Table I. Thermodynamic Values for the Spin Equilibrium of the Azide Complexes

	ΔH, cal/mol	ΔS, eu	T_c,[a] K	K_{25}[b]	low-spin fraction at 25 °C	ref
hemoglobin	−5094	−13.62	374	5.8	0.85	6
	−6700	−17	400	16	0.94	13
myoglobin	−3746	−9.58	391	4.5	0.81	6
	−2740	−6.8	403	3.3	0.77	4
heme peptide	−3890	−8.6	452	9.4	0.90	9
catalase	−505	−5.8	87	0.13	0.11	27
hemin-N_3^--$(CH_3)_2SO$	−136	−0.975	139.5	0.77	0.43	this work

[a] Compensation temperature, where the high- and low-spin states are equally populated. [b] Equilibrium constant = [low spin]/[high spin] at 25 °C.

sociated with the higher spin state (2.9 and 4.7 μ_B at 100 and 294 K, respectively).[30] Thus the decreased low-spin character of hemin-N_3^--$(CH_3)_2SO$ may be related to an increased Fe(III)–OS$(CH_3)_2$ bond length due to an increased thermal motion of the ligated $(CH_3)_2SO$ at higher temperatures. In the extreme of complete rupture of the Fe(III)–OS$(CH_3)_2$ bond, the azide complex is high spin, as evidenced in the EPR and IR spectra of 5-coordinate hemin-N_3^- in Figures 3 and 5.

Although $(CH_3)_2SO$ is not a physiologically meaningful ligand, ligation of an oxygenous base to heme iron may have a relevance to the prosthetic structure of azide catalase.[23,27] Recent X-ray analysis on beef liver catalase demonstrated tyrosine-357 as the proximal heme ligand.[12] Table I compares the thermodynamic values associated with the spin equilibrium in several azide complexes with those of the nitrogen or oxygen axial base. The ΔH and ΔS of catalase and hemin-N_3^--$(CH_3)_2SO$ are similar to each

other and much smaller than those of hemoglobin and myoglobin. The similarity of ΔH, ΔS, and EPR g values (Figure 3) between catalase and the hemin-N_3^--$(CH_3)_2SO$ is consistent with the oxygenous base being the proximal ligand in catalase.[12] However, ΔS of the model is about 5-fold less negative than that of catalase. This is expected from the lack of the rearrangement of the nonbonded interactions in hemin-N_3^--$(CH_3)_2SO$ between porphyrin and globin with temperature change. Comparison of ΔH and K_{25} values in Table I suggests that the stabilization of the low-spin state tends to be associated with a more negative ΔH. Significantly negative ΔH's in the imidazole-ligated complexes may be explained in terms of a stronger axial ligation of histidine than of tyrosine, suggesting an enthalpy effect on spin equilibrium derived from the axial ligand difference.

The appearance of the spin equilibrium in the present model complex suggests that the spin equilibrium in azide catalase is primarily determined by the axial ligands and that the equilibrium is further modulated by the stereochemical changes of the globin surrounding the heme. A comparison of ΔH and ΔS between catalase and hemin-N_3^--$(CH_3)_2SO$ suggests a sizable contribution from the nonbonded interaction to the thermodynamic values in catalase. It is therefore likely that the nonbonded interaction could change the geometry of the Fe(III)–O(Tyr-357) bond[12] and the Fe(III) displacement to modulate the spin equilibrium in azide catalase.

(30) Scheidt, W. R.; Geiger, D. K.; Haller, K. J. *J. Am. Chem. Soc.* **1982**, *104*, 495–499.

Complexation of Calcium by the Synthetic Ionophore McN-4308, [2-(4-(Diphenylmethyl)-1-piperidinyl)-2-oxoethoxy]acetic Acid. Crystal and Molecular Structure of the Free Acid and of the Calcium Complex

Patrick Van Roey,*[1] G. David Smith,[1] William L. Duax,[1] Michael J. Umen,[2] and Bruce E. Maryanoff[2]

Contribution from the Medical Foundation of Buffalo, Inc., Buffalo, New York 14203, and McNeil Pharmaceutical, Spring House, Pennsylvania 19477. Received March 3, 1982

Abstract: McN-4308 is a synthetic monocarboxylic acid that exhibits the properties of a calcium ionophore. We have studied the crystal structures of McN-4308 and its calcium complex. The free acid crystallizes in space group $P2_1/c$ with cell dimensions $a = 20.244$ (4) Å, $b = 5.822$ (2) Å, $c = 16.363$ (4) Å, $\beta = 95.85$ (2)°, and $Z = 4$. The diglycolamic acid moiety shows conformational flexibility about the O3–C3 and the C1–C2 bonds. The calcium complex of McN-4308 crystallizes in space group $P\bar{1}$, $a = 17.460$ (1) Å, $b = 18.089$ (1) Å, $c = 15.834$ (1) Å, $\alpha = 97.24$ (1)°, $\beta = 88.24$ (1)°, $\gamma = 113.74$ (1)° with four calcium ions, each coordinated by two ionophores, in the unit cell ($Z = 4$). The complex exists in the solid state as centrosymmetric dimers possessing two calcium cations, four ionophore anions, and two water molecules. The calcium ions are eight-coordinate with square antiprism geometry. The two dimers observed in the unit cell are stereoisomers but have very similar overall geometry. In contrast to the free acid, the ionophores in the complex have nearly planar diglycolamic moieties. The dimers are held together through bridging carboxylate groups of two of the ionophores.

