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NOVEL LIPOPHILIC CROWN CARBOXYLIC ACIDS

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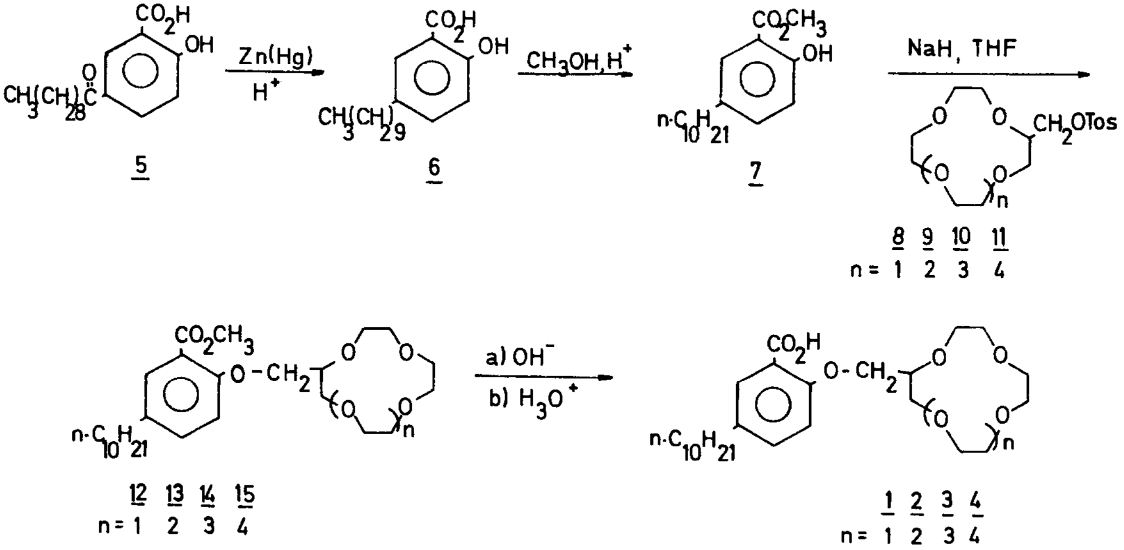
Summary: Four novel ionizable crowns are formed from reactions of methyl 5-(n-decyl)salicylate with tosylates from hydroxymethyl-12-crown-4, -15-crown-5, -18-crown-6 and -21-crown-7 followed by hydrolysis.

Lipophilic crown carboxylic acids are useful for extraction of alkali metal and alkaline earth cations from aqueous solutions into organic media.[1-3] Recently, we have reported the synthesis of lipophilic crown carboxylic acids which contain dibenzo[4] and benzo[5] crown units. In the continuation of our search for more selective and efficient metal ion complexing agents, we now have prepared a new series of crown carboxylic acids 1-4 by a sequence of reactions in which hydroxymethyl crowns without benzo substituents are coupled to the lipophilic carboxylic acid 5-(n-decyl)salicylic acid (Scheme 1).



Scheme 1

The synthetic route to 5-(*n*-decyl)salicylic acid involved 5-(*n*-decanoyl)salicylic acid (5)[6] which was obtained from methyl 2-(*n*-decyloxy)benzoate by a Fries rearrangement[7] in CS_2 (38% yield) followed by basic hydrolysis of the resulting methyl ester in 89% yield. Clemmensen reduction of 5 afforded 5-(*n*-decyl)salicylic acid (6)[8] in 86% yield. Methyl 5-(*n*-decyl)salicylate (7)[9] was obtained in 66% yield by esterification of 6 with methanol and HCl catalyst.

Tosylates 8-11[10,11] were prepared from the corresponding hydroxymethyl crowns[12-18] by reaction with tosyl chloride in pyridine in 98, 70, 90 and 86% yields, respectively. Treatment of methyl 5-(*n*-decyl)salicylate (7) with sodium hydride and tosylates 8-11 gave crown carboxylic acid esters 12-15 which were hydrolyzed to the lipophilic crown carboxylic acids 1-4.[19] Yield, physical property, and spectral data for the crown carboxylic acids and esters are collected in Table 1.

In the general procedure, sodium hydride (50% in mineral oil, 0.60 g, 12.5 mmol) was washed with pentane and suspended in dry THF (15 ml). With stirring under nitrogen, a solution of 7 (2.92 g, 10 mmol) in THF (15 ml) was added dropwise during 45 min. After 1 h, a solution of the hydroxymethyl crown tosylate (10 mmol) in THF (20 ml) was added dropwise during 30 min. The reaction mixture was stirred at room temperature overnight and then refluxed for 48 h. The solvent was removed *in vacuo* and CH_2Cl_2 was added. The resulting mixture was filtered and the filtrate and washings were combined and washed with water. After drying with $MgSO_4$, the solvent was evaporated *in vacuo* and the residue was chromatographed on a silica gel column using EtOAc as eluent to give the crown carboxylic acid ester. The ester (3.0 mmol) was dissolved in EtOH (20 ml) and a solution of NaOH (1.0) g in H_2O (5 ml) was added. The mixture was refluxed for 4 h and evaporated to dryness *in vacuo*. Water (20 ml) was added to the residue and the mixture was acidified with 6 N HCl and extracted with CH_2Cl_2 (3 X 10 ml). The combined extracts were washed with water, dried ($MgSO_4$) and evaporated *in vacuo* to yield the lipophilic crown carboxylic acid.

