New Kemp's Diacid Derivatives Give Efficient Transport and Modifiable Selectivity for Alkaline Earth and Transition Metal Ions

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New derivatives of 1,3,5-trimethyl-*r*-1, *c*-3, *c*-5-cyclohexanetricarboxylic acid (Kemp's triacid) showed high efficiency for alkaline earth and transition metal ion transport through a chloroform liquid membrane. Simple syntheses from Kemp's triacid or its geometric isomer provided chelating agents with a tripodal binding site for metal cations. The tripodal binding site consisted of *r*-1, *c*-3-diaxial carboxyl group and a *c*-5-amide, ester, or C-methyl group. Alkaline earth metal transport was quite variable and sensitive to *c*-5-group changes. For transition metal transport, *c*-5-amide diacids gave high total transport efficiency. For *c*-5-ester or C-methyl diacids, complexation of smaller divalent cations was decreased, resulting in increased selectivity for large cations.

The selective chelation of divalent metal cations is important in studying the action of natural ionophores where biologically active metals must be selectively transported across membranes.[1] For example, biological decontamination requires isolation of poisonous metals while leaving essential metals untouched.[2] Quantitative and qualitative analysis for trace metals is another area for selective ionophores. To indicate the presence of some metals requires methods to concentrate them from mixtures of similar metals.[3] The transport of divalent metals across a chloroform membrane is an effective way of screening ionophores for these applications.

Roughly in the last 15 years, research groups have designed and synthesized ionophores targeted for alkaline earth[4—7] and transition[8—12] metals with the common feature of two carboxyl groups. The theoretically neutral complexes allowed efficient and selective transport ability. We desired to explore the effect of systematic variation of simple functional groups in a constrained binding site on the transport ability of new diacid ionophores.

As an extension of newly reported alkaline earth[13] and transition metal[14] ion selectivity shown by Kemp's acid imide derivatives, we now offer an expanded report on the transport ability and selectivity of Kemp's diacid amides and esters for alkaline earth[7] and transition metals.

Results and Discussion

Ligand Synthesis. The new compounds were synthesized in good yields. Heating Kemp's triacid under reduced pressure and subsequent sublimation of the product (Kemp's acid 1,3-anhydride) followed by nucleophilic attack with amine or alcohol provided *r*-1, *c*-3, *c*-5-isomers **1**, **3**, **4**, **7**, **8**, and **11**—**15** (Scheme 1).[15] Compound **12** was an exception to the rule. Under the basic conditions (TEA) used, this derivative was not isolated. Apparently the hydroxy group of 2-*N*-morpholinoethanol could form a strongly hydrogen bonded 5 member ring of hydroxy hydrogen to the lone pair electrons of the morpholine tertiary amine in basic solution. Such a five membered ring hydrogen bonded structure was previously shown to dramatically retard enzyme catalyzed esterification under neutral conditions.[16] Protonation of morpholino nitrogen smoothly yielded product.

Treatment of the 1,3,5-trimethyl-*r*-1, *c*-3, *t*-5-cyclohexanetricarboxylic acid (Kemp's triacid geometric isomer) with $SOCl_2$ followed by nucleophilic attack with primary amine or alcohol and hydrolysis of the anhydride provided *r*-1, *c*-3, *t*-5-isomers **2**, **5**, **6**, **9**, and **10** (Scheme 2).[17]

Pre-organization of the Ligand. The ability to provide a host molecule with a polar micro-environment pocket surrounded by a nonpolar envelope is normally considered a pre-requisite for effective complexation of metal cations in organic solvents. An important feature of crown ether/metal cation complexes is that the polar cation is surrounded by the polar, but organic soluble, crown ether. A predisposition of our Kemp's diacid compounds, Fig. 1, was demonstrated by single crystal X-ray analysis of compound **8**. The carboxyl groups were enveloped by the phenethyl ester side chains and surrounded by hydrophobic C-methyl groups, suggesting a polar cavity pre-organized for binding of cations.

Transport of Alkaline Earth Metal Ions. From the preoganization of the diacid **8**, efficient transport of divalent cations was expected. Table 1 shows the transport ability for compounds **1**—**15** and Kemp's acid *N*-(4-butylphenyl)-

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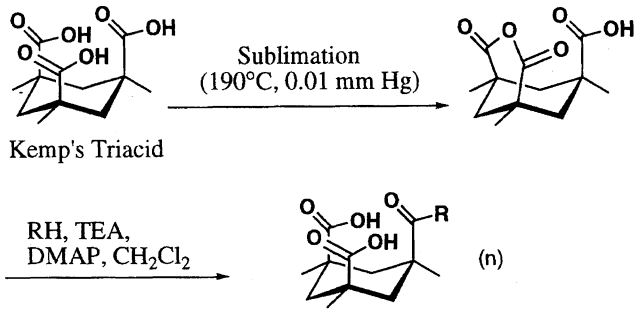
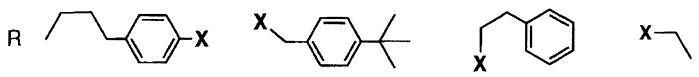
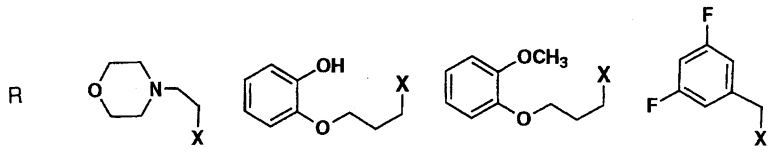




(n)	1	3	4	7	8	11
X	NH	NH	O	NH	O	O
Yield	56%	50%	52%	82%	58%	42%



(n)	12	13	14	15
X	O	O	O	NH
Yield	45%	67%	28%	47%

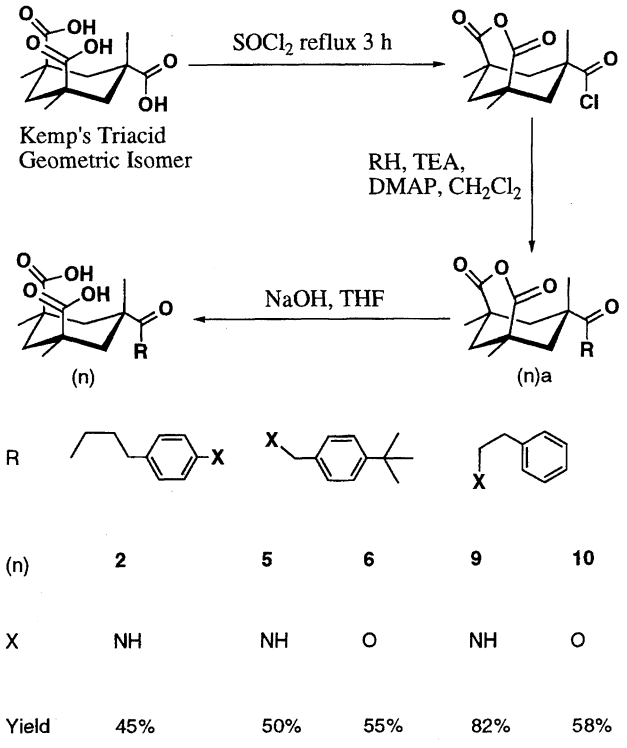
Scheme 1.

