Modification of Kemp's Triacid to Produce New Ligands Showing Efficient Alkaline Earth Metal Ion Transport with Structure Dependent Selectivity

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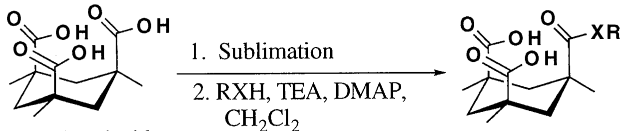
The calcium/barium selectivity ratio for efficient competitive transport among alkaline earth metal ions was controlled by structural isomerism and side chain linker changes in new lipophilic mono-substituted Kemp's diacid ionophores.

Previously we reported the transport ability and selectivity of Kemp's acid imide (KAI) transport agents.[1,2] The transport ability and selectivity among divalent cations by KAI led us to design dicarboxylic acids using the same Kemp's triacid structural motif.

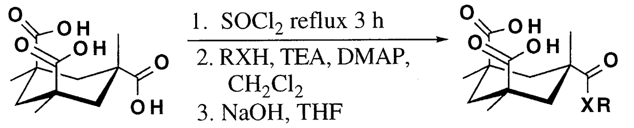
Other groups have designed transport systems showing varying degrees of efficiency and selectivity for alkaline earth metal ions. An array of substituted crown ethers by Fyles *et al.* provided little selectivity among alkaline earth metals, presumably because the carboxylic acid groups only neutralize the charge, without sufficient steric interactions to provide selectivity.[3] Rebek *et al.* showed a convergent diacid diimide effectively transported calcium, but no selectivity was reported.[4] Hiratani *et al.* reported an acyclic polyether diacid had Ba/Ca selectivity of 5.2.[5] However, transport conditions were very different from our own, making a direct comparison difficult. An intriguing calixarene diacid was reported by Gloe *et al.* to selectively extract calcium cations, but the transport ability was not reported.[6] We designed new and simple dicarboxylic acids having sufficient lipophilic and structural characteristics to efficiently and selectively transport alkaline earth metal ions. This led us to modify Kemp's triacid and evaluate the alkaline earth metal ion transport of new diacid mono-amides and mono-esters.

The new compounds were synthesized in good yields. Heating Kemp's triacid under reduced pressure and subsequent sublimation of the product followed by nucleophilic attack with aniline or alcohol provided **1** and **2**.[7] Treatment of the Kemp's triacid geometric isomer with $SOCl_2$ followed by nucleophilic attack with aniline or alcohol and hydrolysis of the anhydride provided **3** and **4**.[8]



Kemp's Triacid

1: X=NH, R=C_6H_4-*p*-*n*-Bu; 56%
2: X=O, R=$CH_2C_6H_4$-*p*-*t*-Bu; 52%



Kemp's Triacid Geometric Isomer

3: X=NH, R=C_6H_4-*p*-*n*-Bu; 45%
4: X=O, R=$CH_2C_6H_4$-*p*-*t*-Bu; 55%

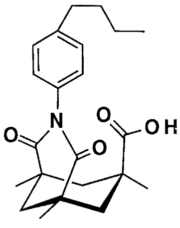
The transport efficiency and selectivity was analyzed by competitive alkaline earth metal ion transport experiments. The apparatus used was a Pyrex U-tube system, described in previous work by Hirose *et al.*[1] Analysis of metal ions was done by atomic absorption spectroscopy (Shimadzu AA-680). Table 1 lists the efficiency and selectivity for ligands **1-4**, KAI and control experiments. KAI showed good Ca/Ba selectivity, but low overall transport efficiency.[1] Table 1 clearly shows the total cation transport efficiency of **1** was twice that of KAI. The efficiency increase resulted in a three-fold decrease in selectivity of calcium over barium. The versatility available in the present synthetic approach to diacid derivatives allowed modification to produce ester **2**. It was thus possible to favor barium ion transport by replacing the anilide with an ester linkage. Diacid ester **2** still maintains good overall efficiency. This synthetic versatility is not available in the Kemp's acid imide system. Using the readily available Kemp's triacid geometric isomer allowed substitution of a methyl group for the carboxyl group in the third axial position, **3** and **4**. This change produced diacids with calcium selectivity and good overall transport efficiency.

