Most of the above proposals follow directly from the assumption of a mobile equilibrium between 4 and 5 coordination, the requirement for steric and dynamic constancy of formal charge on Zn(II), and the special enzyme–substrate–anion complex characterizing the high-pH inhibition of BCA-catalyzed CO_2 hydration by anions. Throughout this study, the strongest simplifying assumption of rapid equilibrium between enzyme species has been employed, with excellent success. It is likely that expansion of this simplified scheme will make it possible to explain in detail certain other kinetic results, such as inhibition at high pH by Br^- and I^-, the diminution of CA catalytic activity at low buffer concentrations,[29,40-42] and other observations.[43] Consequently,

we feel that the proposed mechanism is an appealing working hypothesis with intriguing implications for future investigations.

(40) Pocker, Y.; Bjorkquist, D. W. "Abstracts and Communications", 10th Meeting of the Federal European Biochemistry Society, 1975, Abstract 783. Johnson, B.-H.; Steiner, H.; Lindskog, S. "Abstracts and Communications", 10th Meeting of the Federal European Biochemistry Society, 1975, Abstract 784.

(41) Silverman, D. N.; Tu, C. K. *J. Am. Chem. Soc.* **1975**, *97*, 2263. Silverman, D. N.; Tu, C. K. *Ibid.* **1976**, *98*, 978. Tu, C. K.; Silverman, D. N. *Ibid.* **1975**, *97*, 5935.

(42) Silverman, D. N.; Tu, C. K.; Lindskog, S.; Wynns, G. C. *J. Am. Chem. Soc.* **1979**, *101*, 634.

(43) Simonsson, S.; Jonsson, B.-H.; Lindskog, S. *Eur. J. Biochem.* **1979**, *93*, 409. Koenig, S. H.; Brown, R. D., III *Biophys. J.* **1981**, *35*, 59.

Cryptand Exchange Kinetics

B. G. Cox,* J. Garcia-Rosas,* and H. Schneider*

Contribution from the Department of Chemistry, University of Stirling, Stirling, Scotland FK9 4LA, and the Max-Planck-Institut für Biophysikalische Chemie, D-3400 Göttingen, West Germany. Received August 31, 1981
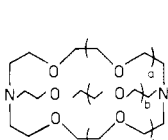
Abstract: The rate constant for some reactions between a metal cryptate $MCry_1^{n+}$ and a free cryptand Cry_2 has been determined. For the case when $M^{n+} = Tl^+$, Ca^{2+}, $Cry_1 = (2,2,2)$, $(2_B,2,2)$ and $Cry_2 = (2,2,1)$ in water or water–methanol mixtures, the observed rate constant corresponds to that of the dissociation of $MCry_1^{n+}$. However, the exchange reactions $Pb(2,1,1)^{2+} + (2,2,1)$ and $Pb(2,1,1)^{2+} + (2,2,2)$ in MeOH present rates that are much larger than the dissociation rate of $Pb(2,1,1)^{2+}$. A mechanism involving a bimolecular reaction between cryptate and free cryptand is proposed.

Previous studies on the kinetics of macrobicyclic diamines (cryptands) and their metal complexes (cryptates) have been mainly concerned with the dissociation and formation rates of the complexes.[1] Proton-transfer reactions between hydroxide ions and some monoprotonated cryptands have also been investigated,[2] as well as the acid-catalyzed dissociation of metal cryptates.[3] As a result of NMR studies[4-6] some metal ion–metal cryptate exchange rates in various solvents and free ligand–complexed ligand exchange rates in water have been measured.
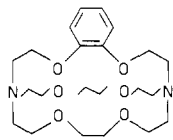
In this paper we wish to report a new aspect of cryptand kinetics. The reactions we have studied are of the type shown in eq 1, where M^{n+} is the metal ion and Cry_1 and Cry_2 are two different cryptands which form the metal cryptates $MCry_1^{n+}$ and $MCry_2^{n+}$, respectively.

$$MCry_1^{n+} + Cry_2 \xrightarrow{k_e} MCry_2^{n+} + Cry_1 \qquad (1)$$

The cations Ca^{2+}, Tl^+, and Pb^{2+} and cryptands $(2,1,1)$, $(2,2,1)$, $(2,2,2)$, and $(2_B,2,2)$ were used in the present study.

