transition metal ions, Fe^{2+} and Cu^{2+} , and, to a lesser extent, Zn^{2+}) could not only find use in metallurgy, but may also explain the wide spectrum of biological activity of the anacardic acids. The phenomena observed may also be used for the study of metal transport across membranes, paramagnetic properties, material sciences (e.g., molecular laminates), and chromatographic separation of metal ions on immobilized salicylic acid type stationary phases. Multivalent transition metal salts also have the potential to bring about several useful redox reactions in organic solvents. Some of these are under investigation in this laboratory.

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