Synthesis and Evaluation of Superior Calcium and Mercury Transport by Simple Monocarboxylic Acids of Kemp's Triacid

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(Received September 28, 1998)

Transport abilities of alkaline earth, transition, and heavy metal ions were examined for three kinds of disubstituted monoacid derivatives of Kemp's triacid as transport agents for a liquid membrane system. Diamide derivatives showed high transport ability for Ca^{II} over Mg^{II}, with selectivity ratios greater than 25. Imide monoacids were also Ca^{II} selective. For transition and heavy metal ions, all monoacids including diester monoacid showed very high Hg^{II} transport, but with different selectivities depending on the functional group. High Hg^{II}/Ag^{I} (= 24), Hg^{II}/Cu^{II} (= 194), and Hg^{II}/Pb^{II} (= 85) selectivities were observed for diamide, diester, and imide monoacids, respectively. The transport mechanisms are discussed for alkaline earth, transition, and heavy metal ions utilizing ion chromatography analysis of anions co-transported.

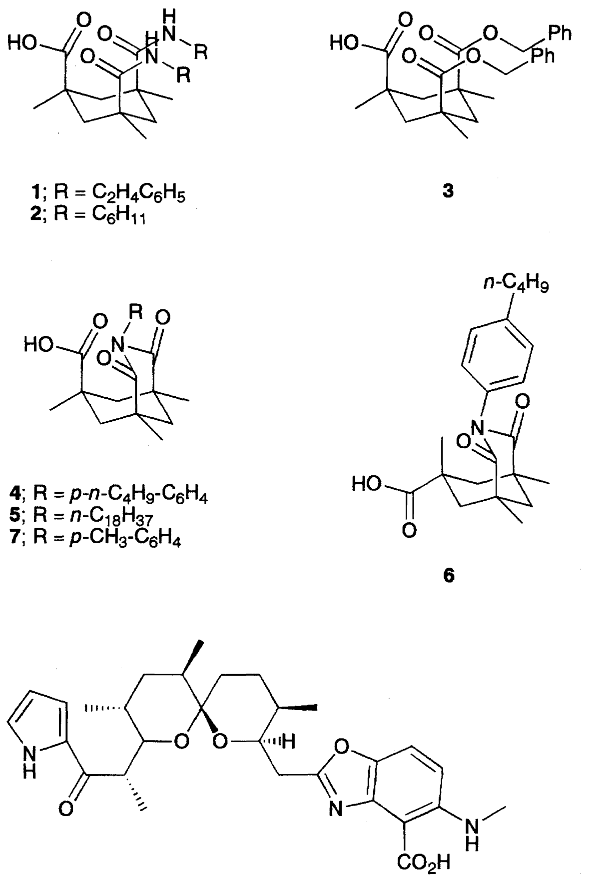
In the study of host–guest chemistry,[1] the interaction between organic compounds and metal ions has received vigorous attention. This interaction forms the basis for the development of artificial ionophores used in metal ion extraction and transport.[2] Because the transport behavior depends on two contradictory factors, uptake and release of metal ions, design of good transport agents is an interesting and useful subject.

A number of transport agents have been developed for divalent alkaline earth[3] and transition[4] metal cations. Many of these synthetic ionophores carry two or more ionizable groups, such as carboxyl, phenolic hydroxy, or carbamoyl groups, for effective 1 : 1 or intramolecular chelation. In contrast, some natural ionophores are known to have only one carboxyl group, for example, monensin and A23187. Lasalocid (X-537A), which has one carboxyl and one hydroxy group on the same phenyl ring, is also regarded as a monobasic ionophore.[5] Among these natural ionophores, A23187 and X-537A are more selective for alkaline earth metal ions than for alkali metal ions, even though they are monobasic ionophores.[5] The X-ray structural analyses of Ca-A23187,[6] Mg-A23187,[7] and Ba-X-537A[8] complexes show 1 : 2 metal/ionophore stoichiometry, where two organic molecules beautifully wrap up a divalent metal cation to shield it from the aqueous environment. The data infer that this intermolecular cooperation of two ionophores makes a significant contribution to effective ion transport.

Recently we reported that Kemp's imide monoacids were effective transport agents for divalent alkaline earth, transition, and heavy metal ions.[9] In accordance with natural ionophore studies, univalent alkali metal ions were not transported by mono-carboxylic acid carriers. Preliminary examination of their binding stoichiometry was performed by ^{13}C NMR titration technique, using Hg^{II} as a guest metal cation.[9a] Although the 1 : 2 Hg^{II}/transport agent ratio was demonstrated, the ratio remains to be investigated for alkaline earth metal ions. To further elucidate the transport mechanism of divalent cation-monobasic transport agent systems and improve their transport ability, we synthesized another series of Kemp's monoacid derivatives, **1**—**3**. This study reports their transport abilities, and the metal to ligand stoichiometry examined by both cation and anion analyses in comparison with imide monoacid derivatives, **4** and **5** (Chart 1). Single crystal X-ray data of monoacids **1** and **7** were used to infer the proposed transport mechanism. Structural effects caused by *cis–trans* isomerization of the cyclohexane ring were also studied by comparison with imide monoacid **6**.

Results and Discussion

Alkaline Earth Metal Ion Transport. Transport ability through a $CHCl_3$ liquid membrane was performed in a typical U-type glass tube cell.[3d,4c,10] The term "transport ability" is defined as 'the amount transported' or 'the ratio of metal ions (μmol) in the source and receiving phases for a certain time period'. On the other hand, "the total transport ability" refers to 'the sum of the amounts transported' or 'a source phase/receiving phase ratio of all metal ions subjected



1; R = $C_2H_4C_6H_5$
2; R = C_6H_{11}

3

4; R = p-n-C_4H_9-C_6H_4
5; R = n-$C_{18}H_{37}$
7; R = p-CH_3-C_6H_4

6

A23187

Chart 1.

to the transport experiment'. Negligible or non-existent ion transport was confirmed by control experiments without monoacids in the chloroform phase (Run 15 in Table 1) except for $\mathrm{Ba^{II}}$; 1—2% $\mathrm{Ba^{II}}$ permeated the liquid membrane without transport agents in one day under the standard conditions. The transport agents were quantitatively recovered from the $CHCl_3$ phase after experiments.