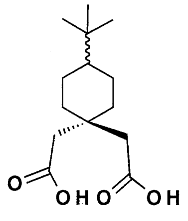
Comparing the transport of KAI to **1-4** indicates a correlation between the rigidity of the ligand/cation interaction and transport efficiency. Examination of molecular models of KAI indicates the bicyclic acid KAI is quite rigid and leaves little space for a metal cation to bind. Contrastingly, the diacid ligands have more flexibility, while maintaining a rigid 1,3-diacid framework. We

Table 1. Competitive alkaline earth metal ion transport by carboxylic acid ligands

Ligand	Metal ions transported to the receiving phase[a] [mol%[b] (μmol)]				Selectivity
	Mg	Ca	Sr	Ba	
1	1 (1.5)	93 (139)	62 (94)	61 (91)	Ca/Ba = 1.5
2	2 (2.6)	68 (101)	58 (87)	82 (123)	Ca/Ba = 0.8
3	3 (4.1)	80 (120)	62 (94)	21 (32)	Ca/Ba = 3.7
4	2 (3.0)	85 (127)	58 (87)	58 (87)	Ca/Ba = 1.5
KAI	20 (30)	70 (105)	4 (6)	13 (20)	Ca/Ba = 5.3[c]
DABC	~0 (0.5)	6 (9.1)	1 (1.5)	0 (0)	
SA	~0 (0.7)	2 (2.4)	~0 (0.5)	2 (2.9)	
none	~0	~0	~0	~0	

[a] Initial transport conditions (25 °C): source phase - 10 mmol dm^{-3} metal chloride tris-buffered solution, pH ~9.0-9.4, 15 cm^3; liquid membrane - 0.15 mmol of acid chloroform solution, 30 cm^3; receiving phase - 0.1 mol dm^{-3} HNO_3, 15 cm^3.
[b] Calculated by mol% = 100 x (μmoles of ion M^{2+} transported) / (initial μmoles of ion M^{2+} in the source phase) after 2 days.
[c] Data taken from reference 1.


KAI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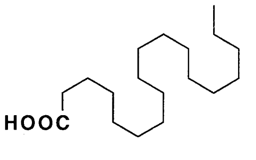
SA

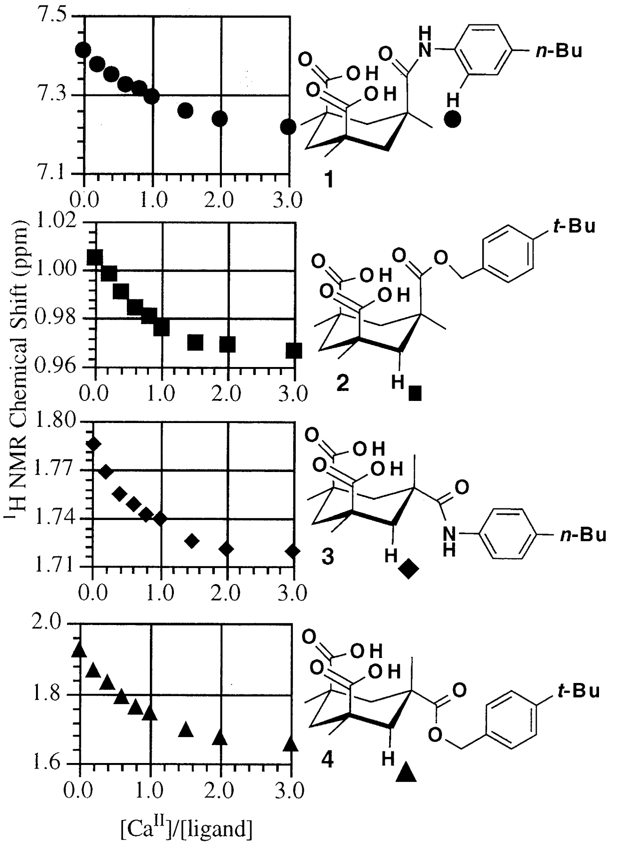

Figure 1. Proton NMR titration of ligands **1**-**4** with $CaCl_2$ in 7.5% $CD_3OD/CDCl_3$.

