in THF (150 mL) at -78 °C was added oxazoline **7d** (2.40 g, 10.5 mmol) in THF (60 mL) dropwise over 75 min. After being stirred for an additional 15 min, the orange solution was quenched by addition of methanol (20 mL) and subsequently allowed to warm to room temperature. The reaction mixture was poured into water and extracted with ether. The combined organic layers were dried and concentrated. The resulting oxazoline **8** (3.07 g) was refluxed with sulfuric acid (1.8 M, 150 mL) for 40 h. On cooling, the mixture was extracted with methylene chloride, dried, and concentrated. Bulb-to-bulb distillation yielded **12** (2.07 g, 96%) as a viscous oil: bp 150 °C/0.3 mmHg; $[\alpha]_D$ = -26.5° (neat); $^1$H NMR ($CDCl_3$) 0.82 (3 H, t, $J$ = 7.1 Hz), 1.05-1.31 (4 H, m), 1.56-1.68 (2 H, m), 2.59 (1 H, dd, $J$ = 15.5, 7.9 Hz), 2.66 (1 H, dd, $J$ = 15.5, 7.1 Hz), 3.06 (1 H, m), 7.15-7.32 (5 H, m), 11.30 (1 H, br s); $^{13}$C NMR ($CDCl_3$) 14.0 (q), 22.6 (t), 29.5 (t), 36.0 (t), 41.6 (t), 41.9 (d), 126.6 (d), 127.5 (d), 128.5 (d), 144.0 (s), 178.7 (s); IR (thin film) 3400-2500, 2958, 2930, 1709, 1454 cm$^{-1}$.

**Determination of Enantiomeric Excesses of Aldehydes 9.** To the aldehyde **9** (10-20 mg) in methanol (1 mL) at 0 °C was added excess sodium borohydride. After being stirred for 15 min, the solution was warmed to room temperature, diluted with water, and extracted with methylene chloride. The combined organic layers were dried and concentrated. The resulting alcohol **10** was converted to the Mosher's ester according to a published procedure using (*S*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid.[10] NMR analysis was performed on base-line resolved signals as ascertained by comparison with the corresponding materials derived from the racemic aldehydes.[15] In all cases, benzene-$d_6$ was employed as solvent. The following resonances were employed: For diastereomeric materials (**11a** and **11c**) the signals at δ = 3.83 (1 H) and 4.09 (1 H) were integrated relative to that at δ = 3.94 (2 H); for **11b** the signals at δ = 3.76 (1 H) and 4.11 (1 H) were integrated relative to the signals observed in the racemic material at δ = 3.76 (0.5 H), 3.87 (0.5 H), 3.98 (0.5 H), and 4.11 (0.5 H); for **11d** the singlet at δ = 0.74 (9 H) was integrated relative to the two singlets observed for the racemic material at δ = 0.78 (4.5 H) and 0.74 (4.5 H), also by integration of the singlet at δ = -43.48 relative to those observed for the racemic material at δ = -43.48 and -43.66 in the $^{19}$F NMR (188 MHz); for **11e** the signal at δ = 3.40 (3 H) was integrated relative to the two signals observed for the racemic material at δ = 3.40 (1.5 H) and 3.44 (1.5 H), also by integration of the singlet at δ = -43.03 relative to those observed for the racemic material at δ = -43.03 and -43.09 in the $^{19}$F NMR.

**Acknowledgment.** We are grateful to the National Institutes of Health for support of this work. A postdoctoral fellowship (to M.S.) from the Science and Engineering Research Council (NATO) is also warmly acknowledged.

(15) Prepared in an analogous fashion utilizing 2,4,4-trimethyl-2-oxazoline.

# Multiarmed Macrocyclic Polyamines Exhibiting Unique Cation-Binding and Cation-Transport Properties toward Alkali-Metal and Alkaline-Earth-Metal Cations

Hiroshi Tsukube,*[†] Hayamitsu Adachi,[‡] and Shiro Morosawa[‡]

*Department of Chemistry, College of Liberal Arts & Science, Okayama University, Okayama 700, Japan, and Department of Chemistry, Faculty of Science, Okayama University, Okayama 700, Japan*

*Received November 27, 1990 (Revised Manuscript Received July 25, 1991)*

A variety of multiarmed macrocyclic polyamines were prepared as a new type of metal carrier, in which amide-, ester-, nitrile-, and ketone-functionalized arms were attached as secondary donor sites. Extraction and $^{13}$C NMR binding experiments revealed that their cation-binding behavior was largely dependent on the nature of the arm donor group as well as the size of the parent polyamine ring. In particular, introduction of an amide-functionalized arm into a suitable polyamine ring significantly enhanced binding ability toward "hard" metal cations, while the parent polyamine ring weakly bound these metal cations. Their unique cation-binding properties offered an effective membrane transport of hard metal cations. Since the cation-binding and -transport profiles of the new multiarmed macrocyclic polyamines differed greatly from those observed with conventional polyamines and related macrocycles, the present study provides a new possibility for designing a novel, macrocyclic polyamine type of synthetic carrier.

## Introduction

Lariat ethers, double-armed crown ethers, and related macrocyclic host molecules have attracted much attention, and all are characterized by parent macrocyclic ligands and flexible cation-ligating arm groups.[1] They form three-dimensional and stable metal complexes via side-arm-macroring cooperativity. Since the rates of formation and dissociation of their metal complexes are often modified by the incorporation of pendant arms, compounds of this class can act as unique carriers of various metal cations.[2] Interestingly, their cation-binding and -transport properties are essentially controlled by the natures of the macrocyclic skeleton and ligating side arm, and we are able to select a structural combination suitable for a new and specific carrier of a target guest cation.

[†] Department of Chemistry, College of Liberal Arts & Science, Okayama University.

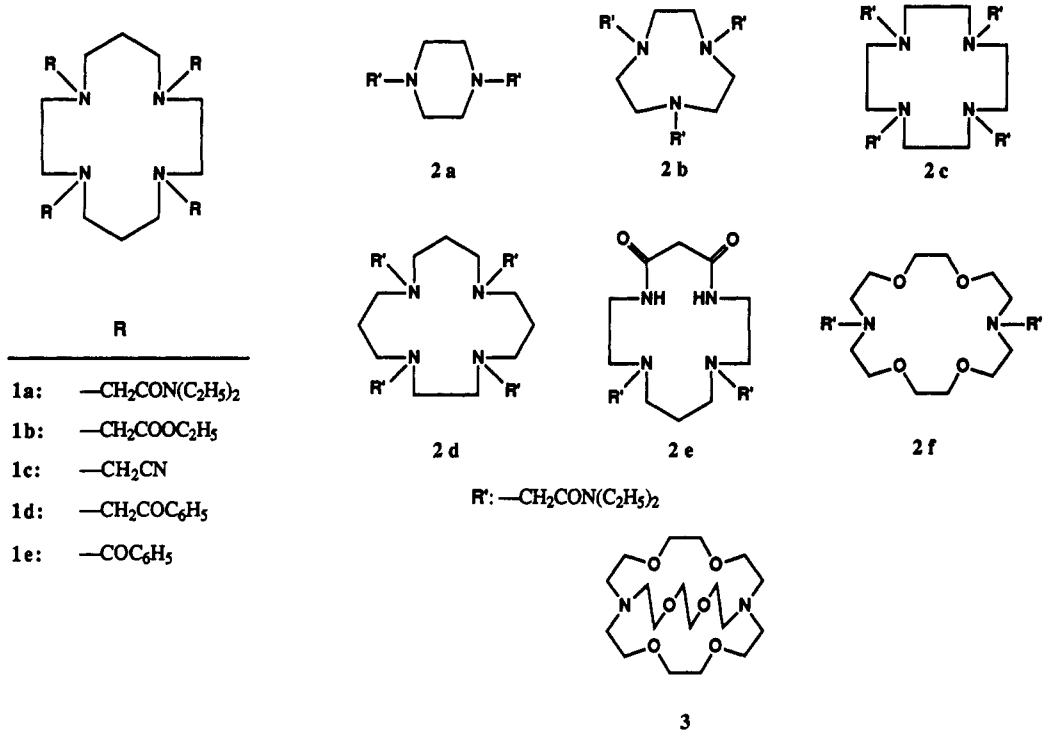
[‡] Department of Chemistry, Faculty of Science, Okayama University.

