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VO(IV) complexes of 3-hydroxypicolinic acid: a solution study and the structure of a supramolecular assembly in the solid state

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Abstract

The complex formation between oxovanadium(IV) and 3-hydroxypicolinic acid (3HPA) was studied in aqueous solution and in the solid state. The ligand displays ambidentate binding properties [Polyhedron 19 (2000) 55]: it forms picolinate-type (N, COO^-), salicylate-type (COO^-, O^-) and mixed-type complexes involving bidentate coordination of the ligand. It can also coordinate in a tridentate way, via the (N, COO^-, O^-) donor set, forming a tetrameric species. Two of complexes formed in equilibrium in solution were isolated in the solid state too: $VOH_2(3HPA)_2$ and $[VO(3HPA)]_4$. The latter was characterized crystallographically; the binding mode was found to be identical in solution and in the solid state. The binding properties of the ligand were compared with those of other substituted picolinic acid derivatives. A possible relationship between the insulin-mimetic activity and the structure of these complexes is discussed.

Keywords: VO(IV) complexes; Picolinic acid derivatives; Insulin-mimics; X-ray crystallography; Speciations

1. Introduction

The coordination chemistry of vanadium has been receiving increasing interest since it was found to be beneficial in various biological systems [1,2]. One of the results of the intensive investigations of vanadium over the past 20 years, has been the discovery that vanadium compounds in various oxidation states have insulin-mimetic properties [3]. Because of low toxicity of VO(IV) large number of its complexes have been isolated, characterized and tested for biological activity [4,5]. VO(IV) forms both five- and six-coordinated complexes (including the oxo group) in tetragonal pyramidal or tetragonal bipyramidal geometries both in solution and in the solid state [6]. On the coordination of two bidentate ligands, one coordination position remains free, which may be occupied by a solvent (S) molecule. When S is incorporated at the sixth coordination site, it may be either *cis* or *trans* to the oxo group (referred to as the *cis* or *trans* isomer). As the coordination geometry and/or the solvation/hydration conditions of the insulin-mimetic complexes may strongly influence their absorption and biotransport properties, not only the composition, thermodynamic stability and kinetic lability, but also the structure in solution has to be studied.

X-ray and detailed EPR studies has clarified that one of the most promising insulin mimics, bis(maltolato)oxovanadium(IV) (BMOV or $VO(malt)_2$) contains five-coordinated VO(IV) in the solid state with square pyramidal geometry (see Structure 1 in Scheme 1), in which the oxo group occupies the axial position and the two maltolato ligands are in the *trans* position [7]. In solution, however, solvation of the coordinatively unsaturated complex may take place [8,9]. In weakly coordinating solvents, such as CH_2Cl_2 or $CHCl_3$-toluene, the complex retains its five-coordinated tetragonal pyramidal structure [8], while in strongly coordinating solvents (S) like pyridine, EtOH or H_2O, a solvent molecule occupies the sixth coordination position [8,9]. EPR and NMR relaxation studies suggest that these six-

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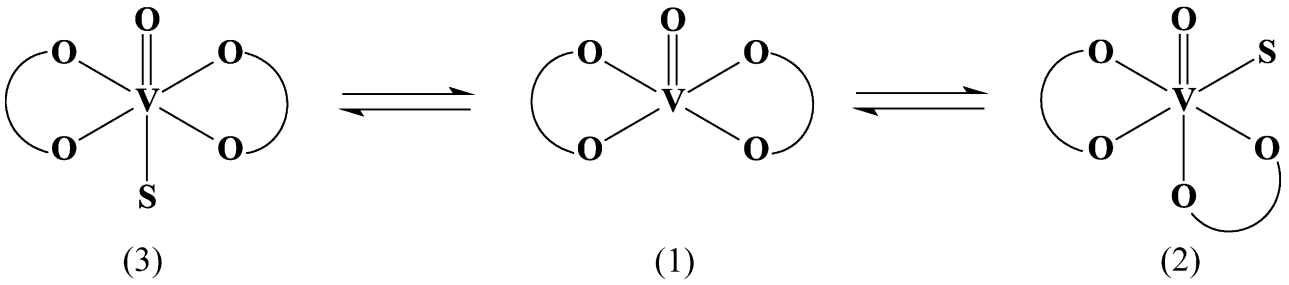

Scheme 1.

coordinated complexes exist in both *cis* (Structure 2) and *trans* form (Structure 3) in solution according to the position of the coordinated solvent molecule to the oxo group. The transformation from one isomer to the other probably takes place through a dissociative mechanism via the formation of the five-coordinated species (Scheme 1). Other promising VO(IV) carrier ligands are picolinic acid, and its ring-substituted derivatives, which have been studied in detail [10–13].