Three new Kemp's monoacids, two diamides **1** and **2** and one diester **3**, were subjected to competitive and single ion transport experiments. Table 1 shows the combined transport results of **1**, **2**, and **3** and those of another class of Kemp's monoacids, imide acids **4** and **5**, reported in our previous paper.[9a)] The driving force of the transport phenomenon is the proton concentration difference between the source phase, pH ca. 9 for alkali and alkaline earth metal ions and pH ca. 6 for transition and heavy metal ions, and the receiving phase, pH ca. 1 in this study [cf. Footnote a) of Tables 1 and 2].[9a,9b)] As seen from the table, the new monoacids transported divalent alkaline earth metal ions very efficiently. The total transport ability of **1** and **2** was about double the imide acid total transport ability. Additionally, their $\mathrm{Ca^{II}/Ba^{II}}$ selectivity after 12 h was better than **4** and **5**. The increased number of functional groups which could interact with metal ions, one carboxyl and two carbamoyl groups for **1** and **2** vs. one carboxyl and one imide group for **4** and **5**, appeared to be the cause of the marked differences.

The increase in alkyl group bulkiness on the amide nitrogen was expected to enhance metal ion selectivity considering the ionic radii of $\mathrm{Ca^{II}}$ (1.14 Å) and $\mathrm{Ba^{II}}$ (1.50 Å).[11)] In fact the higher $\mathrm{Ca^{II}/Ba^{II}}$ selectivity of 48 was obtained for **2** by changing the phenethyl group of **1** ($\mathrm{Ca^{II}/Ba^{II}}$ = 12) to

Table 1. Amount of Alkaline Earth Metal Ions Transported[a)]

Run	Carrier	Metal ions transported to the receiving phase/mol%[b)] (μmol)				Selectivity
	(time)	$\mathrm{Mg^{II}}$	$\mathrm{Ca^{II}}$	$\mathrm{Sr^{II}}$	$\mathrm{Ba^{II}}$	
1	**1** (12 h)	2.7 (4.0)	70 (105)	14 (21)	6.0 (9.0)	Ca/Mg = 26, Ca/Ba = 12
2	**1** (24 h)	4.7 (7.1)	99 (149)	33 (50)	23 (35)	Ca/Mg = 21, Ca/Ba = 4.3
3	**1** (12 h)[c)]	—	99 (148)	—	—	
4	**1** (12 h)[d)]	0.5 (7.0)	22 (330)	1.8 (27)	0.5 (7.0)	Ca/Mg = 47, Ca/Ba = 47
5	**2** (12 h)	2.4 (3.5)	64 (96)	6.4 (9.6)	1.3 (2.0)	Ca/Mg = 27, Ca/Ba = 48
6	**2** (24 h)	1.8 (2.7)	90 (135)	20 (30)	4.4 (6.6)	Ca/Mg = 50, Ca/Ba = 20
7	**3** (12 h)	1.5 (2.2)	18 (27)	5.9 (8.9)	2.6 (3.9)	Ca/Mg = 12, Ca/Ba = 6.9
8	**3** (24 h)	3.2 (4.8)	39 (59)	14 (21)	9.9 (15)	Ca/Mg = 12, Ca/Ba = 3.9
9	**4** (24 h)	14 (21)	56 (84)	1.6 (2.4)	3.3 (5.0)	Ca/Mg = 4.0, Ca/Ba = 17
10	**5** (24 h)	11 (17)	49 (73)	5.3 (8.0)	12 (18)	Ca/Mg = 4.3, Ca/Ba = 4.1
11	**6** (24 h)	0.7 (1.1)	2.2 (3.3)	1.1 (1.7)	1.6 (2.4)	Ca/Mg = 3.0, Ca/Ba = 1.4
12	**A23187** (12 h)	19 (28)	97 (146)	3.3 (5.0)	0.8 (1.2)	Ca/Mg = 5.2, Ca/Ba = 122
13	**A23187** (12 h)[c)]	—	99 (148)	—	—	
14	$C_{17}H_{35}CO_2H$ (48 h)	0.5 (0.7)	ca. 0 (0)	0.7 (1.0)	2.2 (3.2)	
15	None (24 h)	ca. 0	ca. 0	ca. 0	1—2	

a) Initial transport conditions (25 °C): source phase—10 mM (= mmol dm^{-3}) metal chloride tris-buffered solution, pH ≈ 9.0—9.4, 15 ml, liquid membrane—0.15 mmol of monoacid in 30 ml of chloroform, receiving phase—0.1 M (= mol dm^{-3}) HNO_3 15 ml. Each phase was mechanically stirred at 200 rpm. b) mol% = 100× (moles of ion M^{2+} transported)/(initial moles of ion M^{2+} in the source phase). c) The results of single ion transport experiments of $\mathrm{Ca^{II}}$. d) 100 mM $CaCl_2$ solution and 0.2 M HNO_3 were used for the source and receiving phases, respectively.

Table 2. Amount of Transition Metal Ions Transported after 2 Days[a)]

Run	Carrier	Metal ions transported to the receiving phase mol%[b)] (μmol)					Selectivity
		Cu^{II}	Pb^{II}	Zn^{II}	Ni^{II}	Co^{II}	
1	**1**	90 (135)	51 (76)	3.4 (5.1)	1.1 (1.7)	0.5 (0.7)	Cu/Pb = 1.8
2	**2**	81 (121)	11 (17)	0.5 (0.8)	ca. 0	3.7 (5.6)	Cu/Pb = 7.1
3	**3**	9.1 (14)	56 (84)	0.4 (0.6)	0.9 (1.4)	0.8 (1.2)	Cu/Pb = 0.17
4	**4**	65 (98)	27 (40)	1 (1)	0	0	Cu/Pb = 2.5
5	**5**	49 (73)	35 (53)	2 (3)	0	0	Cu/Pb = 1.4
6	**6**	61 (92)	21 (31)	0	3 (4)	0	Cu/Pb = 3.0
7	None	0	0	0	0	0	

a) Initial transport conditions (25 °C): source phase—10 mM metal acetate AcONa–AcOH buffered solution, pH ≈ 6.0—6.4, 15 ml, liquid membrane—0.15 mmol of monoacid in 30 ml of chloroform, receiving phase—0.1 M HNO_3 15 ml. Each phase was mechanically stirred at 200 rpm. b) mol% = 100× (moles of ion M^{2+} transported)/(initial moles of ion M^{2+} in the source phase).

the bulky cyclohexyl group (Runs 1 and 2 vs. Runs 5 and 6). The increased bulkiness of **2** probably improved Ca^{II} metal complex solubility in the liquid membrane phase by more effectively protecting the smaller hydrophilic Ca^{II}.

The transport selectivity of diester **3** was also good for Ca^{II} ions, but the transport ability was not as high (Run 7). This phenomenon was also observed in transport experiments using Kemp's monosubstituted diacids as carriers.[12d)] This result also showed that carbamoyl groups have stronger interaction with Ca^{II} than with ester groups.[12)] The transport efficiency and selectivity was controlled not only by the number of carboxyl groups, but also by changing the other functional groups. The imide group had surprisingly good affinity toward Ca^{II}, considering the number of functional groups: that is, one imide group for **4** and **5** and two amide or ester groups for **1**—**3**.