(1) Reviews: (a) Tsukube, H. *J. Coord. Chem.* **1987**, *B-16*, 101. (b) Krakowiak, K. E.; Bradshaw, J. S.; Zamecka-Krakowiak, D. J. *Chem. Rev.* **1989**, *89*, 929. (c) Hancock, R. D.; Martell, A. E. *Chem. Rev.* **1989**, *89*, 1875. (d) Lindoy, L. F. In *The Chemistry of Macrocyclic Ligand Complexes*; Cambridge University Press: Cambridge, 1989; p 103. (e) Gokel, G. W.; Trafton, J. E. In *Cation Binding by Macrocycles*; Marcel Dekker: New York, 1990, p 253.

(2) (a) Tsukube, H. In *Liquid Membranes: Chemical Applications*; Araki, T., Tsukube, H., Eds.; CRC Press: Florida, 1990; p 51. (b) Tsukube, H.; Yamashita, K.; Iwachido, T.; Zenki, M. *Tetrahedron Lett.* **1988**, *29*, 569. (c) Tsukube, H.; Yamashita, K.; Iwachido, T.; Zenki, M. *Tetrahedron Lett.* **1989**, *30*, 3983. (d) Matsumoto, K.; Minatogawa, H.; Toda, M.; Tsukube, H. *Tetrahedron Lett.* **1990**, *31*, 3923. (e) Tsukube, H.; Yamashita, K.; Iwachido, T.; Zenki, M. *J. Org. Chem.* **1991**, *56*, 268.

0022-3263/91/1956-7102$02.50/0 

**Chart I. Molecular Structures of Armed Macrocyclic Polyamines and Related Macrocycles**




| | R |
|---|---|
| 1a: | —$CH_2CON(C_2H_5)_2$ |
| 1b: | —$CH_2COOC_2H_5$ |
| 1c: | —$CH_2CN$ |
| 1d: | —$CH_2COC_6H_5$ |
| 1e: | —$COC_6H_5$ |

Macrocyclic polyamines are known as potential synthetic ligands for soft transition-metal cations and polyanionic guest species.[3] By introduction of an additional ligating group into such a polyamine ring, its properties can be effectively modified so that unique host–guest complexes are formed and interesting chemical functions are developed. Some kinds of armed macrocyclic polyamines have already been presented as potential ligand molecules for transition-metal cations and have been well investigated from the standpoint of coordination chemistry.[4] Recently we prepared a series of multiarmed macrocyclic polyamines which mediated effective transport of alkali-metal cations.[5] Since their guest selectivities were already different from those observed with the parent polyamines and conventional crown-type carrier molecules, cooperative binding of an arm donor group and a polyamine ring was postulated. In other words, further structural modification of macrocyclic polyamine compounds should offer the possibility of designing a new type of carrier molecule exhibiting characteristic guest selectivity.

Here, we report unique and selective cation-binding and -transport properties of multiarmed macrocyclic polyamines.[6] A variety of multiarmed macrocyclic polyamines were systematically prepared and characterized which incorporated amide, ester, nitrile, and keto carbonyl groups in several different fashions (see Chart I). Extraction and $^{13}C$ NMR binding studies demonstrated that some amide-armed macrocyclic polyamines formed three-dimensional, stable complexes with hard metal cations such as $Li^+$, $Ca^{2+}$ and $Ba^{2+}$, while other macrocyclic polyamines favored soft metal cations. Liquid membrane transport experiments revealed that their unique cation-binding properties offered specific transport of the $Ba^{2+}$ cation. Although many kinds of synthetic carriers have been developed for transport of alkali-metal and alkanline-earth-metal cations,[1a,2a,3a] only a few carrier-mediated transport systems exhibiting high efficiency and excellent selectivity toward alkaline-earth-metal cations have been reported, and this is the first example of macrocyclic polyamine type carriers specific for alkaline-earth-metal cations.[7]

## Results and Discussion

**Multiarmed Macrocylic Polyamines.** Amide, ester, and related functional groups were introduced into the side arms of macrocyclic polyamines having 6-, 9-, 12-, 14-, and 15-membered rings, **1a–e** and **2a–d** (Chart I). These compounds were directly prepared from unsubstituted polyamines and the corresponding halides. While the parent macrocyclic polyamines effectively bind several heavy and transition-metal cations,[8] the introduced amide and related carbonyl groups are known as powerful binding sites for alkali-metal and alkaline-earth-metal cations in some biological[9] and synthetic systems.[10] Thus, a combination of polyamine ring and amide-functionalized arm

(3) (a) Potvin, P. G.; Lehn, J. M. In *Synthesis of Macrocycles*; Izatt, R. M., Christensen, J. J., Eds.; John Wiley & Sons: New York, 1987; p 167. (b) Kimura, E. *Top. Curr. Chem.* **1985**, *128*, 113. (c) Kaden, Th. A. *Top. Curr. Chem.* **1984**, *121*, 157.

(4) (a) Lotz, T. J.; Kaden, Th. A. *Helv. Chim. Acta* **1977**, *61*, 15. (b) Kimura, E. *Pure Appl. Chem.* **1986**, *58*, 1461.

(5) Tsukube, H.; Yamashita, K.; Iwachido, T.; Zenki, M. *Tetrahedron Lett.* **1989**, *30*, 3983.

(6) Preliminary communication: Tsukube, H.; Adachi, H.; Morosawa, S. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1537.

(7) Some macrocyclic polyamines having cation-ligating side arms have been reported to form three-dimensional complexes with alkali-metal and alkaline-earth-metal cations, but they have rarely been examined as cation carriers: (a) Buon, S.; Dale, J.; Groth, P.; Kran, J. *J. Chem. Soc., Chem. Commun.* **1982**, 1178. (b) Norante, G. M.; Varia, M. D.; Mani, F.; Mazzi, S.; Stoppioni, P. *J. Chem. Soc., Chem. Commun.* **1990**, 438.

(8) Izatt, R. M.; Bradshaw, J. S.; Nielsen, S. A.; Lamb, J. D.; Christensen, J. J. *Chem. Rev.* **1985**, *85*, 271.