felt this intermediate flexibility might be important, so the transport ability of 1,1'-diacetic acid-4-*t*-butyl cyclohexane (DABC) was evaluated as a very flexible 1,3-diacid. Relative flexibility appeared to be an important factor, because nearly all transport ability was lost when the diacid moiety was unconstrained, as in DABC. Control experiments with no carrier or stearic acid (SA) showed negligible transport. Comparison of DABC and SA indicate that the addition of one carboxylic acid group to a lipophilic acid should not increase transport efficiency. So the difference between KAI and **1** is more than simple addition of an acid group. Thus the new ligands **1-4** showed unique alkaline earth metal ion transport ability.

Calcium cation binding was studied by examining the relationship between the chemical shift of ligand protons and [Ca^{II}] with ^{1}H NMR spectroscopy (Varian Gemini 300BB) for **1-4** (Figure 1). Data for compound **1** indicates the axial amide group was participating in stabilization of the metal complex. This affect may allow chromogenic ligands to be made. The ligands **2**-**4** showed that neither anilide/ester exchange, nor isomerism of the third quartenary cyclohexane carbon, changed the complex stoichiometry.[9]

The 1/1 stoichiometry was further supported by analysis of the receiving and source phases for the inorganic anions present by high pressure anion chromatography (Tosoh SC-8020). Neither Cl^- in the receiving phase, nor NO_3^- in the source phase were detectable after 2 days transport for all ligands. This indicated the carboxylate anions to be the sole transporting counter anions. Thus, *intramolecular* (bimolecular) dicarboxylate/cation (1/1) complexation was favored over the more entropically demanding *intermolecular* (multi-molecular) dicarboxylate/cation (n/1) interaction.

Compounds **1-4** showed improved transport ability over the structurally related Kemp's acid imide. The diacid system was also easier to modify for control of alkaline earth cation transport selectivity. This was accomplished by the addition of one carboxylic acid group, forming a rigid 1,3-diaxial chelating moiety. Furthermore, the synthetic versatility in the diacid structure allowed the Ca/Ba selectivity to be nearly inverted by simple functional group inter-change between anilide and ester. Thus, the Kemp's triacid structure shows easily alterable transport efficiency and selectivity for alkaline earth metal ion transport.