$(2,1,1), a = 1; b = c = 0$
$(2,2,1), a = b = 1; c = 0$
$(2,2,2), a = b = c = 1$

$(2_B,2,2)$

*Address correspondence as follows: B.G.C., University of Stirling; J.G.-R. and H.S., Max-Planck-Institut für Biophysikalische Chemie.

Ligand-exchange reactions, where the ligands are macrocycles, may be of interest in relation to the transport of ions through membranes by macrocyclic carriers.[7] Simon et al. have shown, using ^{14}C-labeled valinomycin, that exchange of ligands occurs during transport of cations through membranes.[8] Studies on ion-permeability phenomena, such as Na^+ channels, have led others to propose kinetic models where bimolecular reaction with participation of a ligand is involved.[9]

Experimental Section

A. Materials. Cryptands $(2,1,1)$, $(2,2,1)$, $(2,2,2)$, and $(2_B,2,2)$ were purchased from Merck and used without further purification. Doubly-distilled water and dried methanol (Merck, GR, max. 0.01% H_2O) were

(1) See, for example: E. L. Yee, O. A. Gansow, and M. J. Weaver, *J. Am. Chem. Soc.*, **102**, 2278 (1980); V. M. Loyola, R. Pizer, and R. G. Wilkins, *ibid.*, **99**, 7185 (1977); B. G. Cox, J. Garcia-Rosas, and H. Schneider, *ibid.*, **103**, 1054 (1981).

(2) B. G. Cox, D. Knop, and H. Schneider, *J. Am. Chem. Soc.*, **100**, 6002 (1978).

(3) B. G. Cox and H. Schneider, *J. Am. Chem. Soc.*, **99**, 2809 (1977).

(4) Y. M. Cahen, J. L. Dye, and A. I. Popov, *J. Phys. Chem.*, **79**, 1292 (1975).

(5) J. M. Ceraso, P. B. Smith, J. S. Landers, and J. L. Dye, *J. Phys. Chem.*, **81**, 760 (1977).

(6) J. M. Lehn, J. P. Sauvage, and B. Dietrich, *J. Am. Chem. Soc.*, **92**, 2916 (1970).

(7) J. D. Lamb, R. M. Izatt, P. A. Robertson, and J. J. Christensen, *J. Am. Chem. Soc.*, **102**, 2452 (1980).

(8) H. K. Wipf, A. Olivier, and W. Simon, *Helv. Chim. Acta*, **53**, 1605 (1970).

(9) P. L. Dorogi and E. Neumann, *Proc. Natl. Acad. Sci. U.S.A.*, **77**, 6582 (1980).

Cryptand Exchange Kinetics

J. Am. Chem. Soc., Vol. 104, No. 9, 1982 2435

Table I. Rate Constants of Cryptand Exchange (k_e) at 25 °C

$MCry_1^{n+}$	Cry_2	solvent	k_e, s^{-1}	k_d, s^{-1}
$Ca(2_B,2,2)^{2+}$	$(2,2,1)$	H_2O	0.54 ± 0.04	0.55^a
$Tl(2,2,2)^+$	$(2,2,1)$	H_2O	5.2 ± 0.2	5.5 ± 0.5^b
$Tl(2,2,2)^+$	$(2,2,1)$	MeOH–H_2O (90:10)	0.14	0.12 ± 0.01^b

^{a} J. Garcia-Rosas and H. Schneider, unpublished results. ^{b} R. Gresser, D. W. Boyd, A. M. Albrecht-Gary, and J. P. Schwing, *J. Am. Chem. Soc.*, 102, 651 (1980).

used as solvents. The inorganic salts were $Ca(NO_3)_2$, $Pb(NO_3)_2$, and $TlClO_4$.

B. Rate-Constant Measurements. The rates for reaction 1 were measured with a stopped-flow apparatus with optical detection. Pb^{2+} and Tl^+ complexes with $(2,1,1)$, $(2,2,1)$, and $(2,2,2)$ present more or less strong absorbance in the UV region. The $(2_B,2,2)$ cryptand and its calcium complex show also some difference in their absorbance in the UV. This allowed us to monitor reaction 1 by observing the spectral changes upon the addition of an excess of the displacing cryptand (Cry_2) to an equilibrium M^{n+}/Cry_1 mixture. However, these spectral changes are not always sufficiently large to permit the study of a wider range of ligands and metal ions.