imide (KAI) (Chart 1). The additional carboxyl group doubled the transport efficiency compared to KAI, except for compounds **9** and **10**, which were exceptions because of significant aqueous solubility of the ligand/metal complex. The overall cation transport results indicated the 1,3-diaxial carboxyl moiety gave excellent interaction with alkaline earth metal cations. Stabilization of the bound cation resulted from interaction with the third carbonyl group in the *r*-1, *c*-3, *c*-5-derivatives. Replacing *c*-5-amide of **3** with *c*-5-ester of **4** reduced the transport ability of Ca^{2+}, 90% to 68%, and increased the transport of Ba^{2+}, 48% to 82%. This change was uniform for all *c*-5-amides and *c*-5-esters studied. Functionalized calixarenes confirmed that, given charge neutralization of the bound divalent cation, Ca^{2+} was more efficiently extracted by amide groups than by ester groups.[18] Thus strong binding in the relatively small tripodal binding site of our ligands resulted in Ca^{2+} over Ba^{2+} selectivity for amides **3** and **7**. The loose interaction by ester groups apparently allowed the larger Ba^{2+} into the binding site while the smaller Ca^{2+} was not bound well enough for efficient transport, accounting for the Ba^{2+} selectivity of the *c*-5-ester compounds **4**, **8**, **13**, and **14**. Interestingly, the overall transport ability of the *r*-1, *c*-3, *t*-5-diacids **5** and **6** was quite similar to that of **4**, indicating the rigid 1,3-diaxial acid system was the primary factor in transport ability. In fact the 1,3-diaxial acid system of *r*-1, *c*-3, *t*-5-diacids was capable of significant selectivity of Ca^{2+} over Ba^{2+}. This unexpected observation indicated the seemingly less desirable *t*-5-diacid systems have value in cation transport even without the tripodal shape of carbonyl groups as in the *c*-5-Kemp's diacid derivatives. The overall poor transport of Mg^{2+} may result from the high hydration energy. Interestingly, Sr^{2+} was unaffected by functional group changes in the tripodal binding area. Observation of ligand–metal complexes by ^1H NMR spectroscopy gave more information on the function of the third axial group.

Table 1. Transport Abilities of Kemp's Diacid Derivatives for Alkaline Earth Metal Ions

Carrier	Metal ions transported to the receiving phase[a] mol%[b] (μmol)				Total μmol
	Mg	Ca	Sr	Ba	
1	1 (1.5)	93 (139)	62 (94)	61 (91)	326
2	3 (4)	98 (147)	62 (94)	21 (32)	277
3	1 (2)	90 (135)	60 (90)	48 (73)	300
4	2 (2.6)	68 (101)	58 (87)	82 (123)	314
5	0 (0.7)	79 (119)	77 (115)	61 (91)	325
6	2 (3.0)	85 (127)	58 (87)	58 (87)	304
7	2 (3.5)	72 (107)	55 (82)	24 (36)	229
8	3 (3.8)	67 (100)	63 (95)	91 (137)	336
9	1 (0.8)	0 (0)	0 (0)	0 (0.3)	1
10	0 (0.6)	40 (60)	3 (5)	1 (2)	68
11	0 (0.3)	0 (0)	0 (0)	0 (0)	0
12	0 (0.6)	0 (0)	0 (0)	1 (2)	3
13	1 (2)	69 (103)	53 (79)	87 (130)	313
14	2 (2)	52 (77)	49 (73)	85 (128)	280
15	0 (0)	74 (111)	83 (125)	66 (99)	335
KAI[c]	22 (33)	55 (82)	4 (6.4)	22 (32)	153
None	ca. 0	ca. 0	ca. 0	ca. 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 diacid chloroform solution, 30 cm^3; receiving phase–0.1 mol dm^{-3} HNO_3, 15 cm^3. b) mol% = 100 × (μmoles of ion M^{2+} transported)/(initial μmoles of ion M^{2+} in the source phase), after 2 d. c) Data taken from Ref. 13.



Scheme 2.

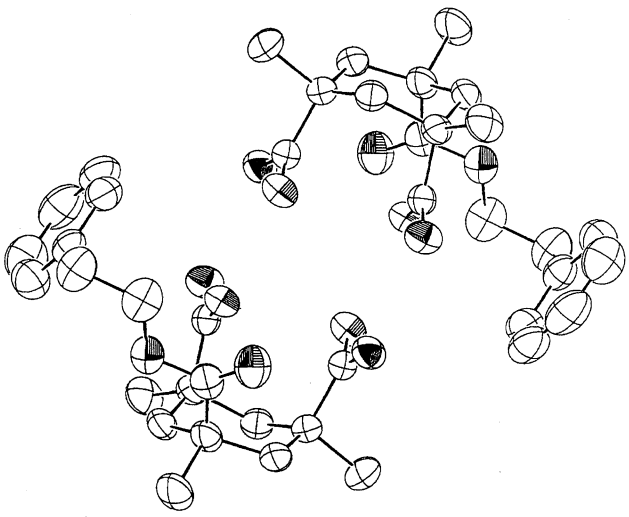


Fig. 1. ORTEP drawing of the dimeric structure of **8**, oxygens atoms were shaded and protons left undrawn for clarity.

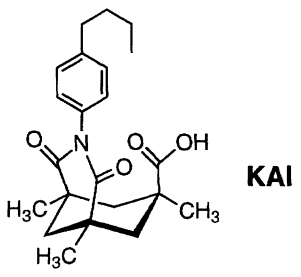


Chart 1.

The titration of compounds **1** and **2** with $CaCl_2$ in 7.5% $CD_3OD/CDCl_3$ suggested the role of the third carbonyl (Fig. 2). The anilide carbonyl group of **1** was conjugated with the aromatic ring. Thus the aromatic ring could donate electron density to the bound $CaCl_2$ species. Marked chemical shift changes in the aromatic region of the ^1H NMR spectrum of **1** were expected, and subsequently observed, as $[CaCl_2]$ was increased. No such chemical shift changes were

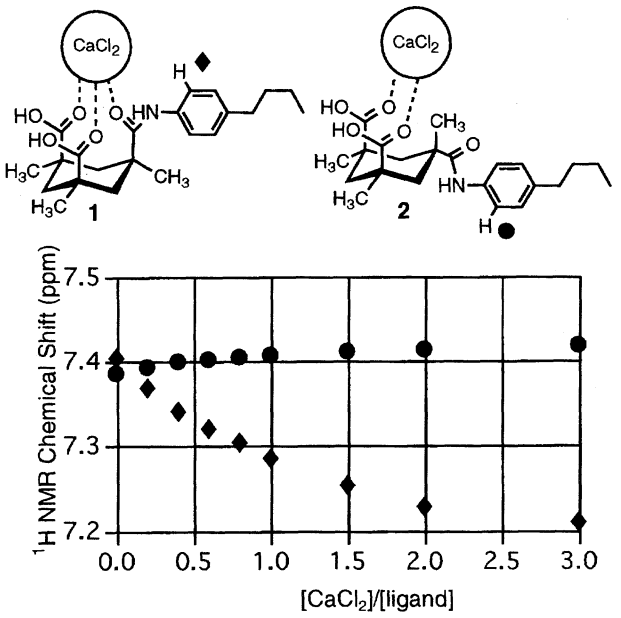


Fig. 2. Proposed binding modes of **1** and **2** with calcium chloride indicated by complexation-induced shift in ^{1}H NMR chemical shift of aromatic resonances of **1** and **2** with increasing [$CaCl_2$]. Titration conditions: [Ligand] = 2.30×10^{-2} mol dm^{-3} and 20 °C.

observed for compound **2**. This result indicated the *t*-5-carbonyl group of **2** did not donate electron density to $CaCl_2$. Interestingly, the theoretically electron deficient carbonyl of **15** resulted in high total cation transport, but little selectivity.