Ionophores are compounds that facilitate the transport of ions across natural and artificial membranes. They have been studied

primarily as potential drugs and as tools to help understand ion transport in biological systems. Until recently, most known
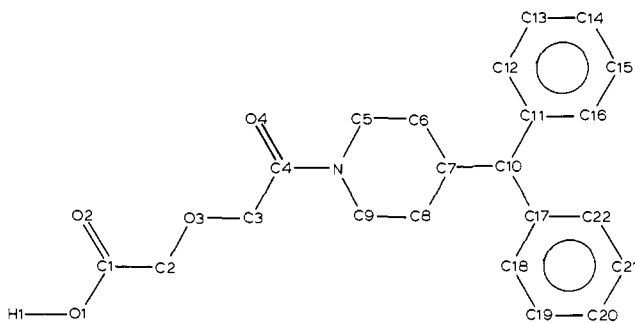
5662 *J. Am. Chem. Soc., Vol. 104, No. 21, 1982*

Van Roey et al.

Figure 1. Structural formula of McN-4308 with the numbering scheme used in this study.

ionophores were antibiotics with complex structures, such as the now-classical calcium-selective ionophore A23187.[3,4] However, in 1978, Umen and Scarpa[5] reported that a relatively simple organic acid, [2-(4-(diphenylmethyl)-1-piperidinyl)-2-oxoethoxy]acetic acid or McN-4308 (Figure 1), was also an effective ionophore, transporting calcium across a chloroform layer at a rate comparable to that observed for A23187. The compound was also found to be highly selective for calcium over magnesium, while not capable of transporting sodium. The study also showed that addition of picrate did not influence the rate of calcium transport, indicating a 1:2 calcium–ionophore ratio in the transported complex.

To better understand how McN-4308 binds and transports calcium ions, we determined the crystal structures of McN-4308 and its calcium complex, crystallized from aqueous medium.

Experimental Section

McN-4308 Free Acid. Single crystals were grown by slow evaporation of a dichloromethane–hexane solution. The crystals are monoclinic, space group $P2_1/c$, $a = 20.244$ (4) Å, $b = 5.822$ (2) Å, $c = 16.363$ (4) Å, $\beta = 95.85$ (2)°, $V = 1918.3$ Å^3, $Z = 4$, and $D_c = 1.269$ g cm^{-3}. A crystal with approximate dimensions of 0.12 × 0.60 × 0.81 mm was used for the data collection. A total of 4446 independent reflections (sin $\theta/\lambda \leq 0.65$ Å^{-1}) were measured on a Nicolet P3 diffractometer using Niobium filtered Mo Kα radiation. The intensities were corrected for Lorentz and polarization factors but not for absorption (μ(Mo Kα) = 0.941 cm^{-1}). Real and imaginary dispersion corrections were applied to the atomic scattering factors.[6] The variance of each structure factor F was calculated according to the method of Stout and Jensen[7] ($\sigma^2(F) = k/4LpI[\sigma^2(I) + (0.01I)^2]$; $\omega(F) = 1/\sigma^2(F)$). On the basis of a $4\sigma(F)$ test, 1796 reflections were considered unobserved and assigned a weight of zero.

The structure was solved by using the direct methods program MULTAN.[8] Positional and thermal parameters were refined by full-matrix least squares. During the refinement of the non-hydrogen atoms with anisotropic thermal parameters, the hydrogen atom contributions to the structure factors were included by calculating their positions on the basis of idealized geometry at the end of each cycle. A difference map with calculated structure factors obtained from the heavy-atom positions, calculated after the latter refinement had converged, revealed the positions of all hydrogen atoms. Positions and isotropic thermal parameters of the hydrogen atoms were refined in the final cycle.

The refinement converged at a residual of 0.058 (0.125 for all data) and a weighted residual of 0.043. The standard deviation of an observation of unit weight was 2.451. The extinction parameter, which was included in the refinement during the last three cycles, refined to a value of $g = 4.6$ (6) × 10^{-7}. The final atomic coordinates are listed in Table I.

Ca^{2+} Complex of McN-4308. The Ca^{2+} salt of McN-4308 was prepared as follows. McN-4308 (3.67 g, 10.0 mmol) was mixed with 50 mL

Table I. Atomic Coordinates (×10^4) for the Free Acid of McN-4308 (Standard Deviations in Parentheses)

atom	x/a	y/b	z/c
O2	-728 (1)	-6075 (3)	8810 (1)
O1	-827 (1)	-4555 (4)	10046 (1)
C1	-645 (1)	-4525 (5)	9290 (1)
C2	-324 (1)	-2268 (5)	9132 (2)
O3	55 (1)	-2530 (3)	8462 (1)
C3	399 (1)	-498 (5)	8270 (2)
C4	1048 (1)	-210 (5)	8811 (1)
O4	1207 (1)	-1517 (3)	9394 (1)
N1	1440 (1)	1515 (4)	8630 (1)
C9	1303 (1)	3135 (5)	7951 (2)
C8	1865 (1)	3102 (5)	7404 (1)
C7	2536 (1)	3629 (5)	7892 (1)
C6	2638 (1)	1973 (5)	8617 (1)
C5	2062 (1)	1976 (6)	9138 (1)
C10	3120 (1)	3481 (4)	7365 (1)
C11	3088 (1)	5064 (4)	6618 (1)
C12	2729 (1)	7092 (5)	6552 (2)
C13	2737 (2)	8482 (6)	5865 (2)
C14	3121 (2)	7914 (6)	5254 (2)
C15	3484 (1)	5923 (6)	5306 (2)
C16	3467 (1)	4500 (5)	5980 (1)
C17	3790 (1)	3774 (4)	7876 (1)
C18	3941 (1)	5756 (5)	8312 (2)
C19	4547 (1)	5981 (6)	8792 (2)
C20	5003 (2)	4238 (7)	8818 (2)
C21	4865 (1)	2285 (7)	8370 (2)
C22	4257 (1)	2048 (6)	7906 (2)