Alkaline earth metal ion transport ability of natural calcium ionophore A23187 was also examined in this study, and the results are summarized in Table 1 (Runs 12 and 13). The time dependence of transported Ca^{II} is shown in Fig. 1 for **1** and A23187. Although the transport ability of **1** was less than A23187 (Runs 1 and 12) for competitive transport, the Ca^{II}/Mg^{II} selectivity, 26, was much higher than A23187, Ca/Mg = ca. 5, due to good affinity between amide and Ca^{II} as mentioned above. In contrast to competitive experiments, Ca^{II} single ion transport showed that diamide **1** was as speedy and efficient as A23187 (Runs 3 and 13 and Fig. 1). In the same way, **1** transported Sr^{II} almost completely in one half day (data not shown). This suggested that diamide **1** contained a proper "space", i.e. a cavity in the center of two carbamoyl and one carboxyl groups for binding Ca^{II}, and the cavity accommodated even the larger Sr^{II}. High transport ability and selectivity was maintained even with increased initial metal ion concentration in the source phase (Run 4).

Wierenga et al.[3a)] prepared acyclic polyether transport agents and Rebek et al.[3c)] prepared chelating and transport agents having two imide acid moieties. Both agents showed high Ca^{II} transport ability comparable to that of natural ionophore A23187, although details, like selectivities, were not reported. From the transport profile shown in Fig. 1, diamide monoacid **1** is comparable to these precedent molecules for Ca^{II} single ion transport.

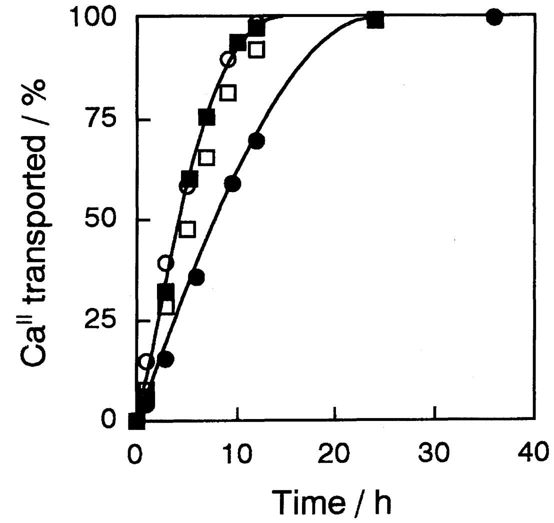


Fig. 1. Time dependence of the amount of Ca^{II} transported by Kemp's diamide monoacid **1** (○, ●) and A23187 (□, ■). The open symbols (○, □) represent single ion transport and the filled symbols (●, ■) represent competitive transport.

The effect of carboxyl group stereo isomerism was examined for *trans*-imide monoacid in Run 11. The transport ability of **6** was much less than that of *cis*-imide monoacids **4** and **5**, and differs greatly from those of the other transport agents. When extraction from the source phase occurred, about 90% of Ca^{II} and 75% Sr^{II}, but very little (1—2%) of these ions were released into the receiving phase. Because no precipitation was observed, highly lipophilic cluster-like complex formation is expected. This appears to result from differences in the metal-carrier ratios of the penetrant complex, which needs further investigation. The *cis* orientation of carboxyl group and imide group worked effectively for alkaline earth ion transport.

Recently, calixarene and related macrocyclic derivatives were reported as new Ca^{II} selective extractants.[13)] The present data, however, show that a macro-size cleft or cavity is not always necessary for ion transport. Efficient transport requires the appropriate balance between formation and decomposition of metal complex at the membrane interfaces. The simple synthesis (cf. Experimental) and compact structures starting from Kemp's triacid are also advantages of artificial ionophores.

Transport of Transition and Heavy Metal Ions. Table 2 summarizes the transport ability of monoacids used in the previous section for five transition and heavy metal ions. New monoacids **1** and **2** also showed higher transport ability than imide monoacids for transition and heavy metal ions (Runs 1 and 2 vs. Runs 4 and 5). Usually, higher ability leads to lower selectivity, but in this case the metal selectivity for Cu^{II} over Pb^{II} was improved over structurally related imide monoacids. Considering the smaller atomic radius of Cu^{II} (0.76 Å for coordination number 4) compared to Pb^{II} (1.32 Å for coordination number 6),[11] we can explain higher Cu^{II}/Pb^{II} selectivity for **2** by the higher steric hindrance of a cyclohexyl group (Runs 1 and 2).

On the other hand, the total transition/heavy metal ion transport ability of diester monoacid **3** was lower than that of other monoacids (Run 3). Interestingly, diester **3** preferred Pb^{II} over Cu^{II}. This selectivity was higher than those of Kemp's monoester diacids examined by Baldwin et al.[12d] The increased affinity toward Pb^{II} appears to result from an increase in the number of ester groups.

While it has been shown that many ligands bearing amide groups extract or transport Cu efficiently and selectively,[4a,4c,14] there are additional reports mentioning Pb over Cu selectivity using ligands bearing oxygen rich functionality, like ether and carboxyl groups.[4d,4e,15] Although a detailed discussion has not been given, one possible explanation for these results, including the present discussion, is the HSAB rule.[16] According to this rule, Cu^{II} and Pb^{II} are classified into the borderline acids. However it was suggested that Pb^{II}, $[Xe][5d]^{10}[6s]^2$ electron configuration, could be harder than Pb^{IV}, $[Xe][5d]^{10}$ electron configuration, because of the shielding effect of the 6s orbital. In analogy, therefore, it is possible that Pb^{II} is harder than Cu^{II}, $[Ar][3d]^9$ electron configuration. On the other hand both ether oxygen and carboxylate are classified as hard bases, while the classification of amide nitrogen is not clear. Consequently, Pb^{II} preferred hard oxygen-containing functional groups, while Cu^{II} preferred nitrogen- containing ones. Nevertheless it is obvious that the HSAB rule does not completely explain the affinity between metal ions and coordinating atoms. Hancock et al.[17] have shown that the affinity of Cu^{II} to nitrogen is much higher than to Zn^{II} and Pb^{II} but Pearson[16] suggested that Zn^{II}, $[Ar][3d]^{10}$ electron configuration, is chemically softer than Cu^{II}.