Rate constants were measured for the following reactions.

(i) $Ca(2_B,2,2)^{2+} + (2,2,1) \rightarrow Ca(2,2,1)^{2+} + (2_B,2,2)$ in water at 25 °C: Total $Ca(NO_3)_2$ and $(2_B,2,2)$ concentrations were 4×10^{-4} M, and $(2,2,1)$ concentrations were in the range 2×10^{-3} M to 10^{-2} M. The measurements were made at 285 nm.

(ii) $Tl(2,2,2)^+ + (2,2,1) \rightarrow Tl(2,2,1)^+ + (2,2,2)$ in water and a 90:10 MeOH–H_2O mixture at 25 °C: Total concentrations were 5×10^{-4} M for $TlClO_4$ and 5.1×10^{-4} M for $(2,2,2)$. $(2,2,1)$ concentration varied in the range 5×10^{-3} M to 10^{-2} M. The reactions were followed at 268 nm.

(iii) $Pb(2,1,1)^{2+} + (2,2,1) \rightarrow Pb(2,2,1)^{2+} + (2,1,1)$ and $Pb(2,1,1)^{2+} + (2,2,2) \rightarrow Pb(2,2,2)^{2+} + (2,1,1)$ in MeOH at different temperatures [5, 10, 15, 20, and 25 °C for the reaction of $Pb(2,1,1)^{2+}$ with $(2,2,1)$ and −3.2, 0.0, 5.2, 10.2, and 14.9 °C for the reaction of $Pb(2,1,1)^{2+}$ with $(2,2,2)$]: The rate constant at 25 °C for this second reaction was calculated from the activation parameters. Total concentrations were 1.5×10^{-4} M to 5.2×10^{-4} M for $Pb(NO_3)_2$, 2×10^{-4} M to 5.6×10^{-4} M for $(2,1,1)$, 10^{-3}M to 6×10^{-3}M for $(2,2,1)$, and 2×10^{-3}M to 2.1×10^{-2}M for $(2,2,2)$. The reactions were followed at 280 nm. In the initial M^{n+}/Cry_1 mixtures, Cry_1 was always slightly in excess.
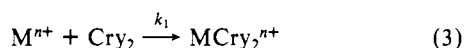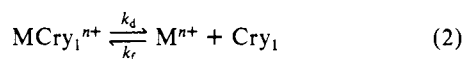
In all cases the incoming ligand forms a complex with the metal ion which is much more stable than that formed between the displaced ligand and the cation.[10,11] The displacing ligand was used in large excess to ensure that the reaction went to completion.

Results and Discussion

Table I shows the observed rate constants (k_e) for reactions i and ii. Rates of dissociation (k_d) for the corresponding cryptates are also given. Table II gives the rate constants for case iii.

For reactions i and ii the observed rate constants were independent of $[2,2,1]$ and of the concentrations of the other species present. In reaction iii, the rate for the first reaction was also independent of $(2,2,1)$ concentration, but for the second reaction, k_e was a function of the concentration of the incoming cryptand $(2,2,2)$ (Figure 1).

From Table I we see that the values of k_e and k_d are practically the same. This suggests that the cryptand exchange in reactions i and ii proceeds via the free metal ion as shown in eq 2 and 3, the dissociation of the cryptate $MCry_1^{n+}$ being the rate-determining step.

$$MCry_1^{n+} \underset{k_f}{\overset{k_d}{\rightleftarrows}} M^{n+} + Cry_1 \qquad (2)$$

$$M^{n+} + Cry_2 \overset{k_1}{\longrightarrow} MCry_2^{n+} \qquad (3)$$

The case of the lead cryptates, however, requires the postulation of an additional mechanism. The observed rate constant for the reaction of $Pb(2,1,1)^{2+}$ with $(2,2,1)$ was independent of $(2,2,1)$ concentration (10^{-3} M $< [2,2,1] < 6 \times 10^{-3}$ M). However, the measured rate constant is around 25 times larger than the dis-