Information on the ligand : metal binding ratio was discovered by observing the effect of increasing [$CaCl_2$] on the ^{1}H NMR spectroscopic chemical shifts of hydrogen atoms in ligands **1**, **2**, **4**, and **6**, as previously reported.[8] Inflection points occurred at approximately equimolar amounts of added $CaCl_2$, indicating 1 : 1 binding of ligands with $CaCl_2$. The rather low binding constants calculated from these data sets, ca. 100 mol^{-1} dm^3, demonstrated that binding strength and transport efficiency may not be easy to correlate. The similar binding constants may reflect the overriding affect of the 1,3-diaxial carboxyl binding group, a common feature among the ligands.

Further study of the transport mechanism by anion cotransport analysis showed 1 : 1 ligand : divalent metal complexation. From Table 2, no counter anions, Cl^-, were detected in the receiving phase for either carrier **7** (Entry 1) or **15** (Entry 2). This meant a metal cation did not need Cl^- when it was transported so the figures in the last columns were small. However, charge balance must be maintained. If anions leaked into the organic phase with the metal ions, some of them should be released by protonation of the carrier at the acidic receiving phase and be detected in it. As a result, we can propose a simple mechanism, that is, when this type of carrier recognizes and chelates alkaline earth metal ions, the metal ion loses both counter anions at the interface of the source phase and the liquid membrane phase to form 1 : 1 carrier^{2-}/metal^{2+} complex. This mechanism was the same as usually believed for the system, where the valence of the metal ion matches the number of ionizable functional groups in the carriers or chelating agents.[19] It should be noted that the concentration of anion was more than twice that of metal ion as the source phase included Cl^-, 5.7 mmol dm^{-3}, from the buffer solution.

Transition Metal Transport. We previously reported transport of transition metals by KAI.[14] Recently we measured the transport of transition metals with the newly synthesized diacids. Now the divalent cations could theoretically be transported as a neutral 1 : 1 ligand/metal complex species, as opposed to previous work with mono-acid KAI. The pK_a's of Kemp's triacid were measured as pK_1 = 3.3, pK_2 = 5.9, and pK_3 = 7.3,[20] indicating a mixture of mono- and di-protonated species of our diacids would exist at the extraction interface with pH 6.2 source phase. Table 3 shows the transport for selected transition metals.

Comparison of the data for compounds **8**—**10** shows that for *c*-5-ester and *c*-5-C-methyl groups, expected to be weakly interacting groups for the bound metal cation, the overall transport of transition metals was very similar. The presence of an interacting group, *c*-5-amide as in compound **7**, increased total transport efficiency by about 35% compared to results from ligands **8**—**10**. In addition, compounds **5** and **6**, with an additional chelating carboxyl group compared to KAI, but little stabilization from across the cyclohexane ring, showed total ion transport increase of 124 and 135%, respectively. Thus it would seem that the main transport interaction was between the two carboxyl groups and the divalent cation.

The transport mechanism was studied by anion chromatographic analysis of the source and receiving phases. For this system, the results were more complex as some counter anion, $CH_3CO_2^-$, was observed as seen in the fourth column of Entry 3 in Table 2. In addition, the amount of anion detected did not exactly correspond to that of cation transported in the system. At present, therefore, we have to accept two forms of chelation or complexation. For transition metal ions bearing $CH_3CO_2^-$, either two or one counter anions were exchanged by the carboxyl groups of the carrier. The ratio of anion and cation detected, 0.6—0.7, suggested that one third of the transport intermediate species were metal^{2+}/carrier^{2-} 1 : 1 form and rest, two thirds, was metal^{2+}/carrier$^-$/$CH_3CO_2^-$ 1 : 1 : 1 form, which should give [X^-]/[M^{2+}] ratio of 0.67 in the receiving phase. For transition metal ions, the concentration of $CH_3CO_2^-$ was 6 (Entry 3) times more than that of metal ion because acetate buffer solution, 200 mmol dm^{-3} as [$CH_3CO_2^-$], was used for the source phase.

Improvement of Pb^{2+}/Cu^{2+} Selectivity. Next improvement of the source phase pH for maximum selectivity was studied. A survey of Pb^{2+} and Cu^{2+} extraction ability over varying pH was performed for compounds **3**—**6**. The *c*-5-ester **4** showed the largest selectivity window of the four analogous compounds studied (Fig. 3a). The extraction profiles of **3**, **5**, and **6** showed significantly less selectivity, so *c*-5-ester **4** was studied in more detail.

Ester **4** was then studied for transport selectivity at various pH values. The transport values for one day indicated high Pb^{2+} transport efficiency at pH 4.5. However, extrapolation

Table 2. Cation and Anion Analyses of Transport Experiments for Some Kemp's Diacid Derivatives

Entry	Carrier (transport time)	Metal M^{2+}	Salts X^-	$[X^-]$ Counter anion transported (mmol dm^{-3})	$[M^{2+}]$ Total cation transported (mmol dm^{-3})	$[X^-]/[M^{2+}]$
1	**7** (48 h)	Mg, Ca, Sr, & Ba[a]	Cl	0	22	0
2	**15** (48 h)	Mg, Ca, Sr, & Ba[a]	Cl	0.6	23	0.03
3	**4** (48 h)	Co, Ni, Cu, Zn, & Pb[b]	CH_3CO_2	16	24	0.67

a) As for Table 1. b) Initial transport conditions (25 °C): source phase–10 mmol dm^{-3} metal acetate(s) AcONa–AcOH buffered solution, pH 6.0—6.4, 15 cm^3, liquid membrane–0.15 mmol of carrier in chloroform, 30 cm^3; receiving phase–0.1 mol dm^{-3} HNO_3, 15 cm^3.

Table 3. Transport Abilities of Kemp's Diacid Derivatives for Transition Metal Ions

Carrier	Metal ions transported to the receiving phase[a] mol%[b] (μmol)					Total μmol
	Cu^{2+}	Pb^{2+}	Zn^{2+}	Ni^{2+}	Co^{2+}	
1	96 (144)	100 (150)	54 (82)	2 (3)	2 (2)	381
2	88 (132)	100 (150)	39 (58)	2.2 (3)	3.6 (5)	348
3[c]	95 (143)	100 (150)	54 (82)	—	—	375
4	83 (124)	100 (150)	49 (73)	4 (5)	6 (8)	360
5[c]	83 (125)	98 (147)	28 (41)	—	—	313
6	74 (111)	99 (148)	29 (43)	0 (0.4)	0 (0)	302
7	96 (144)	99 (149)	54 (80)	3.0 (5)	4.5 (7)	385
8	57 (85)	100 (150)	22 (33)	1.0 (1)	0.5 (1)	270
9	71 (107)	96 (144)	22 (33)	1.1 (2)	1.7 (3)	289
10	70 (105)	99 (149)	23 (35)	1.7 (3)	1.5 (2)	294
KAI[d]	49 (73)	35 (53)	2 (3)	0	0	129
None	0	0	0	0	0	0

a) Initial transport conditions (25 °C): source phase–10 mmol metal acetate AcONa–AcOH buffered solution, pH 6.0—6.4, 15 cm^3, liquid membrane–0.15 mmol of diacid in chloroform, 30 cm^3; receiving phase–0.1 mol dm^{-3} HNO_3, 15 cm^3. b) As for Table 1. c) These transport experiments were run without the presence of Ni^{2+} or Co^{2+} as their transport was insignificant compared with Pb^{2+}, Cu^{2+}, and Zu^{2+}. d) Data taken from Ref. 14.