of deionized water and treated with 10 mL of 1.00 N NaOH. Anhydrous CaCl$_2$ (555 mg, 5.0 mmol) in 10 mL of water was added, and a thick gum separated. The solution was decanted, and the gum was rinsed with fresh water and dried in vacuo to give 3.6 g of the calcium salt. This semisolid was crystallized from 30 mL of warm methanol–water (3:1), cooling slowly to 23 °C and then to 5 °C. The solid was collected and dried in vacuo at 50 °C to give 2.2 g of white powder, mp 175–184 °C (corrected): ^{1}H NMR (Me$_2$SO-d_6) δ 0.7–1.6 (m, 5, CH$_2$CHCH$_2$), 3.3–3.8 (m, 11, s at 3.32 for H$_2$O integrated as five protons, which accounts for 2.5 mol of water remainder: 2CH$_2$N + CH$_2$CO$_2$), 4.0–4.4 (m, 3, Ph$_2$CH, OCH$_2$), 7.0–7.5 (m, 10); IR (KBr) ν_{max} 3414 (OH), 1638 (CO), 1603 (CO), 745, 704 cm^{-1}. Anal. Calcd for Ca·2C$_{22}$H$_{24}$NO$_4$· 5.4H$_2$O: C, 60.73; H, 6.81; H$_2$O, 11.18. Found: C, 60.69; H, 6.78; H$_2$O, 10.86. A sample of this salt was recrystallized from methanol–water by slow evaporation of methanol at 23 °C, affording small colorless prisms. The supernatant was removed carefully by pipet, and the crystals were rinsed quickly with methanol–water and dried in vacuo at 23 °C, mp 175–190 °C (IR was identical with the IR of material before recrystallization).

Single crystals, suitable for X-ray diffraction, were obtained by slow evaporation of a 50% water–methanol solution. X-ray diffraction data were measured at 260 K when it was found that the crystals were unstable to irradiation at room temperature, even when mounted in a capillary. The crystals are triclinic, space group $P\bar{1}$, $a = 17.460$ (1) Å, $b = 18.089$ (1) Å, $c = 15.834$ (1) Å, $\alpha = 97.24$ (1)°, $\beta = 88.24$ (1)°, $\gamma = 113.74$ (1)°, $V = 4540.1$ Å^3, $Z = 4$, and $D_c = 1.304$ g cm^{-3}. A single crystal (1.0 × 0.3 × 0.1 mm) was mounted in a capillary, and a total of 18 602 independent reflections (sin $\theta/\lambda \leq 0.626$ Å^{-1}) were measured on an Enraf-Nonius CAD-4 diffractometer using Ni-filtered Cu Kα radiation. Four standard reflections were measured after every 70 intensities were recorded and varied by less than 15%. Intensities were corrected for Lorentz and polarization factors but not for extinction or absorption (μ(Cu Kα) = 17.18 cm^{-1}). Real and imaginary dispersion corrections were applied to the atomic scattering factors.[7] The variance of each F was calculated as $\sigma^2(F) = k/4LpI[\sigma^2(I) + (0.06I)^2]$; $\omega(F) = 1/\sigma^2(F)$). On the basis of a $6\sigma(F)$ test, 7106 data were considered unobserved and assigned a weight of zero.

The structure was solved by using the direct methods program QTAN.[9] Anisotropic thermal parameters and positional parameters for all non-hydrogen atoms and 11 water molecules, which were located during early stages of Fourier refinement, were refined by least squares. To accommodate the large number of parameters, we conducted the refinement in three blocks. The first block consisted of a cycle of positional parameters for all atoms. Thermal-parameter refinement was carried out in

(1) Medical Foundation of Buffalo, Inc., 73 High Street, Buffalo, NY 14203.

(2) McNeil Pharmaceutical, Spring House, PA 19477.

(3) Puskin, J. S.; Gunter, T. E. *Biochemistry* **1975**, *14*, 187–191.

(4) Case, G. D.; Vanderkooi, J. M.; Scarpa, A. *Arch. Biochem. Biophys.* **1974**, *162*, 174–185.

(5) Umen, M. J.; Scarpa, A. *J. Med. Chem.* **1978**, *21*, 505–506.

(6) "International Tables for X-Ray Crystallography", Vol. IV; Kynoch Press: Birmingham, England, 1974; Tables 2.2B and 2.3.1.

(7) Stout, G. H.; Jensen, L. J. "X-Ray Structure Determination"; MacMillan: New York, 1968; pp 457.

(8) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1971**, *27A*, 368–376.

(9) Langs, D. A.; DeTitta, G. T. *Acta Crystallogr., Sect. A* **1975**, *A31*, S16.
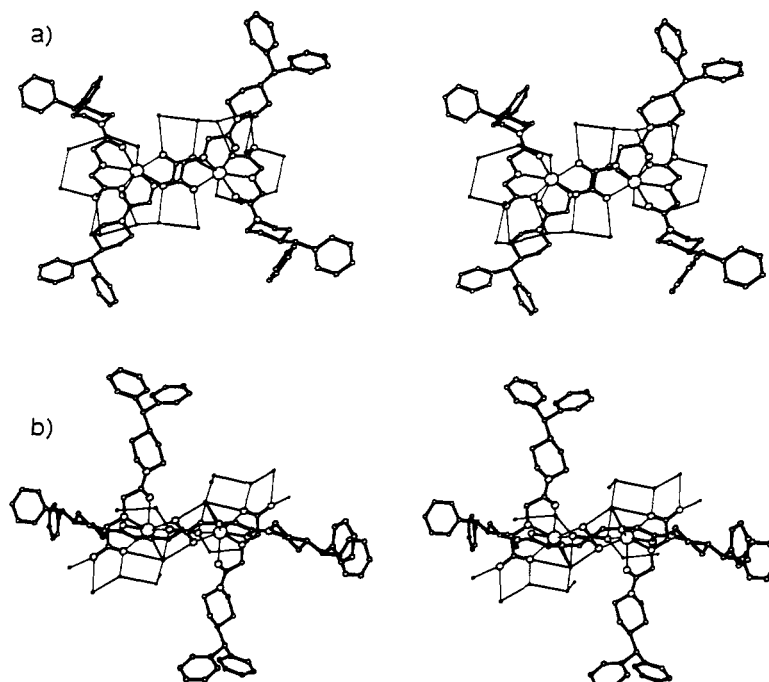
Figure 2. Stereo diagram illustrating the geometry of the two crystallographically independent dimers of the calcium complex of McN-4308, including the water molecules within a 4-Å radius of the calcium ions and the ionophore oxygen atoms.

