HETEROCYCLES, Vol. 95, No. 1, 2017, pp. 127-130. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 20th April, 2016, Accepted, 18th May, 2016, Published online, 9th June, 2016
DOI: 10.3987/COM-16-S(S)1

A WATER-SOLUBLE CAVITAND SEQUESTERS 2-NONENAL, THE ODOR COMPONENT OF THE ELDERLY

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Dedicated to Professor Masakatsu Shibasaki on the occasion of his 70th birthday

Abstract – Long chain aldehydes are principal components of odor in older populations. Here we show that a synthetic container molecule, a deep water-soluble cavitand forms complexes in aqueous (D_2O) solution. The cavitands bind the aldehyde in a compressed conformation that reduces exposure to the medium. The aldehyde is extracted from the complex by tetrachloroethane and sodium dodecyl sulfate, chemical agents of dry cleaning or laundering, respectively. The large-scale synthesis of the cavitand opens possibilities for its attachment to clothing fibers.

The synthesis and characterization of a water-soluble, deep cavitand **1** (Figure 1) was recently reported.[1] Such container compounds provide well-defined hydrophobic spaces capable of sequestering appropriate guests from aqueous solutions. The imidazolium groups of the periphery impart water solubility at concentrations (>1 mM), suitable for NMR detection in D_2O. Small molecules such as Naproxen,[2] the octanoyl group of the lipopeptide ghrelin[3] and bola-amphiphiles[1] such as ω-amino acids fit their hydrophobic parts into the vase-shaped cavity and leave their polar termini exposed to the aqueous medium.

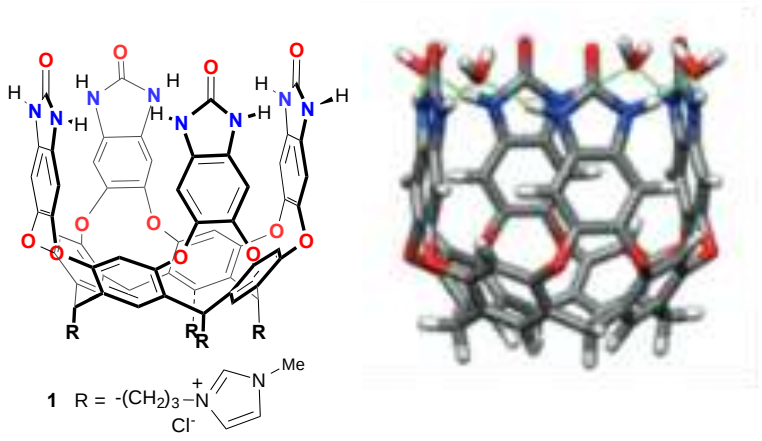

Figure 1. Left, chemical formula of the water-soluble, deep cavitand **1**. Right, a modeled structure of the vase-like form; the 4 water molecules stabilize the vase conformation through hydrogen bonding. The "feet" have been truncated.

One of the compounds associated with body odor in the elderly is *trans*-2-nonenal **2** (Figure 2), a greasy and grassy-smelling compound derived from lipids of the skin surface. Haze et al[4] showed that ω-7 unsaturated fatty acids – (*Z*)-hexadec-9-enoic acid, (palmitoleic acid) and (*E*)-octadec-11-enoic acid (vaccenic acid) – and the corresponding peroxides are components of the skin surface lipids in middle-aged (>40 years old) and/or elderly subjects. They established a correlation between the amount of these lipid peroxides on the skin and the amount of their degradation product, *trans*-2-nonenal. The size, shape and chemical surface of **2** is appropriate for recognition by the cavitand and we studied its binding properties.