to higher pH indicated loss of selectivity as the Pb^{2+} transport was maximized at pH 5.1 and 24 h transport, while Cu^{2+} transport was predicted to be an increasing process even at pH 7 and 24 h (Fig. 3b). A different transport profile (not shown), but similar conclusion, held for *t*-5-ester **6**. The *c*-5-ester **4** gave good Pb^{2+}/Cu^{2+} selectivity, 11/1, and high Pb^{2+} transport for 24 h at pH = 4.5 compared to *t*-5-ester **6** Pb^{2+}/Cu^{2+} selectivity of 4/1 for the same high Pb^{2+} transport ability at pH = 5.4. We therefore expected to see **4** give fast and good separation of Pb^{2+} from Cu^{2+} at pH = 4.5, while **6** would have difficulty in attaining the same high Pb^{2+} transport ability with good selectivity at any of the pH values studied.

The *c*-5-ester **4** was finally studied for Pb^{2+}/Cu^{2+} transport selectivity at optimized pH 4.5 over time. Figure 3c shows the time dependent transport results at pH 4.5 for ligand **4** (other ligand profiles not shown). The Pb^{2+} transport was very similar, nonlinear, for all ligands. The important difference was in the linear transport of Cu^{2+}. The transport of Cu^{2+} for esters **4** and **6** was less than half that of amides **3** and **5**. This feature made plain the superior selectivity of the esters. A special comment on the selectivity shown by *t*-5-ester **6** was the excellent predicted selectivity, ca. 10/1, and efficiency for Pb^{2+} transport even at 100 h. Consequently, similar selectivity and Pb^{2+} transport ability was possible for **6** compared to **4**, however, transport time needed to be quintupled, 24 or 100 h for **4** or **6**, respectively.

Lipophilicity of the Ligands. Finally, the issue of lipophilicity was addressed. This involved the synthesis of a wide range of esters and amides with varying hydrocarbon content. It was found by Fyles et al. that 14 saturated carbon atoms/carboxyl group were sufficient for transport of alkaline earth metal ions.[21] Our work demonstrated the ratio of carbon atoms/carboxyl groups could be as low as 10 : 1 for compounds **1** or **4**. If the ratio was reduced to 9 : 1 as in compounds **7**—**10**, the transport ability from pH 9 source phases was impaired. In the case of **9**, there was almost no transport of alkaline earth cations. In the case of transition metal ions, pH 6 allowed efficient transport. The balance between lipophilicity and source phase pH was important.

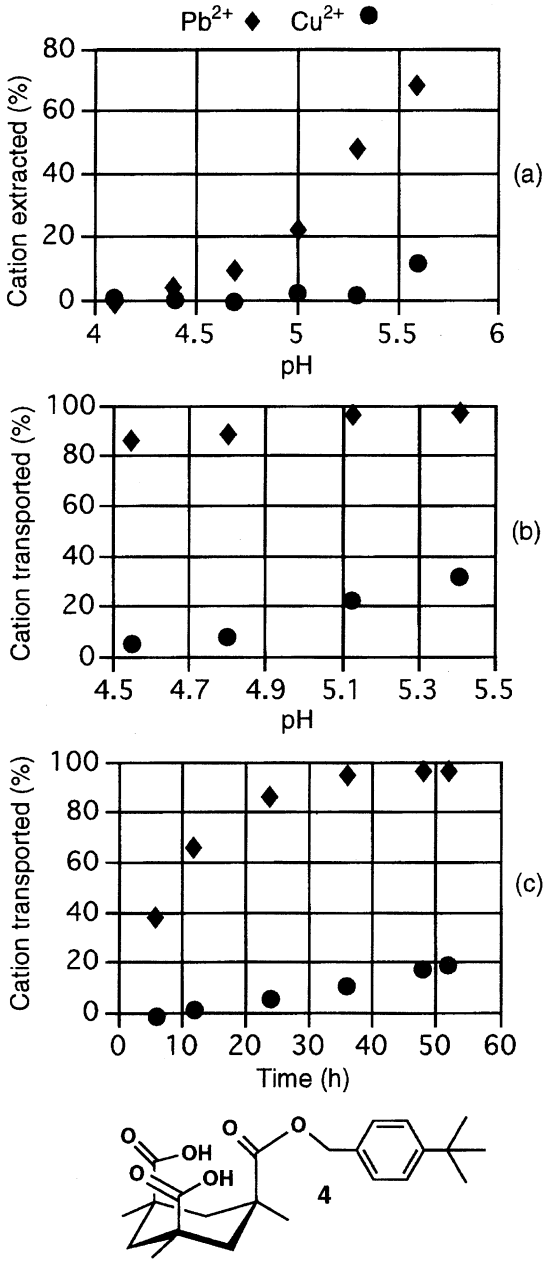


Fig. 3. Pb^{2+} and Cu^{2+} extraction ability (a) from AcONa–AcOH buffered aqueous solutions of varying pH into chloroform by ligand **4** after 16 h shaking at 20 °C, (b) Pb^{2+} and Cu^{2+} transport (%) vs. pH for ligand **4** at 24 h transport, (c) Pb^{2+} and Cu^{2+} transport (%) vs. time (h) for ligand **4** at pH 4.5. Conditions for (b) and (c) were identical to those detailed in Table 1.

More detailed study of pH 9 source phase systems showed that if the ratio of carbon atoms/carboxyl groups was further reduced as in esters **11** and **12**, no transport occurred for alkaline earth metal cations and the recovery of ligand from the chloroform layer after two days transport was minimal. Increasing the number of carbon or oxygen atoms in the lipophilic side group of the *r*-1, *c*-3, *c*-5-esters made little difference in efficiency or selectivity. The transport for 3-(2-hydroxyphenoxy)propyl and 3-(2-methoxyphenoxy)propyl esters **13** and **14** was almost the same as that for **4** and **8** (Table 1). Even the deprotonizable phenol group of **13** at pH≈9 made little difference in the transport of alkaline earth metals.

Conclusion

This paper summarized the synthesis and transport ability of a new series of lipophilic ionophores. Although the carriers had the same basic Kemp's triacid scaffolding as the acid imides previously reported by us, one free carboxyl group was added. Single crystal X-ray diffraction of *c*-5-ester **8** showed pre-organization of a polar cavity protected by a non-polar envelope. Transport efficiency of the diacids was approximately twice that of analogous Kemp's monoacid imides. The mechanism of transport was a 1 : 1 ligand : metal complex for alkaline earth and a mixed 1 : 1 ligand : metal/1 : 1 : 1 ligand : CH_3COO^- : metal complex for transition metals. When the *c*-5-group of the *r*-1, *c*-3, *c*-5-Kemp's diacid derivative was amide, **3** and **7**, Ca^{2+} was selectively transported. When the *c*-5-group of the *r*-1, *c*-3, *c*-5-Kemp's diacid derivative was ester, **4**, **8**, **13**, and **14**, Ba^{2+} was selectively transported. The *t*-5-amides and esters and **15** gave mixed results, but tended to be Ca^{2+} selective. Strongly interacting *c*-5-amide groups gave high total transition metal ion transport while weakly interacting *c*-5-ester and *c*-5-C-methyl groups allowed Pb^{2+} selectivity by destabilizing the interaction with smaller transition metal cations. The *c*-5-ester **4** was found to transport Pb^{2+} at pH 4.5 and 24 h more efficiently with high selectivity than ligands **3**, **5**, and **6**. Finally, side group lipophilicity analysis suggested the amide or ester side groups acted only as lipophilic substituents to keep the complex in the chloroform phase.