the second and third blocks. The calcium ions were included in both blocks of thermal-parameter refinement, but the other atoms included were varied. Hydrogen atom contributions to the structure factors were included during the refinement with anisotropic thermal parameters for the non-hydrogen atoms by calculating their positions on the basis of idealized geometry.

The refinement converged at a residual of 0.071 (0.112 for all data) and a weighted residual of 0.102. The standard deviation of an observation of unit weight was 1.942. A final difference map possessed three peaks with a height of approximately one-third the height of the lowest water molecule but five times larger than the highest hydrogen atom. These peaks may correspond to additional water molecule positions that are only partially occupied. The final atomic coordinates are listed in Table II.

Results

The calcium complex of McN-4308 crystallizes from aqueous solution as centrosymmetric dimers that are composed of two Ca^{2+} ions, four ionophore anions, and two water molecules. The two independent dimers observed in the unit cell are shown in Figure 2. Each calcium ion is eight-coordinate, with the geometry of a distorted square antiprism. Each ionophore anion contributes a carboxylate oxygen (O1), an ether oxygen (O3), and a carbonyl oxygen (O4) to the coordination sphere of the calcium ion. The remaining coordination sites are occupied by a water molecule and a carboxylate oxygen (O2) of an ionophore that is coordinated primarily to the centrosymmetrically related calcium ion in the dimer. Figure 3 shows the environment of the calcium ions. The square antiprisms in the two dimers are stereoisomers corresponding to a position interchange between the water molecules and the bridging carboxylate oxygens. This results in a substantial difference in the contact region of the two halves of each dimer. This contact is mainly provided by the bridging carboxylate groups that interpenetrate more deeply between the two halves of the first dimer than in the second. Consequently, the distance between the calcium ions in the first dimer is larger than in the second (5.979 (3) Å vs. 5.277 (3) Å). However, the overall appearance of the dimers (shown in Figure 4) is very similar.

The geometry at the calcium ions is listed in Table III. None of the calcium–oxygen distances fall outside the expected region.[10,11] Although the water molecule and the bridging car-
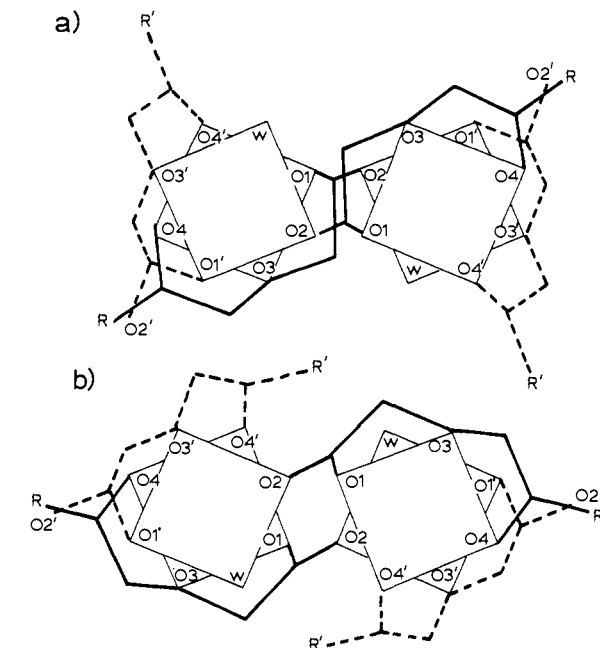

Figure 3. Idealized illustration of the environment of the calcium ions in the McN-4308 complex. Dimer 2 is obtained from dimer 1 by exchange of the water molecule (W) with the bridging carboxylate oxygen (O2) followed by a rotation of 45° clockwise at the right-hand side of the dimer or counterclockwise at the left-hand side.

boxylate oxygen O2 in the first dimer are closer to the calcium ion than the other two carboxylate oxygens, the reverse is observed in the second dimer.

The nine remaining water molecules in the calcium complex are involved in an extensive hydrogen-bonding scheme including also the water molecules coordinated to the calcium ions and the carboxylate oxygens. The water molecules in close proximity to the calciums are shown in Figure 2. The dimers are arranged in the cell in such a manner that the diphenylmethyl groups form hydrophobic bands alternating with bands of hydrophyllic com-

(10) Einspahr, H.; Bugg, C. E. Acta Crystallogr., Sect. B 1980, B36, 264–271.

(11) Einspahr, H.; Bugg, C. E. Acta Crystallogr., Sect. B 1981, B37, 1044–1052.