As previously reported,[9b] Kemp's imide monoacids **4** and **5** transport Hg^{II} most efficiently with high metal selectivities over transition and heavy metals. The same metal selectivities for monoacids **1** and **3** were also examined by dual ion competitive transport experiments; the results are summarized in Table 3. Both **1** and **3** transported Hg^{II} best among seven transition and heavy metal ions studied in Tables 2 and 3. However their selectivities showed differences depending on the functional group. First, **1** and **3** had slightly lower transport ability for Hg^{II} and much lower ability for Ag^{I} transport than **4**. As a result, both had higher Hg^{II}/Ag^{I} selectivity, 24 for **1** and 34 for **3**. As described in the previous paragraph and Table 2, diamide **1** had higher affinity for Cu^{II}, which leads to a lower Hg^{II}/Cu^{II} selectivity of 3.3. On the other hand, diester **3** had lower affinity toward Cu^{II} and showed a very high Hg^{II}/Cu^{II} selectivity of 194. The aliphatic imide monoacid **5** was similar in transport ability to **4**.[9b] An interesting observation from the data in Table 3 is that the coordination ability or affinity of the imide group to soft Hg^{II} and Ag^{I} was higher than amide and ester groups; this functional feature was further developed by design and synthesis of effective chromoionophores for Hg^{II}.

Transport Mechanism. In a liquid membrane transport system, guest species, i.e. metal ions, were expected to be complexed and extracted by transport agents into the organic membrane phase.[10] In order to obtain information about the penetrant form of divalent metal ions, the anions in both the source and receiving phases were analyzed by ion chromatography for selected transport experiments. The results are summarized in Table 4. The concentration of Cl^- ion in the source phase was twice that of Ca^{II} for Runs 1 and 3 because of the tris-buffered system. Nevertheless Runs 1—3 showed that no counter anion of Ca^{II}, that is Cl^-, was transported into the organic phase, independent of the

Table 3. Amount of Transition Metal Ions Competitively Transported[a)]

Run	Carrier	Metal ions transported to the receiving phase mol%[b)] (μmol)				Selectivity
	(time)	Hg^{II}	Ag^{I}	Cu^{II}	Pb^{II}	
1	**1** (12 h)	70 (104)	2.9 (4.4)	—	—	Hg/Ag = 24
2	**1** (12 h)	70 (105)		21 (32)	—	Hg/Cu = 3.3
3	**1** (12 h)	82 (123)	—	—	8.6 (9.5)	Hg/Pb = 13
4	**3** (24 h)	88 (132)	2.6 (3.9)	—	—	Hg/Ag = 34
5	**3** (24 h)	91 (136)	—	0.5 (0.7)	—	Hg/Cu = 194
6	**3** (24 h)	82 (123)	—	—	5.6 (8.3)	Hg/Pb = 15
7	**4** (12 h)	87 (130)	17 (25)	—	—	Hg/Ag = 5.2
8	**4** (12 h)	98 (147)	—	7 (11)	—	Hg/Cu = 13
9	**4** (12 h)	86 (128)	—	—	1.0 (1.5)	Hg/Pb = 85

a) See footnote a) of Table 2. b) See footnote b) of Table 2.

Table 4. Cation and Anion Analyses of Transport Experiments for Kemp's Diamide Monoacid **1** and Imide Monoacid **4**

Run	Transport Agent	Transport Time	Metal Salts	$[X^-]$ $CH_3CO_2^-$ Transported μM	$[M^{2+}]$ Total Cation Transported μM	$[X]/[M^{2+}]$
1	**1**	24 h	$CaCl_2$[a]	0	10	0
2	**1**	24 h	$Ca(OAc)_2$[b]	0	10	0
3	**4**	48 h	$CaCl_2$[a]	0	8	0
4	**4**	48 h	Acetates of Co, Ni, Cu, Zn, & Pb[b]	10	9.9	1.0
5	**4**	24 h	$Hg(OAc)_2$[b]	11	10	1.1
6	**4**	24 h	$Hg(NO_3)_2$[b]	8 (0[c])	10	0.8 (0[c])

a) See footnote a) of Table 1. b) See footnote a) of Table 2. c) The amount of NO_3^-.

original counter anions and the transport agents examined. Therefore, we concluded that the counter anion of alkaline earth metal ions should be the deprotonated transport agents, meaning the metal/transport agent ratio should be 1 : 2. This satisfies the charge cancellation requirements of the complex. This was also the case for alkaline earth metal ion transport by the diacid type transport agents examined by Baldwin et al.[12d)]

On the other hand, for transition and heavy metal ions, their counter anion, $CH_3CO_2^-$, was detected in the receiving phase (Runs 4 and 5). In addition, the amount was equivalent to the amount of metal ions transported as seen from columns 5—7 of Table 4, $[X^-]/[M^{2+}]\approx 1$ but not 2. Our data suggested the major transport mechanism involving divalent transition and heavy metal ions required a 1 : 1 ratio of ligand to acetate anion, that is M^{2+}/transport agents/$CH_3CO_2^-$ = 1 : 1 : 1.

When the original counter anion was changed from $CH_3CO_2^-$ to NO_3^- in the same buffer solution (CH_3CO_2Na–CH_3CO_2H), $CH_3CO_2^-$ was detected as shown in Run 6. In this case, both NO_3^- were replaced with carboxylate as the metal ion needs to be complexed with the transport agent. This result can be explained by the difference of lipophilicity between NO_3^- and $CH_3CO_2^-$. Again the $[X^-]/[M^{2+}]$ ratio (0.8) of $CH_3CO_2^-$ and transported metal ion was close to 1. This proposed mechanism is schematically shown in Fig. 4a in the case of Hg^{II} with the counterpart for alkaline earth metal ions mentioned above (Fig. 4a).

For monovalent ions, like Ag^I, the transport mechanism becomes simple if one considers that the original counter anion should be exchanged with the transport agent in order to be extracted into the organic phase, as written in the textbooks.[10)] The 1 : 1 ratio of metal ions and transport agent for both divalent and monovalent ions principally allows the complete competitive transport even from their mixture.

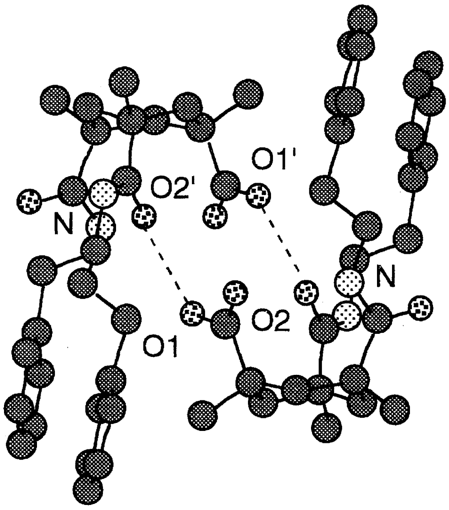


Fig. 2. Chem 3D structure drawing of diamide monoacid **1** based on X-ray crystal analysis data. Hydrogen atoms were omitted for clarity.