Experimental

General Experimental Information. Melting points were obtained on a Mettler FP62 melting point apparatus and were uncorrected. The NMR spectra were obtained from a Varian Gemini 300 Broad Band probe model, using $CDCl_3$, CD_3OD or acetone-d_6 as solvents. Signals were expressed as ppm down field from tetramethylsilane (TMS) used as internal standard. The IR spectra were recorded on a JASCO FT/IR 5300 spectrometer using KBr discs. The elemental analyses were performed at the Materials Analysis Research Center (MARC) at the National Institute of Materials and Chemical Research. Extraction of Pb^{2+} and Cu^{2+} acetate salts was performed by shaking 4 mL of 1.3×10^{-4} M metal acetate salt aqueous solution (1 M = 1 mol dm^{-3}) at various buffered pH with 4 mL of 1.3×10^{-4} M ligand in $CHCl_3$ for 16 h. The transport efficiency and selectivity was analyzed by competitive alkaline earth and transition metal ion transport experiments. The apparatus used was a Pyrex U-tube system, described in previous work by Hirose et al.[9] Analysis of metal ions was done on a Simadzu AA-680 atomic absorption spectrometer.

X-Ray Crystal Structural Analysis of 8. The crystals of **8** belong to a monoclinic system with cell dimensions $a = 17.080(7)$, $b = 12.392(5)$, $c = 8.917(5)$ Å, $\beta = 90.91(4)°$, and $V = 1887(1)$ Å^3. The space group was $P2_1/n$ and $Z = 4$. The empirical formula was $C_{20}H_{26}O_6$, molecular weight 362.40, and calculated density 1.27 g cm^{-3}. The three-dimensional X-ray data were collected with graphite-monochromatic Mo $K\alpha$ radiation ($\lambda = 0.71073$ Å) on a Mac Science MXC18 automatic four-circle diffractometer up to a

maximum 2θ of 55°. The intensity data of 4978 independent reflections were collected and 4339 with $|F_o| > 3\sigma|F_o|$ used in the present X-ray analysis. The structure was solved by the direct method (SIR). All non-hydrogen atoms were located on the initial E synthesis. Remaining hydrogen atoms were located by the difference Fourier map and included in further calculations. Block-diagonal least squares refinements with 26 anisotropic non-hydrogen atoms and 26 isotropic hydrogen atoms converged to a conventional R factor of 0.047. All the calculations were done on a Sun 3/50 work station at the National Institute of Materials and Chemical Research using a structure analysis program system, Crystan-GM.[22—24] Tables of observed and calculated structure factors, listing of atomic positional and anisotropic thermal parameters of non-hydrogen atoms, atomic parameters of hydrogen atoms, complete lists of bond distances, bond angles and torsional angles with their estimated standard deviations have been deposited as Document No. 70028 at the Office of the Editor of Bull. Chem. Soc. Jpn.

Preparation of *r*-1, *c*-3, *c*-5-Kemp's Diacid Starting Material; Kemp's Acid 1,3-Anhydride. At 190 °C and 0.01 mmHg (1 mmHg = 133.322 Pa) pressure, 2.00 g (7.7 mmol) Kemp's triacid was sublimed according to the procedure of Menger et al.[25] This gave white powder (1.61 g, 86.5%): Mp 255—256 °C; IR 3555, 1794, 1761, 1709, 1696, and 1003 cm^{-1}; ^1H NMR (acetone-d_6) δ = 2.60 (d, J = 14 Hz, 2 H), 2.19 (d, J = 14 Hz, 1 H), 1.53 (d, J = 14 Hz, 1 H), 1.42 (d, J = 14 Hz, 2 H), 1.28 (s, 6 H), and 1.24 (s, 3 H); ^{13}C NMR (acetone-d_6) δ = 178.5, 171.8, 50.7, 43.7, 41.1, 39.4, 25.9, 23.0. Found: C, 59.98; H, 6.70%. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71%.

Typical Preparation of *r*-1, *c*-3, *c*-5-Kemp's Diacid Derivatives; *c*-5-[*N*-(4-Butylphenyl)carbamoyl]-1,3,5-trimethyl-*r*-1, *c*-3-cyclohexanedicarboxylic Acid (1). A solution of 500 mg (2.08 mmol) Kemp's acid 1,3-anhydride and 695 mg (6.87 mmol) triethylamine in 10 mL CH_2Cl_2 was made. To this solution 342 mg (2.29 mmol) 4-butyl aniline and a few crystals of 4-dimethylaminopyridine (DMAP) were added. The clear solution was stirred overnight at 40 °C. Then the mixture was diluted with 30 mL CH_2Cl_2, washed with 90 mL of 0.1 M citric acid solution in three portions, dried over $MgSO_4$, and concentrated. The solid residue was recrystallized from ethyl acetate to afford colorless prisms (522.7 mg, 64.5%): Mp 146—147 °C; IR 3297, 1726, 1601 cm^{-1}; ^1H NMR (7.5% $CD_3OD/CDCl_3$) δ = 7.42 (d, J = 6.6 Hz, 2 H), 7.07 (d, J = 6.6 Hz, 2 H), 2.87 (d, J = 15.0 Hz, 1 H), 2.69 (d, J = 15.0 Hz, 2 H), 2.55 (t, J = 7.4 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 = 15.0 Hz, 2 H), 1.08 (d, J = 15.0 Hz, 1 H), 0.91 (t, J = 7.4 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. Found: C, 67.96; H, 8.08; N, 3.57%. Calcd for $C_{22}H_{31}NO_5$: C, 67.84; H, 8.02; N, 3.60%.

In a similar manner, compounds **3**, **4**, **7**, **8**, **11**—**14**, and **15** were prepared from Kemp's acid 1,3-anhydride and the appropriate amine or alcohol.

***c*-5-[*N*-(4-*t*-Butylbenzyl)carbamoyl]-1,3,5-trimethyl-*r*-1, *c*-3-cyclohexanedicarboxylic Acid (3).** A while solid recrystallized from chloroform/pentane to yield colorless needles (50.1% yield): Mp 220—224 °C; IR 3297, 1726, 1601, 1188 cm^{-1}; ^1H NMR (CD_3OD) δ = 7.33 (d, J = 8.6 Hz, 2 H), 7.21 (d, J = 8.6 Hz, 2 H), 4.89 (bs, 1 H), 4.23 (s, 2 H), 2.75 (d, J = 14.7 Hz, 2 H), 2.70 (d, J = 14.7 Hz, 1 H), 1.30 (s, 9 H), 1.25 (s, 6 H), 1.23 (s, 3 H), 1.16 (d, J = 14.7 Hz, 2 H), 1.15 (d, J = 14.7 Hz, 1 H); ^{13}C NMR (CD_3OD) δ = 181.2, 179.9, 151.0, 143.5, 135.0, 128.4, 126.3, 44.2, 44.1, 43.8, 43.3, 42.8, 35.3, 33.7, 31.8, 31.7. Found: C, 68.27; H, 8.24; N, 3.44%. Calcd for $C_{23}H_{33}NO_5$: C, 68.46; H, 8.24; N, 3.47%.