Table II. Atomic Coordinators ($\times 10^5$ for Calcium; $\times 10^4$ for the Others) of the Calcium Complex of McN-4308[a] (Standard Deviations in Parentheses)

	dimer 1						
	molecule 1				molecule 2		
	x/z	y/b	z/c		z/a	y/b	z/c
C1	−272 (2)	5437 (2)	−568 (2)	C1	3596 (3)	5817 (4)	−156 (3)
C2	22 (2)	6212 (2)	63 (2)	C2	3828 (3)	6178 (3)	−986 (3)
C3	1281 (3)	7275 (2)	633 (3)	C3	3201 (3)	6238 (3)	−2252 (2)
C4	2223 (3)	7540 (2)	535 (2)	C4	2375 (3)	6202 (2)	−2580 (2)
C5	3639 (3)	8442 (3)	964 (3)	C5	1572 (3)	6233 (3)	−3798 (3)
C6	4102 (3)	9346 (3)	1061 (3)	C6	1800 (3)	7032 (3)	−4166 (3)
C7	3878 (3)	9750 (2)	1879 (3)	C7	2513 (3)	7169 (3)	−4808 (2)
C8	2933 (3)	9532 (3)	1836 (3)	C8	3259 (3)	7089 (3)	−4389 (3)
C9	2457 (3)	8624 (3)	1753 (3)	C9	2979 (3)	6278 (3)	−4021 (3)
C10	4402 (3)	10668 (3)	2008 (3)	C10	2795 (3)	8016 (2)	−5125 (3)
C11	4210 (3)	11125 (2)	2807 (3)	C11	3526 (3)	8174 (3)	−5721 (3)
C12	3970 (3)	10796 (3)	3564 (3)	C12	3458 (4)	7693 (3)	−6495 (3)
C13	3867 (3)	11273 (3)	4301 (3)	C13	4155 (5)	7855 (4)	−7010 (4)
C14	4036 (3)	12078 (3)	4271 (3)	C14	4899 (5)	8478 (6)	−6784 (6)
C15	4282 (3)	12415 (3)	3525 (4)	C15	4977 (4)	8953 (5)	−6029 (6)
C16	4355 (3)	11943 (3)	2798 (3)	C16	4301 (4)	8804 (4)	−5497 (4)
C17	5339 (3)	10869 (2)	2037 (3)	C17	2097 (3)	8164 (3)	−5532 (3)
C18	5665 (3)	10580 (3)	2632 (3)	C18	1437 (3)	7556 (3)	−6010 (3)
C19	6528 (3)	10795 (3)	2699 (4)	C19	839 (4)	7724 (4)	−6402 (4)
C20	7052 (3)	11312 (4)	2179 (4)	C20	921 (5)	8542 (5)	−6303 (4)
C21	6743 (4)	11622 (3)	1590 (4)	C21	1547 (5)	9136 (4)	−5844 (5)
C22	5876 (4)	11386 (3)	1511 (3)	C22	2128 (4)	8953 (3)	−5453 (4)
N1	2731 (2)	8214 (2)	1012 (2)	N1	2315 (2)	6215 (2)	−3412 (2)
O1	245 (2)	5332 (2)	−1080 (2)	O1	2867 (2)	5625 (2)	97 (2)
O2	−1026 (2)	4951 (2)	−518 (2)	O2	4190 (3)	5740 (3)	221 (2)
O3	917 (2)	6597 (1)	10 (2)	O3	3106 (2)	6188 (2)	−1364 (2)
O4	2484 (2)	7141 (2)	12 (2)	O4	1804 (2)	6161 (2)	−2079 (2)
Ca1	17269 (5)	57730 (4)	−6647 (4)				

	dimer 2						
	molecule 1				molecule 2		
C1	5329 (2)	4181 (2)	5340 (2)	C1	1719 (3)	4078 (2)	6354 (2)
C2	5091 (2)	3687 (2)	6085 (3)	C2	1362 (3)	3801 (3)	5450 (2)
C3	3789 (2)	2724 (2)	6581 (2)	C3	1761 (2)	3586 (2)	4019 (2)
C4	2876 (2)	2427 (2)	6326 (2)	C4	2510 (2)	3564 (2)	3548 (2)
C5	1427 (3)	1532 (3)	6486 (3)	C5	3213 (3)	3484 (3)	2207 (3)
C6	973 (3)	653 (3)	6261 (4)	C6	2957 (3)	2701 (3)	1590 (3)
C7	1135 (3)	195 (3)	6952 (3)	C7	2253 (3)	2623 (3)	985 (2)
C8	2100 (3)	424 (3)	6983 (3)	C8	1518 (3)	2677 (3)	1513 (3)
C9	2529 (3)	1318 (3)	7236 (3)	C9	1787 (3)	3443 (3)	2162 (2)
C10	610 (3)	−682 (3)	6783 (3)	C10	1940 (3)	1816 (3)	384 (3)
C11	724 (3)	−1225 (3)	7392 (3)	C11	1283 (3)	1773 (3)	−263 (3)
C12	929 (3)	−986 (3)	8255 (3)	C12	1450 (3)	2341 (3)	−823 (3)
C13	977 (4)	−1529 (4)	8776 (4)	C13	848 (4)	2302 (4)	−1403 (3)
C14	798 (4)	−2320 (4)	8445 (4)	C14	62 (4)	1665 (5)	−1424 (4)
C15	587 (3)	−2576 (3)	7599 (5)	C15	−118 (3)	1098 (4)	−870 (4)
C16	550 (3)	−2030 (3)	7062 (4)	C16	499 (3)	1158 (3)	−276 (3)
C17	−307 (3)	−842 (3)	6740 (3)	C17	2635 (3)	1622 (3)	−83 (3)
C18	−692 (3)	−581 (3)	7436 (3)	C18	3318 (3)	2194 (3)	−416 (3)
C19	−1546 (3)	−750 (3)	7421 (4)	C19	3907 (4)	1977 (4)	−850 (4)
C20	−2013 (3)	−1180 (3)	6717 (4)	C20	3823 (4)	1192 (5)	−971 (4)
C21	−1667 (3)	−1458 (3)	6019 (4)	C21	3156 (5)	607 (5)	−645 (4)
C22	−818 (4)	−1274 (3)	6024 (3)	C22	2542 (4)	818 (3)	−198 (3)
N1	2323 (2)	1767 (2)	6639 (2)	N1	2488 (2)	3493 (2)	2697 (2)
O1	4749 (1)	4125 (1)	4854 (1)	O1	2485 (2)	4313 (2)	6471 (2)
O2	6095 (1)	4604 (1)	5268 (2)	O2	1182 (2)	4024 (2)	6920 (2)
O3	4200 (2)	3428 (2)	6174 (2)	O3	2027 (2)	3850 (2)	4886 (1)
O4	2662 (2)	2793 (2)	5828 (2)	O4	3132 (2)	3613 (2)	3951 (1)
Ca2	34472 (4)	41359 (4)	54140 (4)				
O1S	4372 (2)	5183 (2)	6494 (2)	O7S	2683 (3)	5470 (3)	3644 (3)
O2S	1604 (2)	4486 (2)	−1416 (2)	O8S	1624 (3)	6249 (3)	1937 (3)
O3S	4769 (2)	4782 (2)	8027 (2)	O9S	4563 (3)	6329 (3)	1857 (3)
O4S	2975 (3)	3973 (3)	8025 (2)	O10S	2871 (3)	5710 (4)	1910 (3)
O5S	98 (2)	5463 (3)	2786 (2)	O11S	953 (4)	5059 (5)	4018 (4)
O6S	4396 (3)	4224 (2)	532 (2)				