References and Notes

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7 The ligands **1** and **2** were synthesized according to the method of T. P. Curran, C. W. Borysenko, S. M. Abelleira, and R. J. Messier, *J. Org. Chem.*, **59**, 3522 (1994).
Physical data of **1**: mp 146.7 - 147.2 °C; IR (KBr) 3297, 1726, 1601 cm^{-1}; ^{1}H NMR (7.5% $CD_3OD/CDCl_3$) δ 7.42 (d, J=6.57 Hz, 2 H), 7.07 (d, J= 6.60 Hz, 2 H), 2.87 (d, J=14.8 Hz, 1 H), 2.69 (d, J=14.4 Hz, 2 H), 2.55 (t, J=7.59 Hz, 2 H), 1.54 (m, 2 H), 1.33 (m, 2 H), 1.31 (s, 3 H), 1.26 (s, 6 H), 1.09 (d, J=15.3 Hz, 2 H), 1.08 (d, J=15.3 Hz, 1 H), 0.91 (t, J= 7.28 Hz, 3 H); ^{13}C NMR (7.5% $CD_3OD/CDCl_3$) δ 180.8, 176.0, 138.4, 136.2, 128.3, 120.8, 43.7, 42.4, 41.4, 35.0, 34.3, 33.8, 30.5, 22.2, 13.9. Anal. Found: C, 67.96; H, 8.08; N, 3.57%. Calcd for $C_{22}H_{31}NO_5$: C, 67.85; H, 8.02; N, 3.60%.
Physical data of **2**: mp 166.0 - 167.0 °C; IR (KBr) 1730, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.37 (d, J=8.46 Hz, 2 H), 7.30 (d, J=8.28 Hz, 2 H), 5.01 (s, 2 H), 3.01 (d, J=14.0 Hz, 2 H), 2.69 (d, J=13.9 Hz, 1 H), 1.32 (s, 9 H), 1.24 (s, 6 H), 1.23 (s, 3 H), 1.05 (d, J=14.5 Hz, 1 H), 0.96 (d, J=15.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 182.4, 176.3, 150.6, 133.7, 127.9, 125.2, 66.1, 44.4, 42.1, 41.9, 41.2, 34.5, 32.9, 31.3, 29.9. Anal. Found: C, 68.24; H, 8.01%. Calcd for $C_{23}H_{32}O_6$: C, 68.30; H, 7.98%.

8 The ligands **3** and **4** were synthesized according to the method of B. Askew, P. Ballester, C. Buhr, K. S. Jeong, S. Jones, K. Parris, K. Williams, and J. Rebek, Jr., *J. Am. Chem. Soc.*, **111**, 1082 (1989).
Physical data of **3**: mp 177.3 - 178.3 °C; IR (KBr) 3283, 1705, 1642 cm^{-1}; ^{1}H NMR ($CDCl_3$/acetone-d_6) δ 8.30 (s, 1 H), 7.48 (d, J=8.43 Hz, 2 H), 7.12 (d, J=8.52 Hz, 2 H), 2.65 (d, J=14.6 Hz, 1 H), 2.57 (t, J=7.67 Hz, 2 H), 2.30 (d, J=14.5 Hz, 2 H), 2.04 (d, J=14.5 Hz, 2 H), 1.57 (m, 2 H), 1.38 (m, 12 H), 0.914 (t, J= 7.31 Hz, 3 H); ^{13}C NMR ($CDCl_3$/acetone-d_6) δ 181.7, 177.2, 139.0, 137.2, 129.3, 121.3, 43.6, 42.1, 40.9, 35.7, 34.5, 30.4, 27.7, 22.9, 14.5. Anal. Found: C, 67.66; H, 8.01; N, 3.55%. Calcd for $C_{22}H_{31}NO_5$: C, 67.85; H, 8.02; N, 3.60%.
Physical data of **4**: mp 163.1 - 164.1 °C; IR (KBr) 1730, 1701 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.37 (d, J=8.5 Hz, 2 H), 7.30 (d, J=8.3 Hz, 2 H), 5.10 (s, 2 H), 2.42 (d, J=14.8 Hz, 1 H), 2.18 (d, J=14.3 Hz, 2 H), 2.06 (d, J=14.3 Hz, 2 H), 1.32 (s, 9 H), 1.24 (s, 3 H), 1.23 (s, 6 H), 1.18 (d, J=14.8 Hz, 1 H) ; ^{13}C NMR ($CDCl_3$) δ 185.4, 178.1, 151.5, 132.6, 128.3, 125.5, 66.6, 42.3, 41.1, 41.0, 38.8, 34.7, 31.3, 28.8, 28.5. Anal. Found: C, 68.30; H, 8.03%. Calcd for $C_{23}H_{32}O_6$: C, 68.30; H, 7.98%.

9 Assuming 1:1 complexation of calcium, the stability constants derived from the ^{1}H NMR data were 100, 93, 110, and 200 (mol^{-1} dm^3) for **1**, **2**, **3**, and **4**, respectively. The authors thank Dr. Toshikazu Takahashi, NIMC, for his help with this calculation.