***c*-5-(4-*t*-Butylbenzyloxycarbonyl)-1,3,5-trimethyl-*r*-1, *c*-3-cyclohexanedicarboxylic Acid (4).** A white solid recrystallized from ethyl acetate/pentane to yield colorless needles (59.9% yield): Mp 166—167 °C; IR 1730, 1709 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 7.37 (d, J = 8.4 Hz, 2 H), 7.30 (d, J = 8.4 Hz, 2 H), 5.01 (s, 2 H), 3.01 (d, J = 14.5 Hz, 2 H), 2.69 (d, J = 14.5 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 = 14.5 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. Found: C, 68.24; H, 8.01%. Calcd for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97%.

***c*-5-(*N*-Phenethylcarbamoyl)-1,3,5-trimethyl-*r*-1, *c*-3-cyclohexanedicarboxylic Acid (7).** A white solid recrystallized from benzene to yield colorless prisms (82.0% yield): Mp 245—246 °C; IR 3349, 1717, 1682, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 8.57 (bs, 2 H), 7.24 (m, 6 H), 3.35 (m, 2 H), 2.82 (m, 4 H), 2.54 (d, J = 12.7 Hz, 1 H), 1.21 (s, 6 H), 1.19 (s, 3 H), 1.06 (d, J = 14.3 Hz, 1 H), 0.970 (d, J = 15.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ = 183.8, 177.5, 139.6, 128.8, 128.4, 126.2, 44.5, 42.7, 42.0, 41.6, 35.4, 29.5. Found: C, 66.66; H, 7.55; N, 3.83%. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88%.

***c*-5-(Phenethyloxycarbonyl)-1,3,5-trimethyl-*r*-1, *c*-3-cyclohexanedicarboxylic Acid (8).** A white solid recrystallized from benzene to yield colorless prisms (57.9% yield): Mp 166—167 °C; IR 1738, 1707, 1175, 748, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 7.25 (m, 5 H), 4.17 (t, J = 7.27 Hz, 2 H), 2.95 (d, J = 14.3 Hz, 2 H), 2.94 (t, J = 7.23 Hz, 2 H), 2.59 (d, J = 14.3 Hz, 1 H), 1.20 (s, 6 H), 1.15 (s, 3 H), 0.996 (d, J = 14.3 Hz, 1 H), 0.905 (d, J = 14.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ = 182.4, 176.3, 138.4, 129.0, 128.2, 126.2, 65.0, 44.3, 42.0, 41.6, 41.1, 34.7, 33.1, 29.7. Found: C, 66.09; H, 7.22%. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23%.

***c*-5-Ethoxycarbonyl-1,3,5-trimethyl-*r*-1, *c*-3-cyclohexanedicarboxylic Acid (11).** Isolation as a mojor sideproduct from unsuccessful synthesis of **12** using ethanol stabilized chloroform afforded a white solid which recrystallized from ethyl acetate/hexane to yield colorless needles (41.7%): Mp 252—253 °C; IR 1728, 1701, 1184 cm^{-1}; ^1H NMR (10% $CD_3OD/CDCl_3$) δ = 4.04 (q, J = 7.2 Hz, 2 H), 2.76 (d, J = 15 Hz, 2 H), 2.73 (d, J = 15 Hz, 1 H), 1.27 (s, 6 H), 1.24 (t, J = 7.2 Hz, 3 H), 1.23 (s, 3 H), 1.04 (d, J = 15 Hz, 1 H), 1.03 (d, J = 15 Hz, 2 H); ^{13}C NMR (10% $CD_3OD/CDCl_3$) δ = 180.2, 177.7, 60.8, 43.0, 41.6, 41.5, 31.4. Found: C, 58.56; H, 7.76%. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.75%.

***c*-5-(*N*-Morpholinoethoxycarbonyl)-1,3,5-trimethyl-*r*-1, *c*-3-cyclohexanedicarboxylic Acid (12).** A mixture of 500 mg (2.08 mmol) Kemp's acid 1,3-anhydride, 682 mg (5.20 mmol) 2-*N*-morpholinoethanol, a few crystals of DMAP, and 20 mL CH_2Cl_2 were stirred at 40 °C overnight. The CH_2Cl_2 was evaporated off and the residue treated with seven successive washes of pentane to afford a white powder (345 mg, 45%): Mp 162—163 °C; IR 1732, 1686, 1169 cm^{-1}; ^1H NMR (10% $CD_3OD/CDCl_3$) δ = 4.30 (m, 2 H), 4.03 (t, J = 7.5 Hz, 4 H), 3.22 (m, 6 H), 2.82 (d, J = 14.5 Hz, 1 H), 2.69 (d, J = 14.5 Hz, 2 H), 1.27 (s, 6 H), 1.20 (s, 3 H), 1.13 (d, J = 14.5 Hz, 1 H), 1.08 (d, J = 14.5 Hz, 2 H); ^{13}C NMR (10% $CD_3OD/CDCl_3$) δ = 183.5, 175.8, 63.7, 56.0, 51.9, 48.9, 48.6, 44.9, 43.2, 41.6, 33.0, 29.5. Found: C, 58.21; H, 7.77; N, 3.67%. Calcd for $C_{18}H_{29}NO_7$: C, 58.20; H, 7.87; N, 3.77%.

***c*-5-[3-(2-Hydroxyphenoxy)propoxycarbonyl]-1,3,5-trimethyl-*r*-1, *c*-3-cyclohexanedicarboxylic Acid (13).** A white solid recrystallized from acetonitrile to yield transparent prisms (66.6% yield): Mp 163—164 °C; IR 3370, 1709, 1304, 745 cm^{-1}; ^1H NMR (acetone-d_6) δ = 6.80 (m, 4 H), 4.16 (t, J = 6.3 Hz, 2 H), 4.11 (t, J = 6.3 Hz, 2 H), 2.72 (d, J = 14 Hz, 3 H), 2.11 (quintet, J = 6.3 Hz, 2 H), 1.26 (s, 6 H), 1.22 (s, 3 H), 1.19 (d, J = 14 Hz, 3 H); ^{13}C NMR

(acetone-d_6) δ = 179.0, 177.3, 122.0, 120.4, 116.0, 113.6, 66.4, 62.0, 43.0, 42.2, 42.1, 31.6, 30.6, 29.1. Found: C, 61.67; H, 6.91%. Calcd for $C_{21}H_{28}O_8$: C, 61.75; H, 6.91%.

***c*-5-[3-(2-Methoxyphenoxy)propoxycarbonyl]-1,3,5-trimethyl-*r*-1, *c*-3-cyclohexanedicarboxylic Acid (14).** A white solid recrystallized from benzene to yield colorless needles (28.0% yield): Mp 108—111 °C; IR 3526, 1738, 1711, 1254, 758 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 6.90 (m, 4 H), 4.20 (t, J = 6.5 Hz, 2 H), 4.14 (t, J = 6.5 Hz, 2 H), 3.86 (s, 3 H), 2.94 (d, J = 15 Hz, 2 H), 2.64 (d, J = 15 Hz, 1 H), 2.18 (quintet, J = 6.5 Hz, 2 H), 1.22 (s, 6 H), 1.21 (s, 3 H), 1.03 (d, J = 15 Hz, 1 H), 0.945 (d, J = 15 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ = 182.3, 176.5, 149.5, 148.4, 128.4, 121.1, 113.3, 111.9, 65.9, 61.5, 56.0, 44.2, 42.3, 41.9, 41.3, 32.9, 30.1, 28.4. Found: C, 62.81; H, 7.26%. Calcd for $C_{22}H_{30}O_8$: C, 62.54; H, 7.16%.