ponents, namely, the calcium ions, the diglycolamic acid moieties, and all the water molecules. In the uncomplexed McN-4308 structure, a strong intermolecular hydrogen bond is observed between the carboxyl group O1 and the carbonyl oxygen O4 of

the molecule at x, $-0.5 - y$, $2.5 + z$, with O1⋯O4 2.609 (3) Å, O1–H1 0.94 (3) Å, H1⋯O4 1.67 (3) Å, and O1–H1⋯O4 170 (2)°.

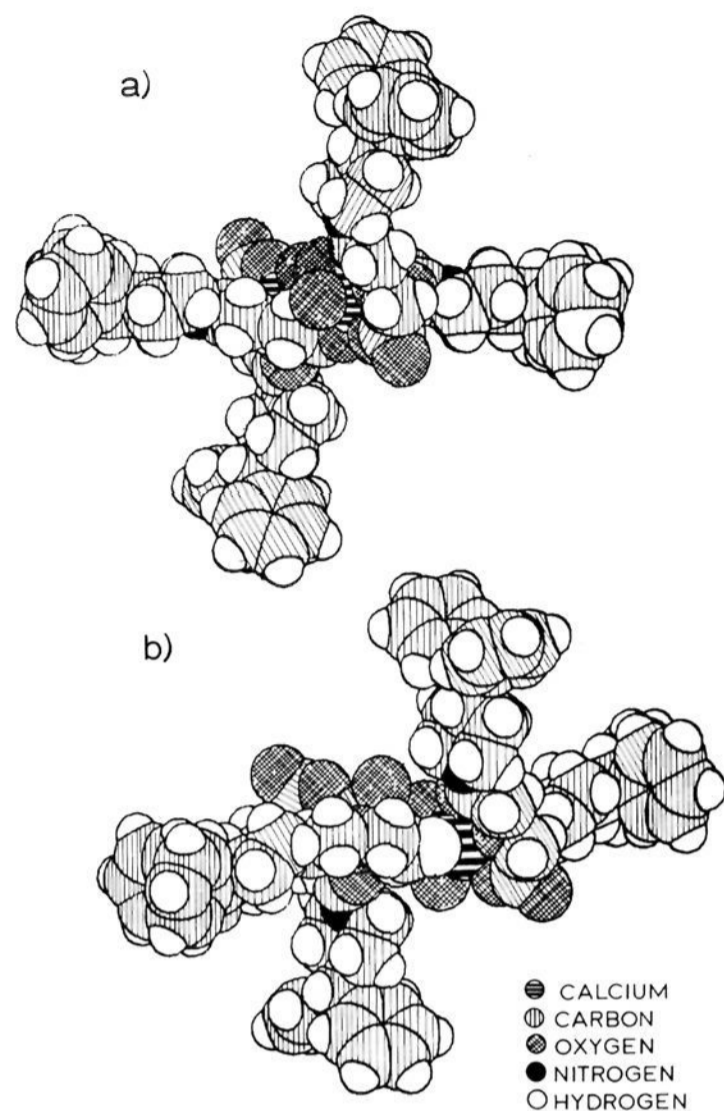The geometries of the free acid and the anions in the Ca²⁺ complex of McN-4308 are compared in Figure 5. The bond

Complexation of Calcium

J. Am. Chem. Soc., Vol. 104, No. 21, 1982 5665

Figure 4. Space-filling models of the calcium complex dimers of McN-4308 illustrating the similarity in the overall geometries.

Table III. Geometry at Calcium[a]

	dimer 1, Å	dimer 2, Å		dimer 1, deg	dimer 2, deg
O1–Ca	2.465	2.422	–O3	61.3	61.0
			–O4	119.2	106.1
			–O1'	152.3	157.6
			–O3'	138.1	138.6
			–O4'	77.0	75.7
			–O2	78.7	82.3
			–H₂O	85.3	83.4
O3–Ca	2.562	2.581	–O4	60.5	60.1
			–O1'	122.9	103.1
			–O3'	131.9	138.8
			–O4'	97.4	113.3
			–O2	76.4	134.9
			–H₂O	145.0	74.5
O4–Ca	2.410	2.425	–O1'	78.6	74.8
			–O3'	77.2	78.8
			–O4'	94.7	90.8
			–O2	103.0	164.2
			–H₂O	154.6	117.5
O1'–Ca	2.479	2.419	–O3'	63.2	63.9
			–O4'	125.7	126.7
			–O2	76.4	102.8
			–H₂O	82.0	76.9
O3'–Ca	2.486	2.469	–O4'	62.8	63.0
			–O2	138.8	86.2
			–H₂O	79.6	132.0
O4'–Ca	2.415	2.381	–O2	154.7	78.1
			–H₂O	83.7	148.8
O2–Ca	2.431	2.470	–H₂O	88.0	76.4
H₂O–Ca	2.408	2.452			