(10) J. M. Lehn and J. P. Sauvage, *J. Am. Chem. Soc.*, 97, 6700 (1975).
(11) B. Spiess, F. Arnaud-Neu, and M. J. Schwing-Weill, *Helv. Chim. Acta*, 63, 2287 (1980).
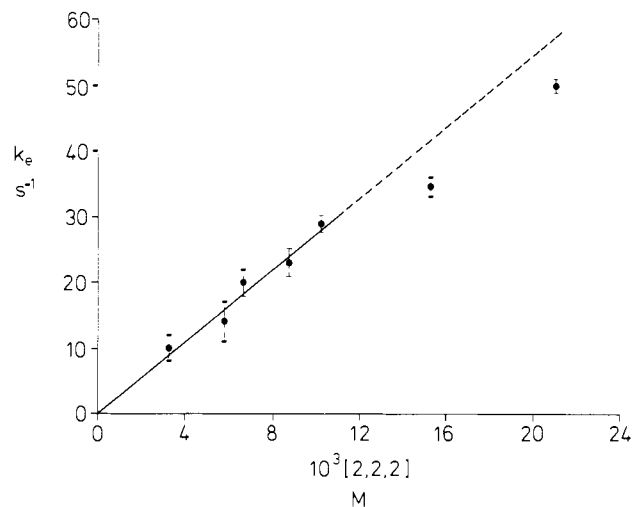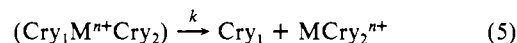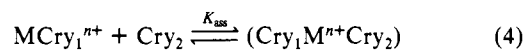

Figure 1. Dependence of the observed rate constant k_e on the concentration of $(2,2,2)$ for the exchange reaction between $Pb(2,1,1)^{2+}$ and $(2,2,2)$ in methanol at 0.0 °C.

sociation rate constant of $Pb(2,1,1)^{2+}$. k_e for the reaction of $Pb(2,1,1)^{2+}$ with $(2,2,2)$ shows a linear dependence on $(2,2,2)$ concentration at $[2,2,2] <$ ca. 10^{-2} M, but at higher concentrations k_e values are somewhat lower than predicted from a linear dependence of k_e on $[2,2,2]$ (Figure 1). A reaction scheme consistent with both results is shown in eq 4 and 5, where $(Cry_1M^{n+}Cry_2)$

$$MCry_1^{n+} + Cry_2 \overset{K_{ass}}{\rightleftharpoons} (Cry_1M^{n+}Cry_2) \qquad (4)$$

$$(Cry_1M^{n+}Cry_2) \overset{k}{\longrightarrow} Cry_1 + MCry_2^{n+} \qquad (5)$$

is an intermediate species formed during the reaction. It can be shown that the kinetic equations for this scheme are given by eq 6, 7, and 8. Now if $K_{ass}[Cry_2] \ll 1$, i.e., only a small fraction

$$\frac{d[MCry_2^{n+}]}{dt} = -\frac{d[MCry_1^{n+}]_T}{dt} = k_e[MCry_1^{n+}]_T \qquad (6)$$

$$k_e = \frac{kK_{ass}[Cry_2]}{1 + K_{ass}[Cry_2]} \qquad (7)$$

$[MCry_1^{n+}]_T =$ total amount of $MCry_1^{n+} =$
$$[MCry_1^{n+}] + [(Cry_1M^{n+}Cry_2)] \qquad (8)$$

of $MCry_1^{n+}$ is associated with Cry_2 at equilibrium, eq 7 gives

$$k_e = kK_{ass}[Cry_2] \qquad (9)$$

which is the case of $Pb(2,1,1)^{2+}$ with $(2,2,2)$ at low $[2,2,2]$. At higher $[2,2,2]$, the term $K_{ass}[Cry_2]$ can no longer be neglected. The value of the observed rate constant is lower than predicted by eq 9. We can write eq 7 as

$$\frac{1}{k_e} = \frac{1}{k} + \frac{1}{kK_{ass}[Cry_2]} \qquad (10)$$

Then a plot of $1/k_e$ against $1/[Cry_2]$ should be a straight line whose intercept with the $1/[Cry_2] = 0$ axis is $1/k$ and has a slope $1/kK_{ass}$ (Figure 2). From this plot we have estimated the values of k (1.8×10^2 s^{-1}) and K_{ass} (1.7×10 M^{-1}) at 0 °C.

If K_{ass} is large and $K_{ass}[Cry_2] \gg 1$, eq 7 gives

$$k_e = k \qquad (11)$$

i.e., the observed rate constant is k. This may be the case of $Pb(2,1,1)^{2+}$ with $(2,2,1)$.