(9) (a) Hilgenfeld, R.; Saenger, W. *Top. Curr. Chem.* **1982**, *101*, 1. (b) Tsukube, H. In *Cation Binding by Macrocycles*; Inoue, Y., Gokel, G. W., Eds.; Marcel Dekker: New York, 1990; p 497.

(10) (a) Kulstad, S.; Malmsten, L. A. *Acta Chem. Scand., Ser. B* **1979**, *33*, 469. (b) Gatto, V. J.; Gokel, G. W. *J. Am. Chem. Soc.* **1984**, *106*, 8240. (c) Tsukube, H.; Adachi, H.; Morosawa, S. *J. Chem. Soc., Perkin Trans. 1* **1989**, 89. (d) Kataky, R.; Nicholson, P. E.; Parker, D. *Tetrahedron Lett.* **1989**, *30*, 4559. (e) Matthe, K. E.; Parker, D.; Buschmann, H. J.; Ferguson, G. *Tetrahedron Lett.* **1987**, *28*, 5573. (f) Kataky, R.; Nicholson, P. E.; Parker, D. *J. Chem. Soc., Perkin Trans. 2* **1990**, 321. (g) Trafton, J.; Li, C.; Mallen, J.; Miller, S. R.; Nakano, A.; Schall, O. F.; Gokel, G. W. *J. Chem. Soc., Chem. Commun.* **1990**, 1266.

**Table I. Single Cation Extraction with Amide-Armed Macrocycles and Related Carriers**

| | extraction percentage | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| guest cation | 1a | 1b | 1c | 1d | 1e | 2b | 2c | 2d | 2e | 2f |
| $Li^+$ | 12 | 1 | 0 | 0 | 0 | 41 | 6 | 3 | 2 | 13 |
| $Na^+$ | 4 | 0 | 0 | 0 | 0 | 12 | 0 | 0 | 0 | 65 |
| $K^+$ | 0 | 0 | 0 | 0 | 0 | 0 | 16 | 0 | 0 | 65 |
| $Ag^+$ | 98 | 96 | 75[a] | 100[b] | 0 | 14[b] | 100[b] | 92[b] | 44[b] | 86 |
| $Mg^{2+}$ | 2 | 1 | 0 | 0 | 0 | 26 | 3 | 2 | 1 | 0 |
| $Ca^{2+}$ | 88 | 0 | 0 | 0 | 0 | 33 | 5 | 10 | 10 | 34 |
| $Ba^{2+}$ | 26 | 3 | 0 | 0 | 1 | 23 | 15 | 4 | 11 | 71 |
| $Pb^{2+}$ | 88 | 22 | 3 | 55[b] | 0 | 51 | 66 | 81 | 12 | 48 |
| $Cu^{2+}$ | 85 | 15 | 0 | 27 | 0 | 28 | 46 | 66 | 2 | 46 |

[a] A precipitate was observed. [b] A slight turbidity appeared.

**Table II. Competitive Cation Extraction with Amide-Armed Macrocycles and Related Carriers**

| | extraction percentage | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| guest cation | 1a | 1b | 1c | 1d | 1e | 2b | 2c | 2d | 2e | 2f |
| $Li^+$ | 0 | 0 | (0)[a] | 1 | 0 | (0) | (0) | (0) | (0) | 0 |
| $Na^+$ | 0 | 0 | (0) | 0 | 0 | (0) | (0) | (0) | (0) | 0 |
| $K^+$ | 0 | 0 | (0) | 0 | 0 | (0) | (0) | (0) | (0) | 0 |
| $Ag^+$ | 2 | 32 | (0) | 66 | 2 | (20) | (85) | (15) | (6) | 16 |
| $Mg^{2+}$ | 0 | 0 | (0) | 0 | 0 | (0) | (0) | (0) | (0) | 0 |
| $Ca^{2+}$ | 1 | 0 | (0) | 0 | 0 | (0) | (2) | (0) | (0) | 0 |
| $Ba^{2+}$ | 0 | 0 | (0) | 0 | 0 | (0) | (0) | (0) | (0) | 0 |
| $Pb^{2+}$ | 28 | 0 | (0) | 0 | 0 | (14) | (24) | (0) | (2) | 58 |
| $Cu^{2+}$ | 62 | 8 | (0) | 15 | 0 | (30) | (41) | (12) | (68) | 9 |

[a] Parentheses indicate a precipitate.

is expected to exhibit unique host–guest complexation and interesting transport functions for both soft and hard metal cations.[11]

**Cation-Extraction Profile.** In order to examine the cation binding properties of multiarmed macrocyclic polyamines, we performed single and competitive extraction experiments using various metal cations. Their extraction abilities were estimated on the basis of partition of the metal perchlorate between methylene chloride and aqueous solution, and Table I summarizes the results of single liquid–liquid extraction experiments.

Introduction of an amide-functionalized side arm to the macrocyclic polyamine ring significantly enhanced cation-extraction ability for alkali-metal and alkaline-earth-metal cations. In particular, amide-armed 14-membered tetraamine **1a** very effectively extracted $Ca^{2+}$ ion as well as $Ag^+$, $Pb^{2+}$, and $Cu^{2+}$ ions (see Table I). Since other 14-membered tetraamines having ester-, nitrile-, and ketone-functionalized arms **1b**, **1c**, and **1d** extracted only soft metal cations, the amide-functionalized arm seemed to provide effective coordination of hard metal cations. The size of the parent macroring is an essential factor in determining extraction efficiency and selectivity. Amide-armed triamine **2b** showed high extraction ability for $Li^+$ ion, and 12- and 15-membered tetraamines **2c** and **2d** exhibited modest extraction ability for $K^+$, $Ca^{2+}$, and $Ba^{2+}$ ions. These observations strongly suggest that cooperative binding of the amide carbonyl group and polyamine nitrogen atom offers characteristic cation binding. Since $Li^+$ and $Ca^{2+}$ ions prefer six and eight coordination, respectively, amide-armed tri- and tetraamines **2b** and **1a** offered suitable geometries for binding of these metal cations.

Amide-armed dioxocyclam **2e** was also examined. Kodama et al. demonstrated that its parent dioxocyclam formed stable 1:1 complexes with $Cu^{2+}$, $Ni^{2+}$, $Co^{2+}$, and $Pb^{2+}$ ions,[12] but amide-armed derivative **2e** exhibited

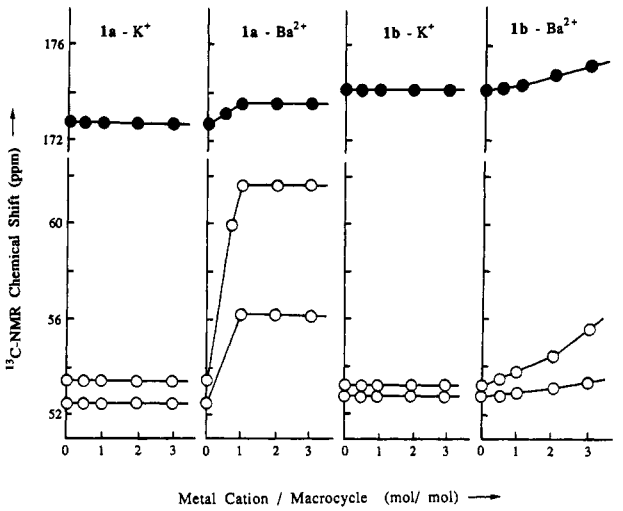



**Figure 1.** $K^+$- and $Ba^{2+}$-induced changes in $^{13}C$ NMR chemical shifts of armed macrocyclic polyamines **1a** and **1b**: ○, polyamine ring carbon as indicated by a in Table III; ●, carbonyl carbon as indicated by b in Table III.