In the present work the results of a comparative study on the VO(IV) complexation of picolinic acid and various ring-substituted picolinic acid (3-Me-, 6-Me- and 3-OH) derivatives are reported, with special emphasis on the 3-OH-substituted ligand.

2. Experimental

2.1. Reagents

All ligands were Aldrich or Fluka products of puriss. quality and were used as received. Their purities were checked and the exact concentrations of the prepared stock solutions were determined by the Gran method [14]. A VO(IV) stock solution was prepared according to Nagypál and Fábián [15] and standardized for metal ion concentration by permanganate titration and for hydrogen ion concentration by pH-potentiometry, using the appropriate Gran function. The ionic strength was adjusted to 0.20 M KCl in each solution studied. In all cases, the temperature was 25.0 ± 0.1 °C.

2.1.1. $[VO(3HPA)_2]\cdot 4H_2O$

One hundred and thirty-six milligram (0.96 mmol) of 3-hydroxypicolinic acid dissolved in 10 ml of water was mixed with 2 ml of 0.195 M VO(IV)Cl_2 stock solution (0.39 mmol) and the pH was adjusted to pH ~6 with concentrated NaOH solution. The bluish-green solution was stirred for 60 min and left overnight at room temperature. The blue crystals obtained were filtered and washed with water and acetone and dried in vacuo. Yield: 81 mg, 50%. (Anal. Found C, 35.44, H, 3.89, N, 6.36, V, 12.40. Calc. for $C_{12}H_8N_2O_7V\cdot 4H_2O$: C, 34.71; H, 3.88; N, 6.75; V, 12.27%.)

2.1.2. $[VO(3HPA)]_4\cdot 7H_2O$

Sixty-eight milligram (0.48 mmol) of 3-hydroxypicolinic acid was dissolved in water (3 ml) and the solution was heated at 50–60 °C while argon was bubbled through it. Two milliliter of VO(IV)Cl_2 stock solution (0.39 mmol) was then added and the pH was adjusted to pH ~6 with concentrated NaOH solution. A green solution was formed with some green precipitate. The precipitate was filtered off and the dark-green solution was left overnight at room temperature. A brown solid had crystallized from the solution by next day. It was filtered off, washed with water and acetone and dried in vacuo. Yield: 54 mg, 55%. (Anal. Found C, 28.27; H, 3.81; N, 5.32; V, 20.85. Calc. for $C_{24}H_{20}N_4O_{20}V_4\cdot 7H_2O$: C, 28.39; H, 3.37; N, 5.52; V, 20.09%. Thermogravimetric analysis proved that from among the water molecules 4 were bound more strongly (coordinated waters) and that the residue of thermal decomposition was V_2O_5 (Anal. Calc. 37.8%, Found 37.1%).

2.2. Physical measurements

Elemental analysis (C, H, N) was carried out with a Perkin-Elmer 240 B elemental analyser. Thermogravimetric data were obtained with a Perkin–Elmer TGS-2 apparatus under a nitrogen flow. pH was measured with a Radiometer pHM 84 instrument equipped with a Metrohm combined electrode (type 6.0234.110), calibrated for hydrogen ion concentration according to Irving et al. [16]. Anisotropic X-band EPR spectra (9.15 GHz) were recorded at 140 K in aqueous solutions, using a Varian E-9 instrument. As usual, the samples for low-temperature measurements contained a few drops of DMSO to ensure good glass formation in the frozen solutions. Absorption spectra were recorded with a Hewlett–Packard HP 8453 spectrophotometer. All manipulations and titrations were performed under an atmosphere of purified argon.