In the most general case, according to eq 7, one would expect that the observed rate constant had the shape shown in Figure 3.

The proposed kinetic scheme, eq 4 and 5, includes a rapid preequilibrium. Indeed, we have observed that there is a very rapid initial increase in absorbance upon mixing the $Pb(2,1,1)^{2+}$ solution with $(2,2,1)$ or $(2,2,2)$. Moreover, the measured reaction between

Table II.   Rate Constants and Activation Parameters of Cryptand Exchange Reaction in MeOH at 25 °C

$MCry_1{}^{n+}$	Cry_2	k_e, s^{-1}	E_a, kJ mol^{-1}	$\Delta H^{\ddagger}$, kJ mol^{-1}	$\Delta S^{\ddagger}$, J mol^{-1} deg^{-1}	$k_d{}',{}^a$ s^{-1}
Pb(2,1,1)$^{2+}$	(2,2,1)	$(1.45 \pm 0.10) \times 10^{-1}$	38 ± 6	36 ± 6	-140 ± 20	
Pb(2,1,1)$^{2+}$	(2,2,2)	(3.5×10^4) [2,2,2]^b	70.2 ± 2	67.8 ± 2	69.2 ± 4	6×10^{-3}

^{a} The following mechanism for the dissociation of Pb(2,1,1)$^{2+}$ seems to occur: Pb(2,1,1)$^{2+}$ (k'_d) $\rightleftarrows$ (Pb. . .)$^{2+}$ $\rightleftarrows$ Pb^{2+} + (2,1,1), where the first step is rated determining.   J. Garcia-Rosas and H. Schneider, to be published. ^{b} At [2,2,2] < ca. 10^{-2} M.   See text.
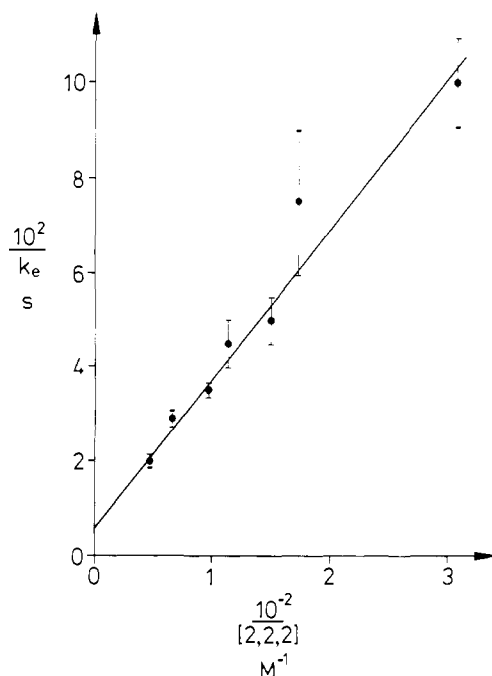

Figure 2. Dependence of the inverse of the observed rate constant on the inverse of the (2,2,2) concentration for the exchange reaction between Pb(2,1,1)$^{2+}$ and (2,2,2) in methanol at 0.0 °C.

Figure 3. Dependence of the observed rate constant on the concentration of the incoming ligand.

Pb(2,1,1)$^{2+}$ and (2,2,1) was the slower decrease in absorbance after a large instantaneous absorbance jump, while that between Pb(2,1,1)$^{2+}$ and (2,2,2) was a continuous increase in absorbance. In both cases, the final absorbance was practically that of Pb-(2,2,1)$^{2+}$ and Pb(2,2,2)$^{2+}$, respectively. At the wavelength used in our measurements (280 nm), Pb(2,2,1)$^{2+}$ and Pb(2,2,2)$^{2+}$ absorb more strongly than Pb(2,1,1)$^{2+}$. From our observations on absorbance, it follows that the optical density of the intermediate (2,1,1)Pb^{2+}(2,2,1) is larger than that for Pb(2,2,1)$^{2+}$ or Pb-(2,1,1)$^{2+}$. This is surprising since Pb^{2+} and the uncomplexed cryptands practically do not absorb. The absorbance showed by the lead cryptates is related to the Pb^{2+}···N bonds. In the intermediate (Cry$_1$Pb^{2+}Cry$_2$), the metal ion is located very probably between the two cryptand molecules. This means that in order to form the intermediate, Pb^{2+} has to be released partially from the Cry$_1$ into Cry$_2$.