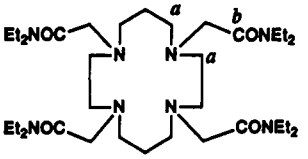
higher extraction ability for $Ag^+$ ion than for $Cu^{2+}$ ion. Amide-armed diaza-18-crown-6 **2f** extracted $Na^+$, $K^+$, $Ca^{2+}$, and $Ba^{2+}$ cations as well as $Ag^+$, $Pb^{2+}$, and $Cu^{2+}$ ions[10c] and was confirmed as a nonselective metal binder. Since these cation-binding behaviors were quite different from those with amide-armed polyamines, arm functionalization of macrocyclic polyamines provides a new and interesting possibility for designing unique cation carriers.

Table II summarizes the results of competitive cation extraction experiments in which the concentration of each guest metal cation is the same as the of the macrocycle added. The polyamine derivatives, except for **1c** and **1e**, effectively extracted $Ag^+$, $Pb^{2+}$, and $Cu^{2+}$ ions under competitive conditions. Although several multiarmed macrocycles showed enhanced cation-binding ability for hard

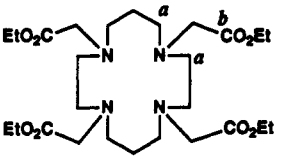
(11) Some amide-armed macrocyclic polyamines have been synthesized, but their carrier activities have not been examined. (a) Reference 3c. (b) Kataky, R.; Matthes, K. E.; Nicholson, P. E.; Parker, D.; Buschmann, H. J. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1425.

(12) Kodama, M.; Yatsunami, T.; Kimura, E. *J. Chem. Soc., Dalton Trans.* **1979**, 1783.

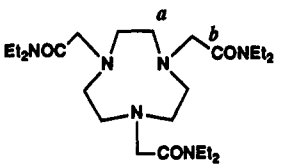
Table III. Guest-Induced Changes in $^{13}C$ NMR Chemical Shifts of Amide-Armed Macrocycles[a]



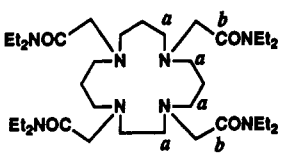

1a



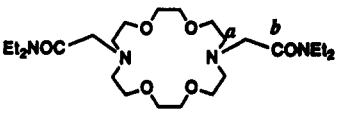

1b




2b




2d




2f

| | | induced chemical shift, ppm | | | | | |
|---|---|---|---|---|---|---|---|
| macrocycle | carbon[b] | $Li^+$ | $Na^+$ | $K^+$ | $Mg^{2+}$ | $Ca^{2+}$ | $Ba^{2+}$ |
| **1a** | a | 2.0 | 1.6 | 0 | (3.9) | [5.1] | 3.7 |
| | | 1.3 | 4.9 | 0 | (3.1) | [4.1] | (8.2) |
| | b | 0.3 | −0.1 | 0 | (0.3) | [1.6] | 0.8 |
| **1b** | a | 0.2 | 0.6 | 0 | 0.1 | (0) | 0.2 |
| | | 0.1 | 1.6 | 0 | 0.1 | (0) | 0.6 |
| | b | 0.1 | 0.3 | 0 | −0.3 | (−0.3) | 0.2 |
| **2b** | a | −4.0 | −3.8 | −1.7 | −4.0 | −2.2 | −1.9 |
| | b | (0.9) | (0.3) | −0.8 | 1.8 | 1.2 | 0.5 |
| **2d** | a | 0.6 | 0.2 | −0.1 | 1.3 | (4.3) | 0.9 |
| | | −0.5 | 0 | 0 | 1.0 | (4.2) | 1.1 |
| | | 0.8 | 0.4 | 0 | 1.9 | (4.0) | 1.8 |
| | b | 0.8[c] | 0.1 | 0 | −1.3[c] | 1.3[c] | 0.7[c] |
| | | 0[c] | | | −2.2[c] | 1.1[c] | 0.3[c] |
| **2f** | a | 1.3 | 0.5 | 0.8 | 0.4 | 2.4 | 0.8 |
| | b | 0.6 | −0.3 | −0.2 | (1.2) | 0.9 | 0.8 |

[a] Conditions: 0.025 mmol of macrocycle; 0.025 mmol of guest perchlorate/0.5 mL of $CH_3CN/D_2O$ (4:1). Positive is downfield shift. (): These signals were broadened. [ ]: These signals were split and could not be unequivocally assigned (see text). [b] See structural formulas above. [c] Two peaks were observed.

metal cations, they were still strong ligands of soft metal cations.

**$^{13}C$ NMR Binding Studies.** Further detailed information on the cation-binding behavior of armed macrocycles was obtained via $^{13}C$ NMR spectrocopy in a $CH_3CN/D_2O$ (4:1) solution. Figure 1 illustrates the $K^+$- and $Ba^{2+}$-induced changes in the $^{13}C$ NMR chemical shifts of the signals for carbonyl and polyamine carbons of amide- and ester-armed macrocyclic tetraamines **1a** and **1b**. In these cases, averaged signals were observed upon addition of metal perchlorates. Since discrete signals were not observed for the complex and the free macrocycle at intermediate stoichiometries, fast binding kinetics and moderate stabilities were suggested in these systems.

Amide-armed macrocycle **1a** formed a three-dimensional complex with $Ba^{2+}$ cation, while $K^+$ ion was rarely bound. Actually, the addition of $Ba(ClO_4)_2$ salt to the tetraamine **1a** solution caused significant changes upon complexation. Since the signals for the carbons on the amide arm and polyamine ring shifted greatly, it is suggested that cooperative action of these two binding sites leads to complete inclusion of the guest $Ba^{2+}$ ion. In contrast, addition of $K^+$ cation hardly influenced the signals for amide carbonyl and polyamine ring carbons. The titration curves shown in Figure 1 indicate that macrocycle **1a** effectively discriminates between divalent $Ba^{2+}$ ion and monovalent $K^+$ ion though their ion sizes are similar.

The $^{13}C$ NMR spectrum of the ester-armed macrocyclic tetraamine **1b** was also changed in the presence of $Ba^{2+}$ cation, but the shifted values of amide carbonyl and polyamine ring carbons were modest (Figure 1). Since $K^+$ ion induced no spectral change, ester-armed macrocycle **1b** was assumed not to act as an effective binder for these metal cations. The origin of these remarkable differences between armed macrocycles **1a** and **1b** almost certainly lies in the relative ligating ability of the amide and the ester groups. Similar observations have been reported in the amide-armed crown ether systems.[10] Therefore, the combination of amide-functionalized arm group and 14-membered tetraamine skeleton was confirmed to offer three-dimensional and dynamic complexation for $Ba^{2+}$ cation.