[a] Standard deviations range from 0.003 to 0.005 Å for the Ca–O bond length and from 0.2 to 0.3° for the O–Ca–O angles.

lengths and angles of the diglycolamic acid moieties are unexceptional. The torsion angles (listed in Table IV) show this moiety to be nearly planar in all four complexed ionophores, although the potential for considerable rotational freedom is present in the single bonds C1–C2, C2–O3, O3–C3, and C3–C4. The major
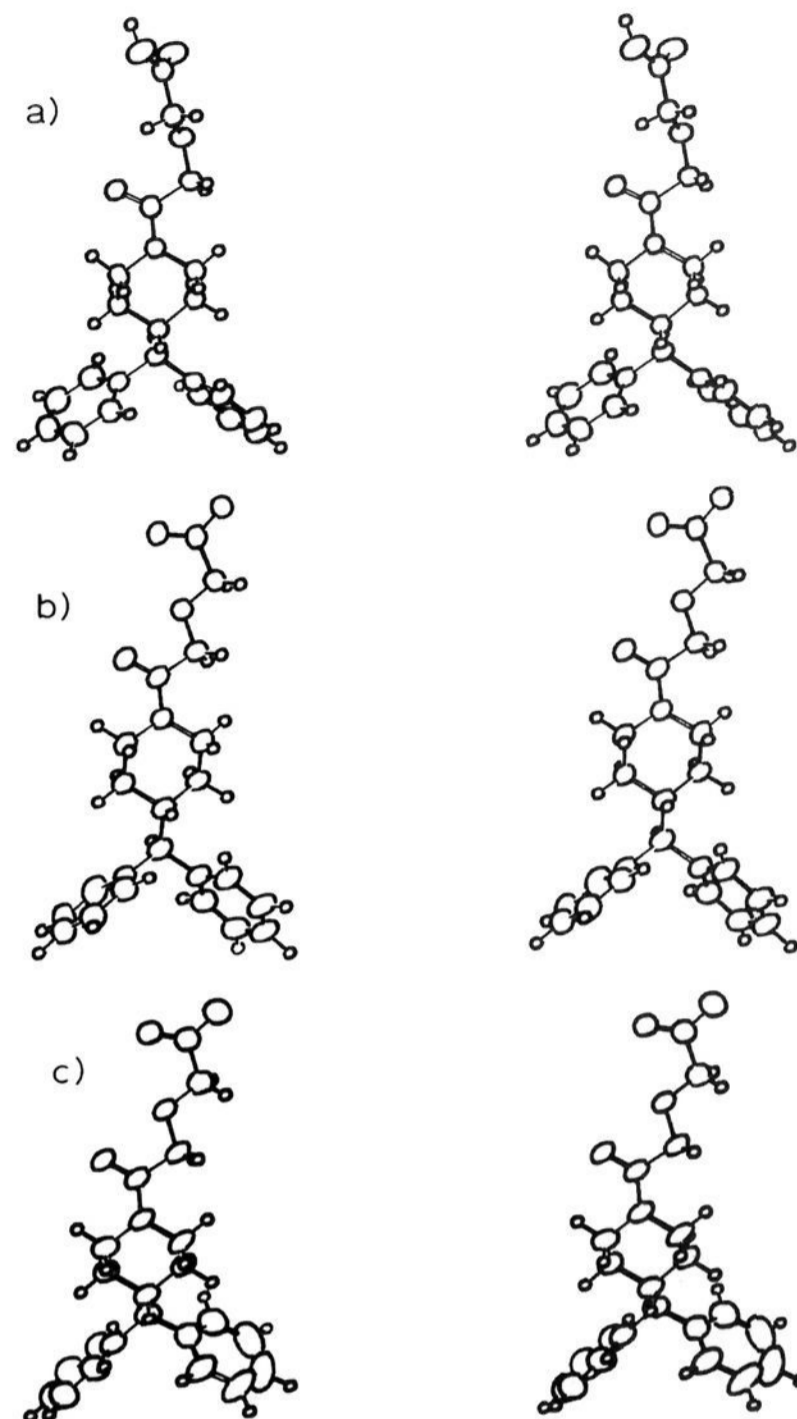

Figure 5. Stereo diagram comparing the geometries of the free acid McN-4308 (a) and the complexed ionophores (b) and (c), viewed perpendicular to the plane containing the atoms C4, N, and C5; (b) and (c) correspond to the nonbridging and the bridging ionophores in dimer 1 of the complex, respectively. The conformations of the ionophores in the second dimer resemble those of the related ones in the first dimer.

differences in the conformations of this part of the anions are the orientation of the bridging carboxylate groups with respect to the *plane of the rest of the diglycolamic acid moiety when compared* to the nonbridging carboxylate groups and the 13° deviation from planarity about the C3–C4 bond in the second molecule of the second dimer. The free acid form shows a torsion angle of almost 90° about the O3–C4 bond and 20° about the C1–C2 bond. This nonplanar conformation relieves short intramolecular contacts that are present in the planar conformation. Removal of the contact between the methylene groups C2 and C3 allows expansion of the O3–C3–C4 angle from an average value of 105.5° in the ionophore ions in the complex to 112° in the free acid.

Three different conformations are observed for the hydrophobic moieties of the ionophore. The position of the diphenylmethyl group relative to the piperidine ring for the nonbridging anions does not differ greatly from the free acid, but the position of this group is inverted in the bridging anions. Although maintaining a typical chair conformation, the piperidine rings appear more planar in the nonbridging than in the bridging anions.