Pb^{2+} has an ionic radius of 1.21 Å.[12]   The cavity radius of (2,1,1) is 0.8 Å.[13]   Therefore, the lead ion in the Pb(2,1,1)$^{2+}$ complex is very likely to be only partially enclosed in the (2,1,1) cavity. NMR studies have suggested the existence of Cs(2,2,2)$^+$ exclusive complexes in which the metal ion is not completely within the ligand cavity.[14]   It has been found that macrocyclic polyethers of the crown type sometimes form 2:1 (ligand to metal ratio) complexes when the cation is too large to fit into the hole of the polyether ring.[15]   Cryptands are bulkier macrocyclic ligands than crown ethers and the formation of 2:1 cryptates may find steric hindrance. So far there is no report in the literature of such 2:1
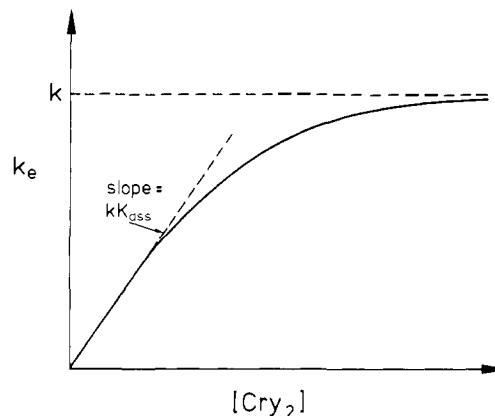
complexes.[16]   However, in spite of the relatively large size of Pb^{2+} compared with that of the (2,1,1) cavity, an extremely stable complex Pb(2,1,1)$^{2+}$ is formed. Values around 10^8 for the stability constant (K_s) of Pb(2,1,1)$^{2+}$ and 10^{15} for Pb(2,2,1)$^{2+}$ and Pb-(2,2,2)$^{2+}$ in methanol are reported in the literature.[11]   These very high values of K_s may be due to the ability of Pb^{2+} to coordinate with the binding centers of the ligands. Therefore it is not unreasonable to consider that an intermediate (2,1,1)Pb^{2+}(2,2,1) or (2,1,1)Pb^{2+}(2,2,2) may be formed during the course of the reaction.

It is not expected that all cryptand exchange reactions involve a bimolecular step, eq 4 and 5. Indeed, we have already shown that the exchange reactions i and ii follow a cryptate dissociation path. Benzo-substituted cryptands such as (2$_B$,2,2) are more rigid and bulky. Therefore a bimolecular reaction is less likely to occur. Solvation of the ligand should also play an important role. Cryptands such as (2,2,2) have a positive free energy of transfer from water to methanol.[17]   This means that the ligand is more strongly solvated, and therefore less reactive, in water than in metanol. If the metal cation is only partially within the ligand, a part of it should be interacting with the solvent. Then, the incoming ligand will have to displace these solvent molecules and substitute them by ligand binding sites. The nature of the metal ions should also be important. Ions capable of forming bonds of partial covalence with the ligand should facilitate the formation of intermediates Cry$_1$M^{n+}Cry$_2$. Indeed, we have found evidence, using a potentiometric technique,[18] that silver cryptates in methanol undergo ligand exchange at rates which are much higher than those expected from a dissociative mechanism, eq 2 and 3.

The rate constant for the inverse reaction in eq 5, k', can be estimated for the case Pb(2,2,2)$^{2+}$ + (2,1,1) from the values of K_{ass}, k, and the reported stability constants (K_s) of Pb(2,1,1)$^{2+}$ and Pb(2,2,2)$^{2+}$ (1.5 × 10^8 M^{-1} and 6.9 × 10^{14} M^{-1} at 25 °C, respectively[11]). A value of $k' = 6.7 \times 10^{-4}$ M^{-1} s^{-1} at 0 °C is obtained assuming that the ratio of K_s(Pb(2,2,2)$^{2+}$)/K_s(Pb-(2,1,1)$^{2+}$) at 0 °C is the same as at 25 °C. This very low value of k' suggests that it is difficult for the reaction between (2,1,1)

(12) L. Pauling, "The Nature of the Chemical Bond", 3rd ed., Cornell University Press, New York, 1960.