Table III summarizes the results of $^{13}C$ NMR binding studies for armed macrocyclic polyamines **1a**, **1b**, **2b**, and **2d** and amide-armed diaza-crown ether **2f**. When $Ca(ClO_4)_2$ salt was added to the solution of amide-armed macrocycle **1a**, several carbon signals were split into two signals corresponding to the free and complexed forms in the presence of excess macrocycle, consistent with slow kinetics on the NMR time scale of cation exchange. Signals due to the free macrocycle completely disappeared when 1 equiv of $Ca^{2+}$ salt was added; this strongly suggests that a very stable (static) 1:1 complex is formed. As described above, macrocycle **1a** extracted $Ca^{2+}$ ion much more effectively than $Ba^{2+}$ and other metal cations. This macrocycle was thought to form a rigid, octadentate complex with $Ca^{2+}$ ion while it forms a three-dimensional but dynamic complex with $Ba^{2+}$ ion. The addition of $Na^+$ cation offered somewhat different spectral changes. The signals for the polyamine ring carbons were greatly shifted, but the amide carbonyl signal was only slightly influenced. These observations indicate that macrocycle **1a** affects circular coordination of $Na^+$ cation in the same way as do

**Table IV. Cation-Transport Properties of Amide-Armed Macrocycles and Related Carriers**[a]

| guest cation | transport rate × $10^6$, mol/h | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **1a** | **1b** | **1c** | **1d** | **1e** | **2a** | **2b** | **2c** | **2d** | **2e** | **2f** | **3** |
| $Li^+$ | 1.4 | * | * | * | * | * | 2.5 | * | * | * | 1.5 | 0.8 |
| $Na^+$ | 0.8 | * | * | * | * | * | 1.4 | * | * | * | 4.3 | 6.5 |
| $K^+$ | * | * | * | * | * | * | * | * | * | * | 7.0 | 1.2 |
| $Cs^+$ | * | * | * | * | * | * | * | * | * | * | 2.2[b] | 1.4 |
| $Ag^+$ | * | * | *[b] | 0.4[b] | * | *[b] | * | *[b] | *[b] | 4.2 | * | 2.0 |
| $Mg^{2+}$ | * | * | * | * | * | * | * | * | * | * | * | * |
| $Ca^{2+}$ | * | * | * | * | * | * | 1.9 | * | * | * | 1.9 | 0.4 |
| $Ba^{2+}$ | 8.9 | * | * | * | * | * | 2.4 | * | * | * | 0.6 | 3.7 |
| $Pb^{2+}$ | * | 0.9 | * | * | * | *[b] | 0.6 | * | * | * | 1.4 | 0.8 |
| $Cu^{2+}$ | 1.0 | * | * | * | * | * | 1.9 | * | * | * | 1.2 | * |
| $Ni^{2+}$ | * | * | * | * | * | * | * | * | * | * | 0.7 | * |
| $Co^{2+}$ | * | * | * | * | * | * | * | * | * | * | 3.4 | * |
| $Zn^{2+}$ | 0.7 | * | * | * | * | * | * | * | * | * | 5.6 | * |

[a] The conditions were as follows. Aq 1: 0.50 mmol of guest perchlorate/5 mL of $H_2O$. Membrane: 0.0372 mmol of macrocycle/12 mL of $CHCl_3$. Aq 2: 5 mL of $H_2O$. (*) Below limit of detection (<0.3). [b] A precipitate was observed.

simple macrocyclic ligands. Since $Li^+$ and $Mg^{2+}$ salts induced similar spectral changes, amide-armed macrocycle **1a** specifically formed encapsulated complexes with $Ca^{2+}$ and $Ba^{2+}$ ions.

The guest-induced changes in $^{13}C$ NMR chemical shifts depended on the size of the polyamine ring as well as on the nature of the arm functional group. Cooperative binding of polyamine ring and amide side arm was also confirmed when 9-membered triamine **2b** and 15-membered tetraamine **2d** were employed. Surprisingly, amide-armed triamine **2b** was thought to form three-dimensional complexes with several hard metal cations. In particular, $Li^+$ and $Mg^{2+}$ cations were nicely accommodated in the hexacoordinating cavity of triamine **2b**. Tetraamine **2d** with a 15-membered ring offered spectral changes similar to those with 14-membered tetramine **1a**. This favors three-dimensional coordination of divalent $Mg^{2+}$, $Ca^{2+}$, and $Ba^{2+}$ ions. Amide-armed diaza-18-crown-6 **2f** was also employed. As observed in the extraction experiment, this effectively bound various metal cations, and its guest selectivity was low.[10c] Therefore, the nature and the size of the parent macroring are important factors in controlling binding selectivity.

**Cation Transport across a Liquid Membrane.** Transport experiments were carried out in a $CHCl_3$ liquid membrane system, multiarmed macrocyclic polyamines being used as synthetic carriers. Table IV summarizes the transport properties of multiarmed macrocyclic polyamines **1a–e** and **2a–e**, comparing them with those of double-armed crown ether **2f** and bicyclic cryptand **3**. Amide-armed macrocyclic polyamines **1a** and **2b** showed much better transport abilities for several metal cations than other functionalized macrocycles **1b–e**, **2a**, and **2c–e**. In particular, amide-armed macrocycle **1a**, having a 14-membered ring, specifically and effectively transported $Ba^{2+}$ ion, while $K^+$, $Na^+$, and $Ca^{2+}$ ions were hardly transported under the same conditions. Since macrocycle **1a** formed an encapsulated and very stable complex with $Ca^{2+}$ ion, this supported that dynamic, three-dimensional binding offered fast cation transport. Amide-armed triamine **2b** also mediated transport of $Li^+$, $Na^+$, $Ca^{2+}$, and $Ba^{2+}$ cations, but 12- and 15-membered tetraamines **2c** and **2e** transported few alkali-metal and alkaline-earth-metal cations.[13] Although the coordination chemistry of the multiarmed macrocycles is quite complicated due to the range of potential donor arms, the cation-transport profile

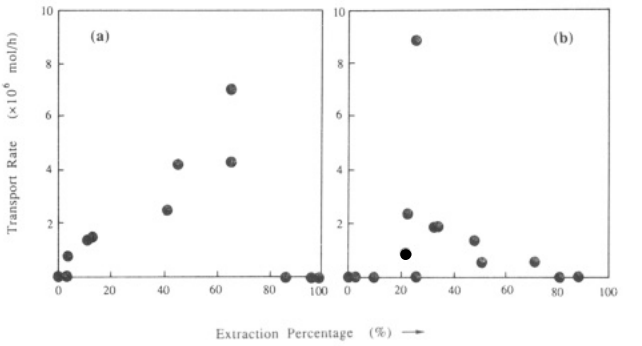



**Figure 2.** Plots of cation-transport rate vs extraction percentage: (a) monovalent metal cation; (b) divalent metal cation. Data from Tables I and IV.

of an armed macrocyclic polyamine clearly depended on the size of the macroring. Crown ether **2f** and cryptand **3** effectively carried a variety of guest cations, and their transport selectivities were much lower than that with armed polyamine **1a**.[10c] Multiarmed polyamines are believed to be selective and useful carriers.