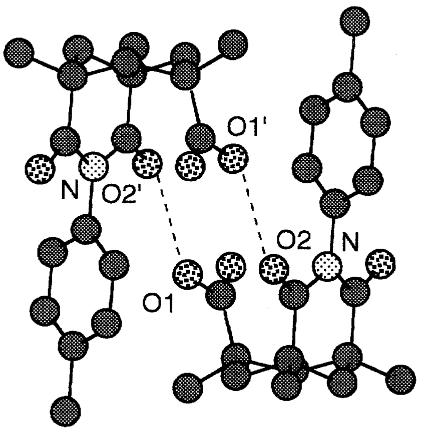


Fig. 3. Chem 3D structure drawing of imide monoacid **7** based on X-ray crystal analysis data. Hydrogen atoms were omitted for clarity.

Crystal Structure. In order to learn more about the mechanism of transport, the crystal structures of Kemp's monoacids **1** and **7** were studied. Both crystal packings obtained, Figs. 2 and 3, clearly indicate hydrogen-bonds between the carboxyl group and carbonyls of amide and imide groups to form a pair of molecules arranged in *anti*-parallel form. The arrangement of imide acid **7** was basically the same as **4**, $P2_1/n$ space group, but satisfactory solution of the data for **4** was prevented by the large thermal mobility

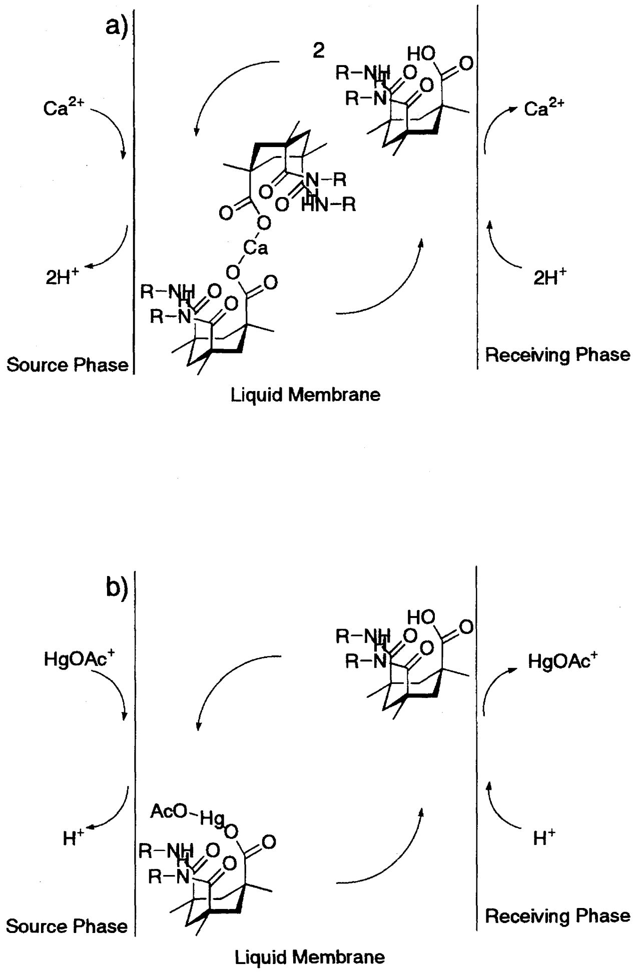


Fig. 4. Proposed transport mechanisms for a) alkaline earth metal ions and b) divalent transition and heavy metal ions.

of the three terminal carbons of the butyl group at ambient temperature.

Although crystal data of metal complexes with **1**—**6** are not available now, similar antiparallel structures are expected for 1 : 2 complexes with alkaline earth metals. The divalent metal ion should sit between two carboxylic acid groups, excluded from other interactions with the solvent. In this form, the Ca^{II} could be wrapped up by two molecules of **1** and would be lipophilic enough to be transported in the present system. The structure is expected to be similar to those of natural monobasic ionophores, like A23187.[6,7] Apparently the complex solubility in the organic liquid membrane is an important factor in designing a transport agent.

Effect of Stereo Isomerism. As seen in Table 2, the stereo isomeric imide monoacid **6** showed similar ability to **4** and **5** (Runs 4, 5, and 6). This result is a good contrast to the case for alkaline earth metal ion transport (Run 11 in Table 1). The transport mechanism mentioned in the previous paragraph and the structural study above, however, support the unexpected transport data of **6**.

It seems that there is not much difference between how **4** and **6** form a 1 : 1 complex for transition and heavy metal ions. On the other hand, for alkaline earth metal ions, requiring formation of a 1 : 2 complex, a large difference exists. The 1 : 2 ratio requires the intramolecular combination or cooperation of carboxylic acid and imide groups, which is possible for **4** and **5** but entropically unfavorable for **6** because of its diverse structure, which might lead to some unknown species soluble in organic phase but not released to the acidic receiving phase.

In addition, this interpretation explains the low transport abilities of the present monoacids for mono-valent alkali metal ions. The 1 : 1 complex allowed by the charge balance, most probably solvent hydrated, was not sufficiently lipophilic for organic phase solubility.

Conclusion

The metal transport abilities of Kemp's monoacids were evaluated using a proton concentration gradient as driving force. The monoacids showed good transport ability for alkaline earth and some transition and heavy metal ions. Among alkaline earth metal ions studied, Ca^{II} was transported very well by diamide monoacids **1** and **2**. The Ca^{II} transport ability of **1** was comparable with natural ionophore A23187. Additionally **1** exhibited good Ca^{II}/Mg^{II} selectivity, 26, and **2** had excellent Ca^{II}/Ba^{II} selectivity, over 40. Among the transition and heavy metal ions, Cu^{II} was effectively transported by imide monoacid **4** as well as by diamide monoacids **1** and **2**. The Cu^{II}/Pb^{II} selectivity was improved by **2** due to its bulky carbamoyl group. On the other hand, diester monoacid **3** was Pb^{II} selective because of the higher affinity of ester groups for Pb^{II} than for Cu^{II}. In addition, Hg^{II} was the most efficiently transported metal ion by the present monoacids studied. The Hg^{II} selectivity changed depending on the functional groups; $Hg^{II}/Ag^{I} = 24$ for **1**, $Hg^{II}/Cu^{II} = 194$ for **3**, and $Hg^{II}/Pb^{II} = 85$ for **4**.

Two transport mechanisms were studied by anion analysis of the aqueous receiving phases. For alkaline earth metal ions, 1 : 2 complexation was expected from the analysis of counter anion. On the other hand, for transition/heavy metal ions, the major penetrant form in the organic phase was divalent metal:transport agent 1 : 1 complex, accompanied by one non-ligand counter anion. The stereo isomer of Kemp's imide monoacid, having carboxylic acid and imide groups in *trans* positions, showed much less transport ability for alkaline earth metals. The *cis* geometry was shown to be important for effective 1 : 2 complexation. Work in progress utilizes this structural feature and the unexpectedly high affinity of the imide group for Hg^{II}, to enable colorimetric ion sensing.[18]

Experimental

General. The IR spectra were recorded with a JASCO FTIR-5300 spectrophotometer. The melting points were determined with a Mettler FP62 melting point apparatus and were reported uncorrected. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded with a Varian Gemini 300 BB spectrometer. The proton and carbon chemical shifts (δ) were reported in parts per million (ppm) relative to the internal standard tetramethylsilane (TMS) and $CDCl_3$, respectively. The molecular weights were measured with a

Hitachi M-80BS mass spectrometer at Material Analysis Research Center (MARC) of the National Institute of Materials and Chemical Research (NIMC). Elemental analysis was done with CHNS-O EA1108 Elemental Analyzer (Carlo Erba Instruments) at MARC.