(13) J. M. Lehn, *Struct. Bonding (Berlin)*, **16**, 1 (1973).

(14) E. Mei, A. I. Popov, and J. L. Dye, *J. Am. Chem. Soc.*, **99**, 6532 (1977).

(15) C. J. Pedersen and H. K. Frensdorff, *Angew. Chem., Int. Ed. Engl.*, **11**, 16 (1972).

(16) Lehn and Sauvage in ref 10 suggest that 2:1 (ligand to metal ratio) complexes of Cs$^+$ with (2,1,1) and (2,2,1) may be formed.

(17) M. H. Abraham, A. F. Danil de Namor, and R. A. Schulz, *J. Chem. Soc., Faraday Trans. 1*, **76**, 869 (1980).

(18) J. Garcia-Rosas, H. Schneider, and B. G. Cox, "Fast Reactions in Solution Meeting", The Chemical Socity, London, and Max-Planck-Gesellschaft, Göttingen FRG, Sept 1980.

and $Pb(2,2,2)^{2+}$ to form the intermediate $(2,1,1)Pb^{2+}(2,2,2)$ to take place. Pb^{2+} is located very probably inside the (2,2,2) cavity. Therefore the (2,1,1) ligand could hardly interact with the metal ion.

Finally, the activation parameters for the $Pb(2,1,1)^{2+}$ exchange reactions studied here are given in Table II. When (2,2,1) is the exchanged ligand, the entropy of activation has a large negative value, while when (2,2,2) is the incoming ligand $\Delta S^{\ddagger}$ is fairly large and positive. The $\Delta H^{\ddagger}$ value for the (2,1,1)–(2,2,2) exchange is about twice as larger as that for the (2,1,1)–(2,2,1) exchange reaction. Although not much information can be drawn from the values of these activation paarameters, the very different $\Delta S^{\ddagger}$ values may suggest that two very different steps are responsible for the observed kinetic behavior of (2,2,1) and (2,2,2) in the exchange reaction with $Pb(2,1,1)^{2+}$.

Solid-State and Solution Conformation of Homo Oligo(α-aminoisobutyric acids) from Tripeptide to Pentapeptide: Evidence for a 3_{10} Helix[1a]

Ettore Benedetti,[*1b] **Alfonso Bavoso,**[1b] **Benedetto Di Blasio,**[1b] **Vincenzo Pavone,**[1b] **Carlo Pedone,**[1b] **Marco Crisma,**[1c] **Gian Maria Bonora,**[1c] and **Claudio Toniolo**[*1c]

Contribution from the Istituto Chimico, University of Naples, 80134 Naples, Italy, and the Biopolymer Research Centre, C.N.R., Institute of Organic Chemistry, University of Padua, 35100 Padua, Italy. Received August 11, 1981

Abstract: The X-ray diffraction and IR absorption conformational analysis in the solid state of the *N*-benzyloxycarbonyl homotri-, tetra-, and pentapeptides from α-aminoisobutyric acid has shown the occurrence of incipient 3_{10} helices, formed by one, two, and three type III (or type III′) β turns, respectively. α-Helical structures, although having closely related pairs of ϕ,ψ torsional angles, are not compatible with the observed intramolecular N—H···O=C hydrogen-bonding schemes of the tetra- and pentapeptides. In solvents of low polarity, the IR absorption data are in favor of the occurrence of the same intramolecular hydrogen-bonded forms as found in the solid state. Aggregation of these structures takes place at high concentrations. Since segments containing up to four α,α-dialkylated, α-amino acid residues in a row have been found in the transmembrane channel-forming peptide antibiotics of the alamethicin family, it is clear that the 3_{10}-helical structure must be taken into account in postulating[a] the model of folding of those parts of their sequences containing a high proportion of these residues.