Table IV also indicates that macrocyclic polyamines having ester-, nitrile-, and keto-functionalized arms, **1b**, **1c**, **1d**, and **1e**, could not act as carriers for any examined alkali-metal or alkaline-earth-metal cations. Similar side-arm effects in cooperative binding and specific transport have been observed in double-armed crown ether systems.[10c]

Figure 2 shows the relationship between the extraction percentage observed above and the transport rate measured here for macrocycles **1a–e** and **2a–e**. These have distinct maxima. As frequently reported for crown ether type carriers,[10c,14] the guest cation which was moderately complexed by the carrier was effectively transported. Our NMR and extraction studies strongly suggest that amide-armed macrocycle **1a** forms too stable and rigid a complex with $Ca^{2+}$ ion to transport it. Since **1a** only moderately bound $Ba^{2+}$ ion, this was the best cation to be transported. Other armed macrocycles have optimal guest cations: triamine **2b** mediated effective transport of $Li^+$ and $Ba^{2+}$ cations, and crown ether **2f** offered fast transport of $K^+$ and $Zn^{2+}$ cations.

We have clearly revealed the unique and effective cation-binding and -transport abilities of armed macrocyclic polyamines. Some of them specifically formed stable

(13) Amide-armed branched polyethylenimine transported $Li^+$, $Na^+$, $Mg^{2+}$, $Ca^{2+}$, and $Ba^{2+}$ ions across a chloroform liquid membrane: Tsukube, H.; Adachi, H.; Morosawa, S. *J. Polym. Sci., Polym. Chem. Ed.* **1990**, *28*, 437.

(14) (a) Lamb, J. D.; Christensen, J. J.; Oscarson, J. L.; Nielson, B. L.; Asay, B. W.; Izatt, R. M. *J. Am. Chem. Soc.* **1980**, *102*, 6820. (b) Behr, J. P.; Kirch, M.; Lehn, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 241. (c) Yoshida, S.; Hayano, S. *J. Am. Chem. Soc.* **1986**, *108*, 3903.

complexes with hard metal cations via side arm–polyamine ring cooperativity. Their three-dimensional coordination character provided both strong cation binding and selective membrane transport properties. To the best of our knowledge, this is the first example of multiarmed macrocyclic polyamines which mediate specific transport of hard alkaline-earth-metal cations.[1,2,15] Further combinations of parent macrorings and ligating side arms may offer new and excellent cation-binding and -transport functions.[2]

## Experimental Section

$^{13}C$ NMR spectra were recorded in $CH_3CN/D_2O$ (4:1). Chemical shifts were determined using the peak of the $CH_3CN$ nitrile carbon ($\delta_C$ 120.00 ppm) as reference.

Chemical reagents employed were purchased from Nacalai Tesque Inc., Kishida Chemical Co., Tokyo Kasei Co., Kanto Chemical Co., Wako Pure Chemical Industries, Alfa Products, and Aldrich Chemical Co. Solvents and commercially available materials including unsubstituted polyamines and cryptand [2.2.2] (3) were used without additional purification. Amide-armed diaza-18-crown-6 **2f** and armed polyamine **1e** were synthesized by methods described in the literature.[10c,16] All new compounds were confirmed as pure materials by TLC analysis and had correct elemental compositions determined by microanalysis and high-resolution mass spectroscopy.

**Preparation of Multiarmed Macrocyclic Polyamines: 1,4,8,11-Tetrakis[(diethylcarbamoyl)methyl]-1,4,8,11-tetraazacyclotetradecane (1a).** A solution of 1,4,8,11-tetraazacyclotetradecane (cyclam, 1 g, 5 mmol), triethylamine (10.3 g, 300 mmol), and *N,N*-diethylchloroacetamide (14.9 g, 100 mmol) in ethanol (20 mL) was refluxed for 20 h and then extracted with chloroform. The organic phase was washed with water and dried over $Na_2SO_4$. The solvent was evaporated, and the residue was chromatographed (alumina activated 200, Nacalai Tesque Inc., chloroform). Recrystallization from methylene chloride and ether gave white crystals of the title product (45%): mp 144–145 °C; IR (Nujol) $\nu$ 1630 $cm^{-1}$; $^1H$ NMR $\delta$ 1.09 and 1.14 (t + t, 24 H, 8 $NCH_2CH_3$), 1.64 (qui, 4 H, 2 $CH_2CH_2CH_2$), 2.61 and 2.67 (t + s, 16 H, 8 $NCH_2$), 3.26 and 3.37 (s + qua + qua, 24 H, 4 $CH_2CO$ + 8 $NCH_2CH_3$). Anal. Calcd for $C_{34}H_{68}N_8O_4$: C, 62.54; H, 10.50; N, 17.16. Found: C, 62.27; H, 10.32; N, 17.17.

**1,4,8,11-Tetrakis[(ethoxycarbonyl)methyl]-1,4,8,11-tetraazacyclotetradecane (1b)** was similarly prepared from cyclam and ethyl chloroacetate (70%): mp 87–89 °C; IR (Nujol) $\nu$ 1717 $cm^{-1}$; $^1H$ NMR $\delta$ 1.26 (t, 12 H, 4 $CH_3$), 1.60 (qui, 4 H, 2 $CH_2CH_2CH_2$), 2.69 and 2.73 (t + s, 16 H, 8 $NCH_2CH_2$), 3.36 (s, 8 H, 4 $NCH_2CO$), 4.12 (qua, 8 H, 4 $OCH_2$). Anal. Calcd for $C_{26}H_{48}N_4O_8$: C, 57.33; H, 8.88; N, 10.29. Found: C, 57.01; H, 8.84; N, 10.31.

**1,4,8,11-Tetrakis(cyanomethyl)-1,4,8,11-tetraazacyclotetradecane (1c)** was prepared from cyclam and chloroacetonitrile (65%): mp 177–178 °C; IR (Nujol) $\nu$ 2230 $cm^{-1}$; $^1H$ NMR $\delta$ 1.62 (qui, 4 H, 2 $CH_2CH_2CH_2$), 2.64 and 2.67 (t + s, 16 H, 8 $NCH_2CH_2$), 3.58 (s, 8 H, 4 $CH_2CN$). Anal. Calcd for $C_{18}H_{28}N_8$: C, 60.65; H, 7.92; N, 31.43. Found: C, 60.30; H, 7.88; N, 31.50.

**1,4,8,11-Tetraphenacyl-1,4,8,11-tetraazacyclotetradecane (1d)** was synthesized from cyclam and phenacyl bromide (40%): mp 145–147 °C; IR (Nujol) $\nu$ 1675 and 1690 $cm^{-1}$;[17] $^1H$ NMR $\delta$ 1.68 (qui, 4 H, 2 $CH_2CH_2CH_2$), 2.39 (t, 8 H, 4 $NCH_2CH_2$), 2.59 (s, 8 H, 4 $NCH_2CH_2$), 3.78 (s, 8 H, 4 $NCH_2CO$), 7.42 and 8.00 (m, 20 H, 4 $C_6H_5$). Anal. Calcd for $C_{42}H_{48}N_4O_4$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.96; H, 7.11; N, 8.42.

***N,N'*-Bis[(diethylcarbamoyl)methyl]piperazine (2a)** was prepared from piperazine and *N,N*-diethylchloroacetamide (35%): mp 83–84 °C; IR (Nujol) $\nu$ 1620 $cm^{-1}$; $^1H$ NMR $\delta$ 1.11 and 1.19 (t + t, 12 H, 4 $CH_3$), 2.57 (s, 8 H, 2 $NCH_2CH_2N$), 3.14 (s, 4 H, 2 $NCH_2CO$), 3.33 and 3.40 (qua + qua, 8 H, 4 $NCH_2CH_3$). Anal. Calcd for $C_{16}H_{32}N_4O_2$: C, 61.51; H, 10.32; N, 17.93. Found: C, 61.63; H, 10.32; N, 18.10.