***c*-5-[*N*-(3,5-Difluorobenzyl)carbamoyl]-1,3,5-trimethyl-*r*-1, *c*-3-cyclohexanedicarboxylic Acid (15).** A white solid recrystallized from chloroform/ethanol/pentane to yield colorless needles (47% yield): Mp 158—159 °C; IR 3291, 1718, 1626, 1192 cm^{-1}; ^1H NMR (7% $CD_3OD/CDCl_3$) δ = 8.07 (t, J = 5 Hz, 1 H), 6.80 (d, J = 9 Hz, 2 H), 6.69 (tt, J = 9 Hz, J = 2 Hz, 1 H), 4.21 (d, J = 5 Hz, 2 H), 2.80 (d, J = 15 Hz, 2 H), 2.70 (d, J = 15 Hz, 1 H), 1.27 (s, 9 H), 1.12 (d, J = 15 Hz, 1 H), 1.06 (d, J = 15 Hz, 2 H); ^{13}C NMR (7% $CD_3OD/CDCl_3$) δ = 181.5, 178.4, 164.7, 142.7, 110.4 (d, J = 25 Hz), 102.4 (t, J = 25 Hz), 43.8, 43.1, 42.8, 42.3, 41.5, 34.2, 30.4. Found: C, 59.31; H, 6.07; N, 3.61%. Calcd for $C_{19}H_{23}F_2NO_5$: C, 59.53; H, 6.05; N, 3.65%.

Preparation of *r*-1, *c*-3, *t*-5-Kemp's Diacid Starting Material; *r*-1, *c*-3, *t*-5-Kemp's acid 1,3-Anhydride-5-chloride. A 25 mL round bottom flask was charged with 3.00 g (11.62 mmol) *r*-1, *c*-3, *t*-5-Kemp's triacid and suspended in 30 mL thionyl chloride. The resulting mixture was heated at reflux for 3 h. After cooling, the thionyl chloride was removed by distillation to yield yellowish crystals. The crystalline residue was dissolved in a minimum of hot chloroform and precipitated by addition of hexane as colorless needles (1.92 g, 64% yield): Mp 196—197 °C; IR 1797, 1786, 1759, 1005 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.18 (d, J = 15 Hz, 2 H), 2.10 (d, J = 15 Hz, 1 H), 1.93 (d, J = 15 Hz, 2 H), 1.43 (s, 6 H), 1.41 (s, 3 H), 1.40 (d, J = 15 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ = 178.6, 171.9, 50.7, 43.8, 41.2, 39.5, 26.0, 23.0. Found: C, 55.63; H, 5.82%. Calcd for $C_{12}H_{15}ClO_4$: C, 55.80; H, 5.85%.

Typical Preparation of *r*-1, *c*-3, *t*-5-Kemp's Acid 1,3-Anhydride Derivatives; *t*-5-[*N*-(4-Butylphenyl)carbamoyl]-1,3,5-trimethyl-*r*-1, *c*-3-cyclohexanedicarboxylic Anhydride (2a). In an oven dried 50 mL round bottom flask 200 mg (0.773 mmol) *r*-1, *c*-3, *t*-5-Kemp's acid 1,3-anhydride-5-chloride was dissolved in 15 mL CH_2Cl_2. To this solution 126.9 mg (0.851 mmol) 4-butyl aniline was added to make a white slurry. To this mixture 234 mg (2.32 mmol) triethylamine was added. After stirring overnight at 40 °C, the reaction mixture was diluted with 20 mL CH_2Cl_2 and washed with three 25 mL portions of 1.0 M aqueous HCl solution. The organic phase was dried over $MgSO_4$ and concentrated to give a white foam, which was recrystallized from benzene to afford colorless plates (217 mg, 75.7%): Mp 157—158 °C; IR 3424, 1796, 1755, 1689, 1007 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 7.36 (m, 3 H), 7.10 (d, J = 9 Hz, 2 H), 2.58 (t, J = 8 Hz, 2 H), 2.12 (m, 3 H), 2.05 (d, J = 15 Hz, 2 H), 1.5—1.3 (bm, 14 H), 0.916 (t, J = 8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ = 174.5, 172.8, 139.6, 135.0, 128.9, 120.3, 44.3, 42.0, 41.2, 39.4, 35.0, 33.6, 26.0, 23.2, 22.2, 13.9. The product was used without further purification.

In a similar manner, compounds **5a**, **6a**, **9a**, and **10a** were prepared from *r*-1, *c*-3, *t*-5-Kemp's acid 1,3-anhydride-5-chloride and the appropriate amine or alcohol.

***t*-5-[*N*-(4-*t*-Butylbenzyl)carbamoyl]-1,3,5-trimethyl-*r*-1, *c*-3-cyclohexanedicarboxylic Anhydride (5a).** A white foam was recrystallized from ethyl acetate/pentane to afford colorless needles (51.2% yield): Mp 165—169 °C; IR 3435, 1795, 1759, 1674, 1005 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 7.36 (d, J = 8.5 Hz, 2 H), 7.16 (d, J = 8.5 Hz, 2 H), 5.92 (t, J = 5.3 Hz, 1 H), 4.37 (d, J = 5.3 Hz, 2 H), 2.06 (d, J = 14.3 Hz, 2 H), 2.15 (d, J = 14.3 Hz, 1 H), 1.94 (d, J = 14.3 Hz, 2 H), 1.45 (d, J = 14.3 Hz, 1 H), 1.37 (s, 6 H), 1.31 (s, 9 H), 1.27 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ = 176.5, 172.8, 150.7, 134.6, 127.4, 125.7, 44.4, 43.7, 41.4, 41.2, 39.3, 34.5, 31.3, 26.1, 23.0. The product was used without further purification.

***t*-5-(4-*t*-Butylbenzyloxycarbonyl)-1,3,5-trimethyl-*r*-1, *c*-3-cyclohexanedicarboxylic Anhydride (6a).** A white powder was recrystallized from ethyl acetate/pentane to afford colorless needles (73% yield): Mp 151—152 °C; IR 1796, 1767, 1738, 1011 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 7.40 (d, J = 8.5 Hz, 2 H), 7.25 (d, J = 8.5 Hz, 2 H), 5.08 (s, 2 H), 2.11 (d, J = 14.7 Hz, 2 H), 2.35 (d, J = 13.6 Hz, 1 H), 1.89 (d, J = 14.7 Hz, 2 H), 1.38 (d, J = 13.6 Hz, 1 H), 1.37 (s, 6 H), 1.33 (s, 9 H), 1.29 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ = 176.3, 172.6, 151.6, 132.5, 127.9, 125.6, 67.0, 43.9, 41.5, 41.3, 39.3, 34.7, 31.3, 26.1, 23.1. Found: C, 71.46; H, 7.79%. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82%.