The α,α-dialkylated, α-amino acid residues Aib[2] and Iva occur extensively in the transmembrane channel-forming peptide antibiotics of the alamethicin family.[3–7] According to a number of theoretical analyses, replacement of the hydrogen atom at the C^{α} carbon atom in the Ala residue by a methyl group produces severe restriction of the conformational freedom of the resulting Aib residue.[8–14]

We have begun an investigation of the conformational preferences of segments of the antibiotics, both in the solid state and in solution. Our initial objective is the study of segments containing exclusively α,α-dialkylated, α-amino acid residues, namely, -(Aib)$_{2,4}$- and -(Aib)$_{1,3}$-Iva.[3–7]

We have synthesized and examined by X-ray diffraction and IR absorption the complete homoligopeptide series (to the pentapeptide) formed by the achiral Aib residue having the general formula Z-(Aib)$_n$-OX (*n* = 1–5; X = H, *t*-Bu). In this paper we describe in detail the results of our conformational analysis of the N-protected homotri-, tetra-, and pentapeptides, i.e., those peptides having folded structures with at least one intramolecular N—H···O=C hydrogen bond. IR absorption data[15] and preliminary crystallographic results[16] of the lower homologue Z-(Aib)$_2$-OH have already been reported. The complex phenomenon exhibited by Z-Aib-OH in the solid state (possibly polymorphism), first

(1) (a) This is part 81 of the *Linear Oligopeptides* series; for part 80 see G. M. Bonora and C. Toniolo, *Gazz. Chim. Ital.*, **111**, 239 (1981). (b) University of Naples. (c) University of Padua.

(2) The following abbreviation are used in the text: Aib, α-aminoisobutyric acid or α-methylalanine; Iva, isovaline or α-ethylalanine; Ala, alanine; Leu, leucine; Val, valine; Pro, proline; Ac, acetyl; *t*-Boc, *tert*-butyloxycarbonyl; Z, benzyloxycarbonyl; Piv, pivaloyl; Tos, tosyl or *p*-toluenesulfonyl; OMe, methoxy; OBzl, benzyloxy; OEt, ethoxy; O-*t*-Bu, *tert*-butoxy; NHMe, methylamino; MeOH, methanol.

(3) G. Jung, W. A. König, D. Leibfritz, T. Ooka, K. Janko, and G. Boheim, *Biochim. Biophys. Acta*, **433**, 164 (1976).

(4) T. Fujita, Y. Takaishi, and T. Shiromoto, *J. Chem. Soc., Chem. Commun.*, 413 (1979).

(5) T. Fujita, Y. Takaishi, A. Okamura, E. Fujita, K. Fuji, N. Hiratsuka, M. Komatsu, and I. Arita, *J. Chem. Soc., Chem. Commun.*, 585 (1981).

(6) K. L. Rinehart, Jr., R. C. Pandey, M. L. Moore, S. R. Tarbox, C. R. Snelling, J. C. Cook, Jr., and R. H. Milberg in "Peptides: Structure and Biological Function", E. Gross and J. Meienhofer, Eds., Pierce, Rockford, IL, 1979, pp 59–71.

(7) W. A. König and M. Aydin in "Peptides 1980", K. Brunfeldt, Ed., Scriptor, Copenhagen, 1981, pp 711–718.

(8) A. W. Burgess, Y. Paterson, and S. J. Leach in "Peptides, Polypeptides, and Proteins", E. R. Blout, F. A. Bovey, M. Goodman, and N. Lotan, Eds., Wiley, New York, 1974, pp 79–88.

(9) M. E. Johnson and T. T. Wu, *J. Theor. Biol.*, **60**, 183 (1976).

(10) G. R. Marshall and F. A. Gorin in "Peptides", M. Goodman and J. Meienhofer, Eds., Wiley, New York, 1977, pp 84–87.

(11) G. D. Smith, V. Z. Pletnev, W. L. Duax, T. M. Balasubramanian, H. E. Bosshard, E. W. Czerwinski, N. E. Kendrick, F. S. Mathews, and G. R. Marshall, *J. Am. Chem. Soc.*, **103**, 1493 (1981).

(12) B. V. Venkataram Prasad and V. Sasisekharan, *Macromolecules*, **12**, 1107 (1979).

(13) Y. Paterson, S. M. Rumsey, E. Benedetti, G. Němethy, and H. A. Scheraga, *J. Am. Chem. Soc.*, **103**, 2947 (1981).

(14) V. Z. Pletnev, E. P. Gromov, and E. M. Popov, *Khim. Prir. Soedin.*, 224 (1973).

(15) M. Crisma, Doctorate Thesis, Institute of Organic Chemistry, University of Padua, 1979.

(16) E. Benedetti, C. Pedone, and C. Toniolo in "Peptides 1980", K. Brunfeldt, Ed., Scriptor, Copenhagen, 1981, pp 619–624.