Dry tetrahydrofuran (THF) was distilled from sodium in the presence of benzophenone as an indicator. Other reagents and solvents of extra-pure grade were used without further purification. Wakogel C-300 (silica gel of 200—300 mesh) was used for column chromatography.

Apparatus and Procedure for Metal ion Transport. A U-type glass tube cell was used to determine the transport ability of ionophores through a liquid membrane of chloroform.[3d,10] At the bottom of the cell, 30 mL $\mathrm{CHCl_3}$ solution of ionophore, 1.5×10^{-4} mol was used as the organic phase. Two aqueous solutions, 15 mL, were slowly and simultaneously poured over the liquid membrane from both sides of the cell as the source and receiving phases. While the former solution was prepared by dissolving an appropriate amount of metal salts in a buffer solution, the latter one was always 0.1 M (= mol dm^{-3}) nitric acid solution.

Ion Analysis. Samples were taken from the receiving and source phases at certain periods, suitably diluted, and analyzed for cation and anion content. The concentration for metal cation was determined by atomic absorption spectroscopy. The type and concentration of anion was determined by ion chromatography (IC). The IC system used was set up by the combination of an ion exchange column (TSKgel IC-Anion-PW$_{\mathrm{XL}}$PEEK, particle size 6 mm, 75mm $\times$ 4.6 mm i.d.), eluent (TSKeluent IC-Anion-A, 1 mL min^{-1}), and a conductimetric detector (CM 8020) was used at 40.0 ± 0.1 °C column temperature.

Synthesis of *cis*,*cis*-1,3,5-Trimethyl-3,5-bis(phenethylcarbamoyl)cyclohexane-1-carboxylic Acid (1). The synthesis followed the literature[19] with some modifications. The acid anhydride acid chloride of Kemp's triacid **8** was prepared under reflux of $\mathrm{SOCl_2}$.[20] After distillation of $\mathrm{SOCl_2}$ under reduced pressure, the remaining solid was washed by $\mathrm{CH_2Cl_2}$, dried under vacuum, and used without further purification.

Under $\mathrm{N_2}$ atmosphere, phenethylamine (1.0 mL, 7.92 mmol) was added to a mixture of **8** (1.000 g, 3.87 mmol), $\mathrm{Et_3N}$ (1.1 mL, 7.94 mmol), and a catalytic amount of DMAP (4-dimethylaminopyridine) in dry THF (150 mL) at room temperature. After the temperature was raised to 50 °C, the reaction mixture was stirred for 12 h. After being cooled to room temperature, the solution was diluted with AcOEt (300 mL) and consecutively washed with 2 M HCl soln ($\times$2), $\mathrm{H_2O}$, and brine. The organic solution was dried over $\mathrm{MgSO_4}$, concentrated under reduced pressure, and the remaining impurity was removed by short column chromatography on silica gel eluting with AcOEt. This product was further purified by recrystallization from $\mathrm{CH_2Cl_2}$–hexane to produce colorless prisms (1.456 g, 81%), mp 149—150 °C. IR (KBr) 3299, 3063, 2959, 1705, 1642, 1609, and 698 cm^{-1}; ^{1}H NMR ($\mathrm{CDCl_3}$) δ = 7.15—7.28 (m, 10 H), 7.06 (t, J = 5.5 Hz, 2 H), 3.35—3.40 (m, 4 H), 2.76—2.82 (m, 7 H), 1.29 (s, 3 H), 1.14 (s, 6 H), 1.05 (d, J = 15.3 Hz, 2 H), 1.02 (d, J = 15.3 Hz, 1 H); ^{13}C NMR ($\mathrm{CDCl_3}$) δ = 180.36, 177.06, 139.00, 128.75, 128.42, 126.28, 43.34, 43.19, 42.78, 42.43, 41.30, 35.11, 33.69, 32.97. MS m/z 465 (M$^+$; 78), 344 (100). Anal. Calcd for $\mathrm{C_{28}H_{36}N_2O_4}$: C, 72.39; H, 7.81; N, 6.03%. Found: C, 72.61; H, 7.84; N, 6.02%.

Synthesis of 3,5-Bis(cyclohexylcarbamoyl)-*cis*,*cis*-1,3,5-trimethylcyclohexane-1-carboxylic Acid (2). In the same way as described for **1**, cyclohexylamine (0.263 g, 2.65 mmol) was reacted with **8** (0.342 g, 1.32 mmol) in the presence of $\mathrm{Et_3N}$ (0.268 g, 2.65 mmol) and a catalytic amount of DMAP in dry THF. The crude product was purified by column chromatography on silica gel eluting with a gradient mixture of 1 : 1—2 : 1 AcOEt/hexane. Removal of the solvent gave white solid, which yielded colorless prisms of the product after recrystallization from AcOEt–hexane (yield 0.262 g, 47%), mp 177—180 °C. IR (KBr) 3281, 2930, 2853, 1707, and 1630 cm^{-1}; ^{1}H NMR ($\mathrm{CDCl_3}$) δ = 6.72 (d, J = 8.4 Hz, 2 H), 3.57—3.69 (m, 2 H), 2.90 (d, J = 15.2 Hz, 1 H), 2.83 (d, J = 15.1 Hz, 2 H), 1.81—1.89 (br, 2 H), 1.66—1.81 (br, 6 H), 1.54—1.63 (br, 2 H), 1.34 (s, 3 H), 1.21 (s, 6 H), 1.13—1.31 (m, 10 H), 1.10 (d, J = 15.1 Hz, 2 H), 1.06 (d, J = 15.2 Hz, 1 H); ^{13}C NMR ($\mathrm{CDCl_3}$) δ = 180.29, 175.96, 49.16, 43.76, 43.00, 42.54, 42.27, 34.08, 33.61, 32.21, 25.47, 24.93. HRMS m/z 420.3116 (M$^+$). Anal. Calcd for $\mathrm{C_{24}H_{40}N_2O_4}$: C, 68.53; H, 9.59; N, 6.66%. Found: C, 68.72; H, 9.58; N, 6.64%.