***t*-5-[*N*-Phenethylcarbamoyl]-1,3,5-trimethyl-*r*-1, *c*-3-cyclohexanedicarboxylic Anhydride (9a).** A white foam was recrystallized from ethyl acetate/hexane to afford colorless needles (72.6%): Mp 137—138 °C; IR 3366, 1801, 1769, 1639, 1013 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 7.27 (m, 5 H), 5.58 (s, 1 H), 3.53 (d, J = 6.8 Hz, 1 H), 3.48 (d, J = 6.8 Hz, 1 H), 2.81 (t, J = 6.8 Hz, 2 H), 2.03 (d, J = 13.6 Hz, 1 H), 1.96 (d, J = 14.6 Hz, 2 H), 1.82 (d, J = 14.6 Hz, 2 H), 1.41 (d, J = 13.6 Hz, 1 H), 1.35 (s, 6 H), 1.15 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ = 176.6, 172.8, 138.5, 128.8, 126.8, 44.5, 41.5, 41.3, 41.0, 39.4, 35.4, 26.1, 23.0. Found: C, 69.99; H, 7.35; N, 4.03%. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.33; N, 4.08%.

***t*-5-(Phenethyloxycarbonyl)-1,3,5-trimethyl-*r*-1, *c*-3-cyclohexanedicarboxylic Anhydride (10a).** A white powder was recrystallized from ethyl acetate/pentane to afford colorless needles (36.6% yield): Mp 136—137 °C; IR 1796, 1767, 1732, 999 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 7.28 (m, 5H), 4.31 (t, J = 6.8 Hz, 2 H), 2.95 (t, J = 6.8 Hz, 2 H), 1.99 (d, J = 13.0 Hz, 1 H), 1.98 (d, J = 15.0 Hz, 2 H), 1.75 (d, J = 15.0 Hz, 2 H), 1.34 (s, 6 H), 1.30 (d, J = 13.0 Hz, 1 H), 1.20 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ = 176.4, 172.6, 137.4, 129.0, 128.6, 126.8, 65.6, 43.9, 41.4, 41.2, 39.2, 35.0, 26.1, 23.0. Found: C, 69.93; H, 7.09%. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02%.

Typical Procedure for Preparation of *r*-1, *c*-3, *t*-5-Kemp's Diacid Derivatives; *t*-5-[*N*-(4-Butylphenyl)carbamoyl]-1,3,5-trimethyl-*r*-1, *c*-3-cyclohexanedicarboxylic Acid (2). A solution of 500 mg (1.35 mmol) anhydride amide **2a** in 15 mL tetrahydrofuran was mixed with 0.5 mL aqueous 1 M NaOH solution at 45 °C overnight. The mixture was taken up in 20 mL diethyl ether, and the organic layer washed with three 20 mL portions of aqueous 5% HCl solution. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was washed with pentane to promote crystallization, then recrystallized from 1% ethanol/chloroform to yield colorless needles (345 mg, 65.6%): Mp 177—178 °C; IR 3283, 1705, 1642 cm^{-1}; ^1H NMR ($CDCl_3$/acetone-d_6) δ = 8.30 (s, 1 H), 7.48 (d, J = 8.5 Hz, 2 H), 7.12 (d, J = 8.5 Hz, 2 H), 2.65 (d, J = 14.5 Hz, 1 H), 2.57 (t, J = 7.5 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 = 7.5 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. Found: C, 67.66; H, 8.01; N, 3.55%. Calcd for $C_{22}H_{31}NO_5$: C, 67.84; H, 8.02; N, 3.60%.

In a similar manner, compounds **5**, **6**, **9**, and **10** were prepared from the corresponding *r*-1, *c*-3, *t*-5-Kemp's acid 1,3-anhydride 5-amide or 5-ester.

***t*-5-[*N*-(4-*t*-Butylbenzyl)carbamoyl]-1,3,5-trimethyl-*r*-1, *c*-3-cyclohexanedicarboxylic Acid (5).** The residue was washed with pentane to promote crystallization, then recrystallized from benzene/ethyl acetate to yield colorless needles (64% yield): Mp 212—213 °C; IR 3400, 1703, 1620 cm^{-1}; ^1H NMR (5% $CD_3OD/CDCl_3$) δ = 7.37 (d, J = 8.4 Hz, 2 H), 7.19 (d, J = 8.4 Hz, 2 H), 6.19 (t, J = 5.2 Hz, 1 H), 4.38 (d, J = 5.2 Hz, 2 H), 2.80 (d, J = 14.8 Hz, 1 H), 2.26 (d, J = 14.2 Hz, 2 H), 1.70 (d, J = 14.2 Hz, 2 H), 1.31 (s, 9 H), 1.28 (s, 6 H), 1.21 (s, 3 H), 1.16 (d, J = 14.8 Hz, 1 H); ^{13}C NMR (5% $CD_3OD/CDCl_3$) δ = 182.1, 178.2, 150.6, 135.1, 127.6, 125.7, 43.6, 42.5, 41.9, 41.3, 40.9, 34.5, 31.3, 31.0, 24.9. Found: C, 68.38; H, 8.23; N, 3.45%. Calcd for $C_{23}H_{35}NO_5$: C, 68.12; H, 8.70; N, 3.45%.

***t*-5-(4-*t*-Butylbenzyloxycarbonyl)-1,3,5-trimethyl-*r*-1, *c*-3-cyclohexanedicarboxylic Acid (6).** The residue was washed with pentane and recrystallized from ethyl acetate/pentane to yield colorless needles (83% yield): Mp 163—164 °C; IR 1730, 1701 cm^{-1}; ^1H 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. Found: C, 68.30; H, 8.03%. Calcd for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97%.

***t*-5-[*N*-Phenethylcarbamoyl]-1,3,5-trimethyl-*r*-1, *c*-3-cyclohexanedicarboxylic Acid (9).** The residue was washed with pentane to promote crystallization, then recrystallized from ethyl acetate/pentane to yield colorless needles (57.2% yield): Mp 182—183 °C; IR 3349, 1711, 1640, 1528 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 7.26 (m, 5 H), 5.61 (s, 1 H), 3.55 (d, J = 6.8 Hz, 1 H), 3.51 (d, J = 6.8 Hz, 1 H), 2.83 (t, J = 6.8 Hz, 2 H), 2.53 (d, J = 15 Hz, 1 H), 2.15 (d, J = 15 Hz, 2 H), 1.76 (d, J = 15 Hz, 2 H), 1.33 (d, J = 15 Hz, 1 H), 1.24 (s, 6 H), 1.13 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ = 184.7, 177.8, 138.6, 128.7, 126.7, 42.4, 41.3, 41.1, 40.8, 39.7, 35.4, 29.3, 28.3. Found: C, 66.63; H, 7.55; N, 3.79%. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88%.

***t*-5-(Phenethyloxycarbonyl)-1,3,5-trimethyl-*r*-1, *c*-3-cyclohexanedicarboxylic Acid (10).** The residue was washed with pentane and recrystallized from ethyl acetate/pentane to yield colorless needles (48.0% yield): Mp 127—130 °C; IR 1718, 1705, 1169 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 7.26 (m, 5 H), 4.33 (t, J = 6.9 Hz, 2 H), 2.97 (t, J = 6.9 Hz, 2 H), 2.43 (d, J = 15 Hz, 1 H), 2.14 (d, J = 14.3 Hz, 2 H), 1.99 (d, J = 14.3 Hz, 2 H), 1.18 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ = 185.3, 178.2, 137.5, 128.9, 128.5, 126.7, 65.3, 42.1, 41.1, 40.9, 38.7, 35.0, 28.7, 28.4. Found: C, 66.21; H, 7.35%. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23%.

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