**1,4,7-Tris[(diethylcarbamoyl)methyl]-1,4,7-triazacyclononane (2b)** was synthesized from 1,4,7-triazacyclononane and *N,N*-diethylchloroacetamide (yellow oil, 40%): IR (neat) $\nu$ 1630 $cm^{-1}$; $^1H$ NMR $\delta$ 1.10 and 1.16 (t + t, 18 H, 6 $CH_3$), 2.88 (s, 12 H, 3 $NCH_2CH_2N$), 3.38 (s + qua + qua, 18 H, 3 $CH_2CO$ + 6 $NCH_2CH_3$); HRMS (*m/e*) calcd for $C_{24}H_{48}N_6O_3$ 468.3788, found 468.3791.

**1,4,7,10-Tetrakis[(diethylcarbamoyl)methyl]-1,4,7,10-tetraazacyclododecane (2c)** was obtained by reaction of 1,4,7,10-tetraazacyclododecane tetrahydrochloride with *N,N*-diethylchloroacetamide (40%): mp 177–178 °C; IR ($CHCl_3$) $\nu$ 1640 $cm^{-1}$; $^1H$ NMR $\delta$ 1.06 and 1.16 (t + t, 24 H, 8 $CH_3$), 2.51 (br s, 16 H, 4 $NCH_2CH_2N$), 3.23 (m, 24 H, 4 $CH_2CO$ + 8 $NCH_2CH_3$); HRMS (*m/e*) calcd for $C_{32}H_{64}H_8O_4$ 624.5050, found 624.5059.

**1,4,8,12-Tetrakis[(diethylcarbamoyl)methyl]-1,4,8,12-tetraazacyclopentadecane (2d)** was prepared from 1,4,8,12-tetraazacyclopentadecane and *N,N*-diethylchloroacetamide (yellow oil, 45%): IR (neat) $\nu$ 1620 $cm^{-1}$; $^1H$ NMR $\delta$ 1.06 and 1.13 (t + t, 24 H, 8 $CH_3$), 1.59 (qui, 6 H, 3 $CH_2CH_2CH_2$), 2.53 and 2.64 (t + s, 16 H, 8 $NCH_2CH_2$), 3.23 and 3.36 (m, 24 H, 4 $CH_2CO$ + 8 $NCH_2CH_3$); HRMS (*m/e*) calcd for $C_{35}H_{70}N_8O_4$ 666.5520, found 666.5520.

**1,11-Bis[(diethylcarbamoyl)methyl]-1,4,8,11-tetraazacyclotetradecane-5,7-dione (2e)** was derived from 1,4,8,11-tetraazacyclotetradecane-5,7-dione (75%): mp 111–112 °C; IR ($CHCl_3$) $\nu$ 1660 and 1625 $cm^{-1}$; $^1H$ NMR $\delta$ 1.11 and 1.17 (t + t, 12 H, 4 $CH_3$), 1.54 (quin, 2 H, $CH_2CH_2CH_2$), 2.63 and 2.69 (t + t, 8 H, 4 $NCH_2CH_2$), 3.23–3.43 (m, 18 H, $COCH_2CO$ + 2 $NCH_2CO$ + 2 $NHCH_2CH_2$ + 4 $CH_2CH_3$), 7.80 (m, 2 H 2 NH). Anal. Calcd for $C_{22}H_{42}N_6O_4$: C, 58.12; H, 9.31; N, 18.49. Found: C, 58.23; H, 9.33; N, 18.20.

**Extraction Experiment.** Single cation extraction experiments (Table I) were carried out by adding a methylene chloride solution of carrier molecule (0.02 mmol/2 mL) to an aqueous solution of metal perchlorate (0.02 mmol/2 mL). Competitive cation extraction experiments (Table II) were performed using a mixture of $LiClO_4$, $NaClO_4$, $KClO_4$, $AgClO_4$, $Mg(ClO_4)_2$, $Ca(ClO_4)_2$, $Ba(ClO_4)_2$, $Pb(ClO_4)_2$, and $Cu(ClO_4)_2$ (0.02 mmol each/2 mL) as an aqueous solution. After the mixture had been stirred for 2 h, the aqueous phase was separated. The concentrations of metal cations were determined by atomic absorption or a flame spectroscopic method (performed at Exlan Technical Center, Okayama).

**Transport Experiments.** Transport experiments were performed at room temperature (ca. 20 °C) in a U-tube glass cell (2.0-cm i.d.).[1a] The carrier, dissolved in chloroform, was placed in the base of the U-tube, and two aqueous phases were placed in the tube arms, floating on the chloroform membrane phase. The membrane phase was constantly stirred with a magnetic stirrer. The transport rates indicated in Table IV were calculated from the initial rates of appearance of cotransported $ClO_4^-$ anion into the Aq 2 phase, which was determined by a $ClO_4^-$ ion-selective electrode (Orion 93-81). Reproducibliilties were confirmed as ±15% or better. The transported amount of each guest cation was also determined by atomic absorption or a flame spectroscopic method (carried out at Exlan Technical Center, Okayama) and was almost equal to that of the cotransported anion. We confirmed that all guest salts were rarely transported in the absence of carrier (transport rate < $0.3 \times 10^{-6}$ mol/h).

**Acknowledgment.** We are grateful to Professor K. Maruyama and Dr. H. Sohmiya of Kyoto University for mass spectrometric measurements. We also express our thanks to Professors Y. Yoshikawa, M. Kimura, and K. Satake and Mr. H. Okamoto of Okayama University for valuable discussions. This research was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas ("Multiplex Organic System") from the Ministry of Education, Science, and Culture, Japan.

**Registry No.** **1a**, 126320-56-7; **1b**, 126320-57-8; **1c**, 136576-67-5; **1d**, 136576-68-6; **2a**, 136576-69-7; **2b**, 126320-55-6; **2c**, 136599-72-9; **2d**, 136576-70-0; **2e**, 136576-71-1; $Li^+$, 17341-24-1; $Na^+$, 17341-25-2; $K^+$, 24203-36-9; $Cs^+$, 18459-37-5; $Ag^+$, 14701-21-4; $Mg^{2+}$, 22537-22-0;

(15) Menger, F. M. *Top. Curr. Chem.* **1986**, *136*, 1.
(16) Tsukube, H.; Takagi, K.; Higashiyama, T.; Iwachido, T.; Hayama, N. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1541.
(17) Several ketone derivatives similarly exhibited two C=O characteristic bands. See: Pouchert, C. J. In *The Aldrich Library of Infrared Spectra*; Aldrich Chem. Co., Inc.: Milwaukee, WI, 1970; p 631.