2.3. Determination of X-ray structure of $[VO(3HPA)(H_2O)]_4\cdot 9H_2O$

Light brown needle crystals were obtained on slow evaporation of an aqueous solution of VO(IV) and

3HPA. A suitable single-crystal with dimensions of $0.4 \times 0.07 \times 0.03$ mm was mounted on a fibre glass with epoxy resin. During data collection, three standard reflections were monitored every reflections and revealed no decay. Lorentz polarization and psi-scan absorption corrections were applied. Formula $C_{24}H_{38}N_4O_{29}V_4$, $M = 1050.34$ (with nine water molecules in the crystal), triclinic, $a = 11.261(2)$ Å, $b = 11.871(2)$ Å, $c = 14.994(2)$ Å, $\alpha = 98.09(1)^\circ$, $\beta = 92.28(1)^\circ$, $\gamma = 93.99(1)^\circ$, $V = 1977{,}1(7)$ Å^3, $Z = 2$, space group: $P\bar{1}$, $\rho_{calc} = 1.764$ g cm^{-3}. X-ray diffraction data were collected at 293(1) K with an Enraf Nonius MACH3 diffractometer, Mo Kα radiation, $\lambda = 0.71073$ Å, ω–2θ method, $\theta_{max} = 25.01^\circ$. Five thousand eight hundred and eighty three reflections of which 3078 were unique with $I > 2\sigma(I)$. The structure was solved with SIR-92 software [17] and refined on F^2 values using the SHELX-97 program [18]. C–H hydrogen atoms were placed into geometric positions, while O–H hydrogen atoms were found in the electron difference map. The coordinates of these H atoms were refined while the O–H and H–H distances were constrained, which resulted in unusually small O–H distances in a few cases. The residual error in the refinement was $R(F) = 0.08$ and $wR(F^2) = 0.1949$ for 5883 reflections and 604 parameters; the residual peaks in the electron density map gave 0.507 and -0.666 e Å^{-3}. The published material was obtained with the WINGX-97 suite [19]; hydrogen bonds and other structural features were analysed by using the PLATON program [20].

3. Results and discussion

3.1. Chemical studies

When the ligands were applied in at least a twofold excess over the metal ion, neutral bis-complexes, could be isolated from solution, as described earlier [10,11] (see also Section 2). Precipitation of the solid compounds was promoted by the addition of a less polar solvent, such as ethanol. The complexes were characterized by spectroscopic (UV–VIS, IR, EPR) and magnetic measurements and the respective physico-chemical parameters [10–13] are listed in Table 1.

These parameters, together with the elemental analysis data suggest the formation of VO(VI) complexes in which the metal ion–ligand stoichiometry is 1:2; in the case of the title ligand its composition is $VO(3HPA)_2H_2$. According to earlier reports, the solid complexes are five-coordinated and have a *trans* arrangement [21,22]. However, when the complexes are dissolved in water (in the case of 3HPA in the presence of an excess of ligand, see below), the EPR spectra clearly indicate the occurrence of the *cis* isomer. In accordance with expectation, in water, in a strongly coordinating solvent, a water molecule saturates the coordination sphere of the metal ion and in parallel a rearrangement to the *cis* form takes place. The *cis* isomer is found to be the predominant isomer under such conditions. Interestingly, this rearrangement is less extensive with 6-Me-picolinic acid, where the presence of the methyl group in position 6 seems to hinder the axial–equatorial coordination of the second carrier ligand molecule. It probably has somewhat larger spatial requirements, than those of the other carriers, because of the presence of the CH_3 group. At the same time, the methyl groups in the 3-Me- and 6-Me derivatives increase the hydrophobicity of their VO(IV) complexes, which is reflected in the higher partition coefficients (between *n*-octanol and water) (see last column in Table 1).

It was interesting that, when the neutral bis complex of 3HPA was dissolved in water, the EPR spectrum was not simple, relating to magnetically dilute mononuclear VO(IV) complexes, but also indicated the presence of other complexes, with a fairly strong interaction between the paramagnetic metal ion centres. This was in accordance with our earlier solution speciation studies of this system [12], when we found that a tetranuclear species $(VOA)_4$ is formed in parallel with the mononuclear bis complexes. The speciation curves calculated with the stability constants reported in Ref. [12] are depicted in Fig. 1.

The tetranuclear complex was assumed to have a cyclic arrangement, which can be formed without any strain provided that one of the carboxylate oxygens coordinates to vanadium in the apical position and there is a water molecule in the equatorial plane of the metal ion (see Fig. 2 in this paper and Scheme 2 in Ref. [12]), i.e. each metal centre would have a *cis* arrangement. The

Table 1
Spectroscopic (UV–VIS, IR, EPR) and magnetic properties and other physical–chemical parameters of various insulin-mimetic VO(IV) complexes