Synthesis of 3,5-Bis(benzyloxycarbonyl)-*cis*,*cis*-1,3,5-trimethylcyclohexane-1-carboxylic Acid (3). In the same way as described for **1**, benzyl alcohol (1.62 mL, 15.70 mmol) was added to a mixture of **8** (1.340 g, 5.18 mmol), $\mathrm{Et_3N}$ (2.2 mL, 15.88 mmol), and a catalytic amount of DMAP in dry toluene (60 mL), and the mixture was heated to reflux for 36 h. After being cooled to room temperature, the solution was diluted with AcOEt (300 mL), washed with 2 M HCl soln ($\times$2), $\mathrm{H_2O}$, and brine. After drying over $\mathrm{MgSO_4}$ and concentration, the crude product was purified by silica-gel chromatography eluting with $\mathrm{CHCl_3}$ first and then with AcOEt to give white solid (955 mg, 42%), which was recrystallized from hexane-$\mathrm{Et_2O}$ to give colorless needles (650 mg, 29%), mp 114—116 °C. IR (KBr) 3034, 2967, 2934, 1736, 1703, 760, and 702 cm^{-1}; ^{1}H NMR ($\mathrm{CDCl_3}$) δ = 7.30—7.37 (m, 10 H), 5.07 (s, 4 H), 2.82 (d, J = 13.8 Hz, 2 H), 2.79 (d, J = 14.6 Hz, 1 H), 1.31 (s, 3 H), 1.26 (s, 6 H), 1.06 (d, J = 14.9 Hz, 2 H) 1.05 (d, J = 14.8 Hz, 1 H); ^{13}C NMR ($\mathrm{CDCl_3}$) δ = 178.74, 177.12, 136.38, 128.36, 128.14, 127.86, 66.69, 43.79, 43.34, 42.25, 41.53, 32.17, 30.57. MS m/z 439 (M$^+$, 30), 167 (100). Anal. Calcd for $\mathrm{C_{26}H_{30}O_6}$: C, 71.21; H, 6.90%. Found: C, 71.28; H, 6.90%.

Synthesis of 3-(4-Butylphenyl)-*cis*,*cis*-1,5,7-trimethyl-2,4-dioxo-3-azabicyclo[3.3.1]nonane-7-carboxylic Acid [*N*-4-Butylphenyl Imide of Kemp's Triacid] (4). Imidation Method 1: To a suspension of **8** (1.035 g, 4.0 mmol) in dry THF (15 mL) was slowly added a dry THF solution (10 mL) of 4-butylaniline (0.614 g, 4.11 mmol), $\mathrm{Et_3N}$ (0.445 g, 4.40 mmol), and a catalytic amount of DMAP. The mixture was heated to 60 °C and stirred overnight. After cooling to room temperature, triethylammonium chloride was filtered off and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with 3 : 2 hexane/AcOEt. Removal of the solvent gave a white solid, which yielded colorless prisms after recrystallization from benzene (yield 1.300 g, 87%), mp 223—226 °C. IR (KBr) 3404, 2959, 1734; 1705, 1512, and 1180 cm^{-1}; ^{1}H NMR ($\mathrm{CDCl_3}$) δ = 7.15 (d, J = 8.3 Hz, 2 H), 6.94 (d, J = 8.3 Hz, 2 H), 2.81 (d, J = 13.8 Hz, 2 H), 2.58 (t, J = 7.7 Hz, 2 H), 2.12 (d, J = 13.2 Hz, 1 H), 1.57 (q, J = 7.8 Hz, 2 H), 1.47 (d, J = 13.2 Hz, 1 H), 1.40—1.32 (m, 2 H), 1.32 (s, 9 H), 1.26 (d, J = 14.3 Hz, 2 H), 0.91 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($\mathrm{CDCl_3}$) δ = 178.59, 176.39, 142.61, 133.00, 128.80, 127.55, 44.03, 43.89, 41.72, 40.67, 35.27, 33.31, 31.17, 25.92, 22.32, 13.91. HRMS m/z 371.2076 (M$^+$). Anal. Calcd for $\mathrm{C_{22}H_{29}NO_4}$: C, 71.13; H, 7.87; N, 3.77%. Found: C, 71.31; H, 7.91; N, 3.70%.

Imidation Method 2:[21] In a 18 $\times$ 180 mm Pyrex test tube, Kemp's triacid **9** (0.416 g, 1.61 mmol), *p*-butylaniline (0.254 g, 1.70 mmol), and imidazole (0.211 g, 3.10 mmol) were wetted with 5 drops of DMF. The heterogeneous mixture was irradiated in a microwave oven at 500 watts power (full) for 4 min. After being cooled for a few minutes, the mixture was diluted with 20 mL $CHCl_3$, and was shaken with three 20 mL portions of 1 M HCl solution, and three 20 mL portions of $NaHCO_3$ aq solution. The basic solution was acidified with concd HCl and back-extracted into $CHCl_3$. After drying with $MgSO_4$ and concentration, the white powder was recrystallized from benzene to yield colorless prisms (0.454 g, 76%), mp 223—225 °C. IR (KBr) 1734, 1703, and 1181 cm^{-1}; ^1HNMR ($CDCl_3$) δ = 7.14 (d, J = 8.3 Hz, 2 H), 6.93 (d, J = 8.3 Hz, 2 H), 2.80 (d, J = 13.7 Hz, 2 H), 2.58 (t, J = 7.7 Hz, 2 H), 2.10 (d, J = 13.3 Hz, 1 H), 1.56 (q, J = 7.5 Hz, 2 H), 1.46 (d, J = 13.3 Hz, 1 H), 1.35 (q, J = 7.7 Hz, 2 H), 1.32 (s, 6 H), 1.31 (s, 3 H), 1.25 (d, J = 14.5 Hz, 2 H), 0.91 (t, J = 7.3 Hz, 3 H); ^{13}CNMR ($CDCl_3$) δ = 179.0, 176.5, 142.7, 133.0, 128.9, 127.6, 44.1, 43.9, 41.8, 40.7, 35.3, 33.4, 31.3, 26.0, 22.4, 14.0. Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77%. Found: C, 71.33; H, 7.93, N, 3.79%.

Synthesis of *cis*,*cis*-1,5,7-Trimethyl-3-octadecyl-2,4-dioxo-3-azabicyclo[3.3.1]nonane-7-carboxylic Acid (5). The synthesis of **5** was already reported.[19] Application of method 2, from octadecylamine (0.270 g, 1 mmol) and **9** (0.259 g, 1.0 mmol) produced a white solid. The product was recrystallized from CH_3CN to produce white platelet microcrystalline material (0.321 g, 65%), mp 96—99 °C. IR (KBr) 2920, 2851, 1730, 1699, 1211, and 1128 cm^{-1}; ^1HNMR ($CDCl_3$) δ = 3.45 (t, br, J = 2.5 Hz, 2H), 2.64 (d, br, J = 14.3 Hz, 2H), 1.90 (d, br, J = 14.3 Hz, 1 H), 1.5—1.0 (m, 44 H), 0.880 (t, br, J = 5.4 Hz, 3 H); ^{13}CNMR ($CDCl_3$) δ = 180.6, 176.0, 61.1, 44.1, 43.6, 41.8, 40.2, 32.0, 30.5, 29.94, 29.91, 29.7, 29.6, 29.52, 29.48, 29.4, 29.3, 27.6, 27.1, 25.5, 22.7, 14.2. HRMS m/z 491.3972 (M^+). Anal. Calcd for $C_{30}H_{53}NO_4$: C, 73.27; H, 10.86; N, 2.85%. Found: C, 73.48; H, 11.03; N, 2.85%.