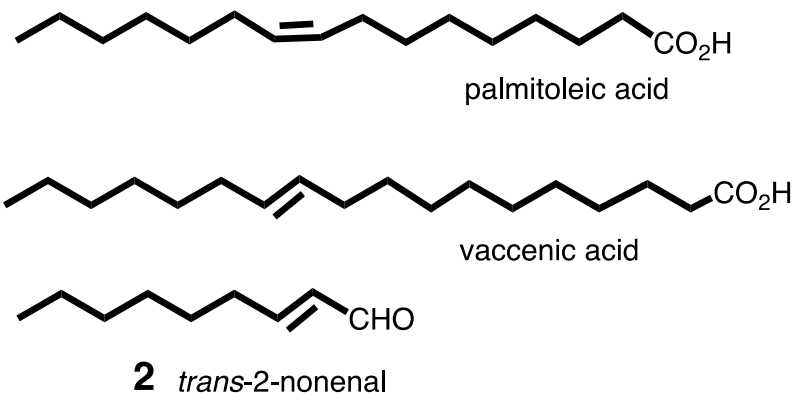

Figure 2. Structures of ω-7 acids found on the skin surface of the elderly, and their autoxidation product, nonenal, the cause of body odor.

Brief sonication of increasing concentrations of 2-nonenal with **1** in D_2O in an NMR tube gave rise to the spectra shown in Figure 3. The characteristic upfield shifted (+0.7 to -3.1 ppm) signals of the aldehyde (**a-c**) reveal its position inside the vase-like space with the terminal methyl group deep in the cavity.[5] The

broadened signals at higher concentrations (**d-g**) show the exchange rate of free and bound **2** occurs on the NMR timescale.

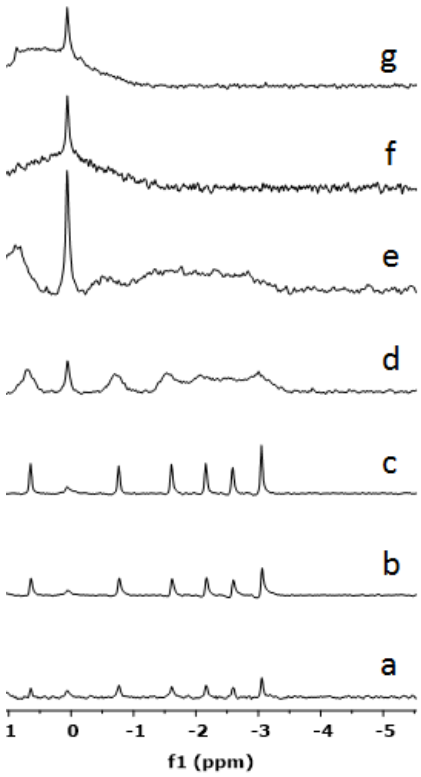

Figure 3. Partial ^{1}H NMR (600 MHz, D_2O, 298 K) spectra of the complexes of **1** (1.0 mM) with sub-stoichiometric amounts and excess of 2-nonenal **2**; The upfield shifts of the CH_2 and CH_3 groups place them deep in the cavity of **1**. Spectra after addition of (a) 0.05 equiv., (b) 0.2 equiv., (c) 0.6 equiv., (d) 0.85 equiv., (e) 1.1 equiv., (f) 1.6 equiv., (g) 2.0 equiv. of aldehyde.

Typically, hydrophobic guests bound in the water-soluble cavitand can be released by extraction with organic solvents or by addition of reagents that alter the medium. For the case of nonenal, release was accomplished by exposure to tetrachloroethane, the principle agent of dry cleaning procedures. Extraction with this solvent completely cleared the upfield NMR signals. A second method of nonenal release was observed with sodium dodecyl sulfate (SDS), a typical detergent added to the solution. The cavitand binds 8-9 carbon chains optimally: shorter guests do not fill the space properly and longer guests induce capsule formation.[1] The efficient extraction of nonenal from the cavitand complexes with organic solvents bodes well for application of the cavitand to garments in contact with the skin.

In conclusion, one of the main themes of "green" chemistry is the wholesale movement of chemical reactions out of organic solvents and into water.[6] The deep, water-soluble cavitand offers much promise in this regard. The convenient, large-scale synthesis of the cavitand[7] opens possibilities for its attachment

to clothing fibers and other solid supports to sequester nonenal. This aldehyde causes not only unpleasant odors in humans, but is also known to contribute the "cardboard flavor" of stale beer.[8]

ACKNOWLEDGEMENTS

We are grateful to the National Science Foundation (CHE 1506266) and a Marie Curie International Outgoing Fellowship within the 7th European Community Framework Programme. Grant PIOF-GA-2013-627403 provided a postdoctoral fellowship to S.M.

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