Discussion

The interesting aspects of the structure of the calcium complex of the ionophore McN-4308 are the formation of dimers of the 4:2 ionophore–calcium complex through bridging carboxylate groups, the further inclusion of water molecules into the coor-

Table IV. Torsion Angles (Deg) of McN-4308[a]

	uncomplexed	dimer 1		dimer 2	
		molecule 1	molecule 2	molecule 1	molecule 2
O1-C1-C2-O3	160.6 (2)	−10.2 (5)	3.4 (7)	−15.1 (5)	1.9 (5)
O2-C1-C2-O3	−19.5 (4)	169.4 (3)	176.6 (5)	165.4 (3)	−176.6 (4)
C1-C2-O3-C3	−178.4 (2)	−173.2 (3)	−159.0 (4)	156.1 (3)	178.6 (3)
C2-O3-C3-C4	82.7 (3)	174.2 (3)	177.4 (4)	−161.1 (3)	−172.0 (3)
O3-C3-C4-O4	−6.4 (3)	−2.9 (5)	1.8 (5)	2.3 (5)	13.0 (5)
O3-C3-C4-N	173.6 (2)	175.4 (3)	−178.1 (4)	−178.4 (3)	−166.9 (3)
C3-C4-N-C5	177.5 (2)	175.9 (4)	−176.3 (4)	172.4 (4)	178.9 (4)
C3-C4-N-C9	0.0 (3)	13.6 (6)	−1.4 (7)	1.9 (6)	0.8 (6)
C4-N-C5-C6	124.6 (2)	145.6 (6)	114.0 (5)	137.4 (4)	122.2 (4)
N-C5-C6-C7	54.6 (3)	55.1 (5)	55.8 (5)	54.5 (6)	58.3 (5)
C9-N-C5-C6	−56.9 (3)	−50.5 (5)	−60.6 (5)	−51.2 (5)	−59.5 (5)
C5-C6-C7-C8	−53.2 (3)	−60.0 (5)	−53.0 (5)	−60.4 (5)	−55.5 (5)
C5-C6-C7-C10	−177.6 (2)	175.7 (4)	−175.3 (4)	173.8 (4)	−176.7 (4)
C6-C7-C10-C11	−180.0 (2)	179.2 (4)	177.0 (4)	177.5 (4)	−175.7 (4)
C6-C7-C10-C17	−52.4 (3)	−58.2 (5)	−56.9 (5)	−57.2 (5)	−50.0 (5)
C7-C10-C11-C12	24.4 (3)	33.8 (6)	62.7 (6)	32.9 (7)	58.6 (6)
C7-C10-C17-C18	−60.6 (3)	−57.0 (6)	−34.3 (6)	−58.8 (6)	−40.4 (7)
C11-C10-C17-C18	70.1 (3)	69.1 (5)	92.4 (6)	70.9 (6)	86.4 (6)
C17-C10-C11-C12	−104.1 (3)	−91.5 (5)	−65.7 (6)	−93.8 (6)	−69.8 (6)

[a] Molecule 1 and molecule 2 refer to the bridging and nonbridging ionophores in the dimers, respectively. Standard deviations are in Parentheses.

dination sphere of the calciums to achieve a coordination number of eight, and the almost planar conformation of the diglycolamic acid moieties of the ionophores.

In both the six- and seven-coordinate forms of the 1:2 calcium complex of A23187,[12,13] the ionophore is bound to the metal through a carboxylate oxygen atom, a nitrogen atom, and a carbonyl oxygen. The additional ligand in the seven-coordinate form is a water molecule. The coordinating atoms in both of these complexes of A23187 are not significantly different from those available in the McN-4308 ions. However, the coordinating groups and the hydrophobic moiety in McN-4308 are separated while they are closely integrated in A23187. Thus, with McN-4308–calcium complexes, the formation of dimer units rather than monomers may be primarily a result of the inability of a pair of ionophores to adequately span the space surrounding the cation.

The planar conformation of the diglycolamic acid moiety of the ionophore in the complex differs greatly from that in the free acid and is most likely of higher energy because of intramolecular contacts, mainly between the methylene groups C2 and C3. However, the spacing between the carboxylate, the ether, and the carbonyl oxygens in the ionophore in this stretched-out conformation may well be ideal for the occupation of three sites in the square-antiprism coordination of calcium. Since a pair of such groups is not sufficient to fill out the coordination sphere of calcium, additional ligands are required. This is achieved in this case by addition of a water molecule and formation of the dimer. This may also explain the selectivity of McN-4308 for calcium over magnesium. Since the latter cation is smaller and requires

shorter metal–ligand distances as well as a lower coordination number, the McN-4308 anion may well not provide an adequate ligand geometry.

The two dimers observed for the calcium complex of McN-4308 are stereoisomers but have very similar overall geometries. In either case, the hydrophobic diphenylmethyl groups appear stretched out as far as possible from the central part of the complex, which is easily accessible and surrounded by a large number of ordered, hydrogen-bonded, water molecules. Therefore, while the transporting species is proposed to be a 1:2, or 2:4, complex as is observed, rearrangement of the complex, probably involving removal of the water from the coordination sphere of the calcium ions, appears necessary for transport into a hydrophobic medium. The fact that two different environments of the calcium ions are observed in this structure suggests that such a rearrangement may be possible and that the observed complexes may well represent intermediate forms between the capture of the cation by the ionophore and the species capable of transporting the cation across the chloroform layer.

Supplementary Material Available: Tables of bond distances, bond angles, structure factors, thermal parameters, and hydrogen atom coordinates (119 pages). Ordering information is given on any current masthead page.

(12) Chaney, M. O.; Jones, N. D.; Debone, M. J. *J. Antibiot.* **1976**, *24*, 424-427.

(13) Smith, G. D.; Duax, W. L. *J. Am. Chem. Soc.* **1976**, *98*, 1578-1580.