Synthesis of 3-(4-Butylphenyl)-*cis*,*trans*-1,5,7-trimethyl-2,4-dioxo-3-azabicyclo[3.3.1]nonane-7-carboxylic Acid (6). According to method 2 for **4** mentioned above, *cis-trans* Kemp's triacid (0.416 g, 1.61 mmol), p-butylaniline (0.254 g, 1.70 mmol), and imidazole (0.211 g, 3.10 mmol) were wetted with 5 drops of DMF and the mixture was subjected to irradiation in the microwave oven. The resulting beige solid was dissolved in benzene, treated with activated carbon, filtered, and cooled to yield colorless needles (0.296 g, 51.5%), mp 175—177 °C. IR (KBr) 1732, 1698, and 1181 cm^{-1}; ^1HNMR ($CDCl_3$) δ = 7.25 (d, J = 8.2 Hz, 2 H), 6.97 (d, J = 8.2 Hz, 2 H), 2.63 (t, J = 7.7 Hz, 2 H), 2.17 (d, J = 14.5 Hz, 1 H), 2.10 (d, J = 14.5 Hz, 2 H), 1.91 (d, J = 14.5 Hz, 2 H), 1.60 (quin, J = 7.7 Hz, 2 H), 1.50 (d, J = 14.5 Hz, 1 H), 1.43 (s, 3 H), 1.36 (s, 6 H), 1.34 (quin, J = 7.4 Hz, 2 H), 0.92 (t, J = 7.4 Hz, 3 H); ^{13}CNMR ($CDCl_3$) δ = 177.7, 143.3, 132.7, 129.2, 127.5, 43.2, 42.7, 40.0, 35.4, 33.4, 26.8, 24.6, 22.4, 14.0. Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77%. Found: C, 71.26; H, 8.21; N, 3.91%.

Synthesis of *cis*,*cis*-1,5,7-Trimethyl-3-(4-methylphenyl)-2,4-dioxo-3-azabicyclo[3.3.1]nonane-7-carboxylic Acid (7). In a manner similar to the procedure for **4** above, p-toluidine (0.228 g, 2.13 mmol) and **9** (0.500 g, 1.94 mmol) were microwave oven-irradiated in a mixture of imidazole (0.263 g, 3.87 mmol) and 5 drops DMF for 2.5 min. The reaction mixture was dissolved in benzene and the insoluble substances were filtered off. After drying with $MgSO_4$ and concentration of the filtrate, the white solid was recrystallized from AcOEt to yield colorless prisms (0.465 g, 67%), mp 291—293 °C. IR (KBr) 3188, 2982, 2934, 1734, 1718, 1670, 1512, 1186, and 1161 cm^{-1}; ^1HNMR ($CDCl_3$) δ = 7.14 (d, J = 7.8 Hz, 2 H), 6.93 (d, J = 7.8 Hz, 2 H), 4.6—4.1 (br, 1 H), 2.80 (d, J = 13.3 Hz, 2 H), 2.07 (d, J = 13.2 Hz, 1 H), 1.46 (d, J = 13.3 Hz, 2 H), 4—1.1 (m, 14 H); ^{13}CNMR ($CDCl_3$) δ = 178.5, 176.5, 137.7, 132.8, 129.5, 127.6, 44.0, 43.9, 41.7, 40.7, 31.1, 25.9, 21.2. HRMS m/z 329.168 (M^+). Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25%. Found: C, 69.21; H, 7.36; N, 4.26%.

X-Ray Analysis. The three-dimensional X-ray data were collected at room temperature, 293 K, by a graphite-monochromated Mo $K\alpha$ radiation (λ = 0.71073 Å) on a Mac Science MXC18HF automatic $\varkappa$-type four-circle diffractometer up to a maximum 2θ of 55°. The structure was solved by direct methods (SIR). All non-hydrogen atoms were located on the initial E synthesis. Remaining hydrogen atoms were located by the difference Fourier map and were included in further calculations. All the calculations were done on a Silicon Graphics 4D Indy computer of MARC using a structure analysis program system CRYSTAN.

Crystal Data of 1. The crystals of **1** (crystal size 0.5×0.5×0.4 mm^3) belonged to a monoclinic system with cell dimensions a = 16.567(3), b = 11.279(2), c = 14.119(3) Å, β = 96.39(1)°, and V = 2622.0(8) $Å^3$. The space group was $P2_1/n$ and Z = 4. The empirical formula was $C_{28}H_{36}N_2O_4$, molecular weight 464.60 g mol^{-1}, and calculated density 1.18 g cm^{-3}. The intensity data of 6033 independent reflections were collected and 3391 with $|F_o| > 3\sigma|F_o|$ were used in the present X-ray analysis. Full matrix least square refinements with 34 anisotropic non-hydrogen atoms and 36 isotropic hydrogen atoms converged to conventional R and R_w factors of 0.068 and 0.065, respectively.

Crystal Data of 7. The crystals of **7** (crystal size 0.1×0.1×0.1 mm^3) belonged to a monoclinic system with cell dimensions a = 12.735(3), b = 16.890(3), c = 8.318(2) Å, β = 101.71(2)°, and V = 1752(1) $Å^3$. The space group was $P2_1/n$ and Z = 4. The empirical formula was $C_{19}H_{23}NO_4$, molecular weight 329.40 g mol^{-1}, and calculated density 1.25 g cm^{-3}. The intensity data of 4491 independent reflections were collected and 4032 with $|F_o| > 3\sigma|F_o|$ were used in the present X-ray analysis. Full matrix least square refinements with 24 anisotropic non-hydrogen atoms and 23 isotropic hydrogen atoms converged to conventional R and R_w factors of 0.042 and 0.040, respectively.

The authors, T. H. and Z.-H. W., thank Dr. Midori Goto of MARC of NIMC, Prof. Colin H. L. Kennard of the University of Queensland, and Mr. Hironao Inoue of MAC Science for their helpful suggestions and discussion about the X-ray analyses. The authors, Z.-H. W. and B. W. B., thank the New Energy and Industrial Technology Development Organization (NEDO) for partial financial support.

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