$Ca^{2+}$, 14127-61-8; $Ba^{2+}$, 22541-12-4; $Pb^{2+}$, 14280-50-3; $Cu^{2+}$, 15158-11-9; $Ni^{2+}$, 14701-22-5; $Co^{2+}$, 22541-53-3; $Zn^{2+}$, 23713-49-7; cyclam, 295-37-4; *N,N*-diethylchloroacetamide, 2315-36-8; ethyl chloroacetate, 105-39-5; chloroacetonitrile, 107-14-2; phenacyl bromide, 70-11-1; piperazine, 110-85-0; 1,4,7-triazacyclononane, 4730-54-5; 1,4,8,12-tetraazacyclopentadecane, 15439-16-4; 1,4,8,11-tetraazacyclotetradecane-5,7-dione, 63972-19-0; 1,4,7,10-tetraazacyclododecane tetrahydrochloride, 10045-25-7.

**Supplementary Material Available:** $^1H$ and/or $^{13}C$ NMR spectra for compounds **2b–d** (6 pages). Ordering information is given on any current masthead page.

# Nucleic Acid Related Compounds. 70. Synthesis of 2′(and 3′)-Deoxy-2′(and 3′)-methyleneadenosines and Bis(methylene)furan 4′,5′-Didehydro-5′-deoxy-2′(and 3′)-methyleneadenosines. Inhibitors of *S*-Adenosyl-L-homocysteine Hydrolase and Ribonucleotide Reductase[1]

Vicente Samano and Morris J. Robins*

*Department of Chemistry, Brigham Young University, Provo, Utah 84602*

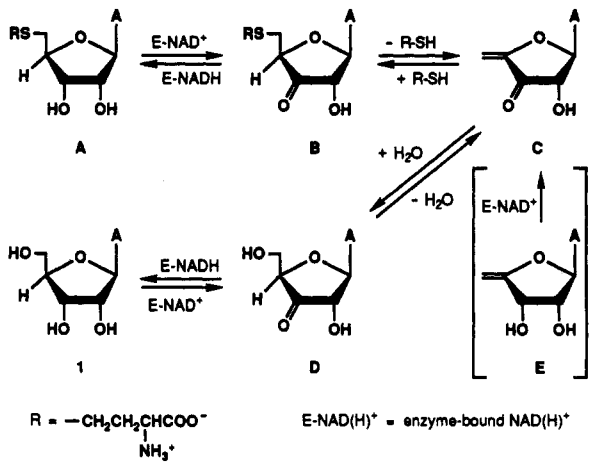
*Received June 25, 1991*

Wittig treatment of 3′,5′(or 2′,5′)-bis-*O*-silyl-2′(or 3′)-ketoadenosine derivatives with methylenetriphenylphosphorane and deprotection gave the 2′(or 3′)-deoxy-2′(or 3′)-methyleneadenosines, respectively. Enzymatic deamination afforded the 2′(or 3′)-deoxy-2′(or 3′)-methyleneinosines. Treatment of 2′-*O*-(*tert*-butyldimethylsilyl)-3′-deoxy-3′-methylene-5′-*O*-tosyladenosine (**14**) with sodium 2-methyl-2-butoxide and deprotection gave 9-(3,5-dideoxy-3-methylene-β-D-*glycero*-pent-4-enofuranosyl)adenine (**20**). Analogous treatment of a protected 2′,5′-dideoxy-5′-iodo-2′-methyleneadenosine derivative gave 9-(2,5-dideoxy-2-methylene-β-D-*glycero*-pent-4-enofuranosyl)adenine (**22**). Biochemical aspects of the putative mechanism-based inhibition of *S*-adenosyl-L-homocysteine hydrolase and ribonucleotide reductase by these compounds are discussed.

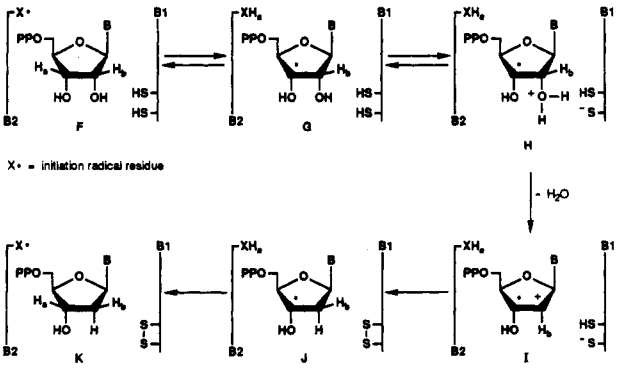
*S*-Adenosyl-L-homocysteine (AdoHcy) hydrolase (SAHase) (EC 3.3.1.1) and ribonucleoside diphosphate reductase (RDPR) (1.17.4.1) are important enzymes in the nucleic acid manifold. SAHase catalyzes the reversible hydrolysis of AdoHcy (A, Scheme I) to adenosine (1) and L-homocysteine.[2] This is crucial for continuing biosynthesis and cell division since the accumulation of AdoHcy results in feedback inhibition of important *S*-adenosylmethionine(AdoMet)-dependent transmethylation reactions.[3,4] Therefore, the targeted inhibition of SAHase is attractive for the development of pharmacologically active agents.[3,5,6] The accepted mechanism for SAHase[7] (Scheme I) is initiated by oxidation of the secondary alcohol function at C3′ of AdoHcy (A) by enzyme-bound $NAD^+$ to give 3′-ketonucleoside B. This activates H4′ for elimination of L-homocysteine to give enone C. Michael-type addition of water gives 3′-ketoadenosine (D) that is reduced by NADH to give adenosine (1). All steps in this sequence are reversible, and AdoHcy (A) is formed from adenosine and L-homocysteine in the presence of SAHase. It has been demonstrated[7b,c] that 9-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine (4′,5′-didehydro-5′-deoxyadenosine) (E) is oxidized at C3′ by the enzyme-bound $NAD^+$ of SAHase to give enone C directly.

Reduction of ribonucleoside 5′-diphosphates catalyzed by RDPR gives the essential 2′-deoxyribonucleotide building blocks for DNA synthesis in dividing cells.[8–10] Thus, RDPR plays a crucial role in cell growth. The

**Scheme I**




**Scheme II**




(1) The previous paper in this series is: Samano, M. C.; Robins, M. J. *Tetrahedron Lett.*, in press.
(2) de la Haba, G.; Cantoni, G. L. *J. Biol. Chem.* **1959**, *234*, 603.
(3) Ueland, P. M. *Pharmacol. Rev.* **1982**, *34*, 223.
(4) Cantoni, G. L. In *The Biochemistry of Adenosylmethionine*; Salvatore, F., Borek, E., Zappia, V., Williams-Ashman, H. G., Schlenk, F., Eds.; Columbia University Press: New York, 1977; pp 557–577.
(5) Keller, B. T.; Borchardt, R. T. In *Biological Methylation and Drug Design: Experimental and Clinical Roles of S-Adenosylmethionine*; Borchardt, R. T., Creveling, C. R., Ueland, P. M., Eds.; Humana: Clifton, NJ, 1986; pp 385–396.
(6) (a) Wolfe, M. S.; Borchardt, R. T. *J. Med. Chem.* **1991**, *34*, 1521. (b) De Clercq, E. *Nucleosides Nucleotides* **1987**, *6*, 197.
(7) (a) Palmer, J. L.; Abeles, R. H. *J. Biol. Chem.* **1976**, *251*, 5817. (b) Palmer, J. L.; Abeles, R. H. *J. Biol. Chem.* **1979**, *254*, 1217. (c) Parry, R. J.; Askonas, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 1417.
(8) Follmann, H. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 569.

0022-3263/91/1956-7108$02.50/0 