Crown carboxylic acids 1-4 bear a resemblance to a variety of 15-crown-5 and 18-crown-6 derivatives with non-ionizable pendant groups which have been prepared by other workers.[12,14,20-24] However for solvent extraction of metal cations from aqueous solutions into organic solvents, crown carboxylic acids have the important advantage that metal ion extraction does not involve concomitant transfer of the aqueous phase anion into the organic medium.[25] We have shown that crown carboxylic acids are much more efficient reagents for metal ion extraction than was a closely-related non-ionizable crown.[25]

Competitive extraction of alkali metal cations from aqueous solutions of the alkali metal chlorides into chloroform by crown carboxylic acids 1-4 was examined by the standard method.[1,2] All four compounds were sufficiently lipophilic to remain in the organic phase without detectable loss even when the aqueous phase pH $\geq$ 12. Extraction selectivities with lipophilic crown carboxylic acids 1-4 were found to be: $Li^+ > Na^+ > K^+ > Rb^+ > Cs^+$: $Na^+ > K^+ > Rb^+ > Li^+ \approx Cs^+$; $K^+ > Rb^+ > Li^+ > Cs^+ > Na^+$; $Cs^+ > Rb^+ > K^+ > Li^+ > Na^+$, respectively.

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Table 1. Data for Crown Carboxylic Acids and Esters

Crown	Percent Yield	Melting point, °C	NMR spectra (60 MHz in $CDCl_3$), ppm	IR spectra (neat), cm^{-1}
1	83	54-56	0.7-1.8 (m, 19H), 2.56 (t, 2H), 3.4-4.5 (m, 17H), 6.85-7.9 (m, 3H) 10.7 (br s, 1H)	3600-2350 (COOH), 1724 (C=O), 1134, 1101 (C-O)
2	84	42-44	0.7-1.8 (m, 19H), 2.56 (t, 2H), 3.4-4.5 (m, 21H), 6.9-8.0 (m, 3H), 9.1 (br s, 1H)	3600-2400 (COOH), 1732 (C=O), 1128 (C-O)
3	81	oil	0.7-1.8 (m, 19H), 2.56 (t, 2H), 3.4-4.5 (m, 25H), 6.9-8.0 (m, 3H)	3650-2350 (COOH), 1732 (C=O), 1114 (C-O)
4	79	oil	0.7-1.8 (m, 19H), 2.60 (t, 2H), 3.4-4.5 (m, 29H), 6.9-8.0 (m, 3H)	3650-2350 (COOH), 1732 (C=O), 1116 (C-O)
12	58	oil	0.7-1.75 (m, 19H), 2.55 (t, 2H), 3.4-4.15 (m, 20H), 6.75-7.55 (m, 3H)	1732, 1709 (C=O), 1132, 1082 (C-O)
13	61	oil	0.7-1.8 (m, 19H), 2.52 (t, 2H), 3.4-4.15 (m, 24H), 6.8-7.6 (m, 3H)	1732, 1709 (C=O), 1132 (C-O)
14	68	oil	0.7-1.8 (m, 19H), 2.53 (t, 2H), 3.4-4.2 (m, 28H), 6.75-7.65 (m, 3H)	1730, 1709 (C=O), 1118 (C-O)
15	78	oil	0.75-1.75 (m, 19H), 2.55 (t, 2H), 3.4-4.2 (m, 32H), 6.75-7.7 (m, 3H)	1730, 1709 (C=O), 1140, 1116 (C-O)

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8. Data for 6: m.p. 89-91°C (from 90-120° pet. ether); NMR [$(CD_3)_2CO$, δ], 0.65-1.9 (m, 19H),

2.57 (t, 2H), 6.81, 7.31, 7.67 (3 approx. d, 3H); IR [mull, cm^{-1}], 3400-2300 (COOH, OH), 1666 (C=O). Elemental analysis: Calculated for 6, 73.35% C, 9.41% H; Found, 73.47% C. 9.22% H.

9. Data for 7: m.p. 27-28°C; NMR [$CDCl_3$, δ], 0.7-1.9 (m, 19H), 2.53 (t, 2H), 3.95 (s, 3H), 6.77-7.80 (m, 3H); IR [neat, cm^{-1}], 3205 (OH), 1682 (C=O). Elemental analysis: Calculated for 7, 73.93% C, 9.65% H; Found, 74.15% C, 9.58% H.
10. Tosylates 8-11 were colorless, viscous oils which gave the anticipated NMR and IR absorptions. Elemental analyses: Calculated for 8, 53.32% C, 6.71% H; Found, 53.21% C, 6.59% H. Calculated for 9, 53.45% C, 6.98% H; Found, 53.32% C, 7.05% H. Calculated for 10, 53.56% C, 7.19% H; Found, 53.54% C, 7.27% H. Calculated for 11, 53.64% C, 7.37% H; Found 53.79% C, 7.37% H.
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19. Elemental analyses: Calculated for 1, 66.93% C, 9.07% H; Found, 66.74% C, 9.14% H. Calculated for 2, 65.86% C, 9.08% H; Found, 65.79% C, 9.17% H. Calculated for $3 \cdot 0.75\ H_2O$ (3 was very hygroscopic), 63.41% C, 9.13% H; Found, 63.37% C, 9.10% H. Calculated for 4, 64.19% C, 9.09% H; Found, 63.90% C, 9.18% H.
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