Complex	EPR parameters, g, A (10^{-4} cm^{-1})						VIS parameters, λ (nm), ε (M^{-1} cm^{-1})				IR (cm^{-1})	*n*-Octanol–water
	go	$g_\parallel$	$g_\perp$	A_o	$A_\parallel$	$A_\perp$	λ	ε	λ	ε	ν(V=O)	
$VO(PA)_2$	1.980	1.945	1.998	93	168	54	731	32	576	14	980	0.33
$VO(3MPA)_2$	1.975	1.947	1.989	92	168	55	743	34	540	12	968	no data
$VO(6MPA)_2$	1.981	1.941	2.002	92	164	53	749	49	620	25	948	0.60
$VO(3HPA)_2$	1.975	1.944	1.991	95	173	57	764	30	553	10	959	no data

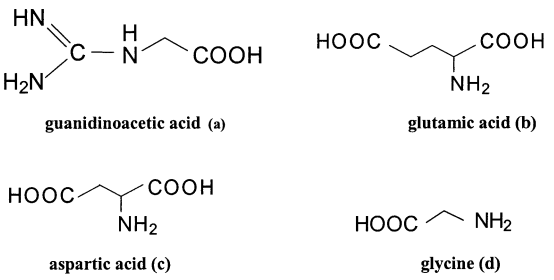

Fig. 1. Speciation curves for the complexes formed in the VO(IV)–3HPA system at 1:2 metal ion to ligand ratio, $c_{VO(IV)} = 0.001$ mol dm^{-3}.

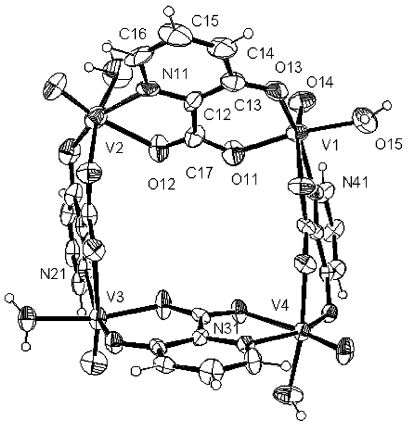

Fig. 2. ORTEP view of the tetranuclear $[VO(3HPA)(H_2O)]_4 \cdot 9H_2O$ complex drawn at 35% probability level with partial numbering scheme. Solvent water molecules were omitted for clarity.

EPR spectrum of this species, obtained in equimolar solution, shows a broad, featureless band at $g \sim 2$, superimposed by signals of the 'normal' bis complexes formed in low concentration (see figure 4 in Ref. [12]). We made several attempts to isolate this unusual tetrameric species from solution. Finally, our efforts to obtain a single-crystal suitable for X-ray determination succeeded when a solid precipitated from an equimolar solution of VO(IV) and the ligand during slow evaporation.

3.2. Crystallographic determination

The ORTEP view of the tetranuclear $[VO(3HPA)(H_2O)]_4 \cdot 9H_2O$ complex, drawn at a 35% probability level with the partial numbering scheme, is given in Fig. 2. Solvent water molecules were omitted for clarity. The structure of the complex closely resembles those of VO(V) complexes of other picolinic acid derivatives, e.g. potassium oxodiperoxo(pyridine-2-carboxylato)vanadate(V), $K_2[VO(O_2)_2(PA)] \cdot 2H_2O$; potassium oxodiperoxo(3-hydroxypyridine-2-carboxylato)-vanadate(V), $K_2[VO(O_2)_2(3HPA)] \cdot 3H_2O$ [23] and $K_3[VO(O_2)_2(2,4\text{-pyridinedicarboxylato})] \cdot 2H_2O$, bpV-(2,4-pdc); and K_3 $[VO(O_2)_2(3\text{-acetatoxypicolinato})] \cdot 2H_2O$, bpV(3-acetpic) [24,25]. Table 2 gives a comparison of selected bond distances and angles for these compounds. In our case, range of values are shown without standard deviations as there is the whole tetranuclear $[VO(3HPA)(H_2O)]_4 \cdot 9H_2O$ complex in the asymmetric unit. Coordination of water (O_{water}), phenolic (O_{phen}), and the two different carboxylate (O_{carb1}, 'trans' to the coordinating water, and O_{carb2}, 'trans' to the vanadyl oxygen) oxygen atoms to vanadium atoms are shown in respect of bond angles and distances. However, a surprising feature of the new structure is the highly symmetric cyclic assembly of the complex. Four vanadium atoms are almost perfectly in one plane with RMS deviation of 0.1835 Å, angles of facing planes of ligands with the same orientation, i.e. mean planes of N11–C12–C13–C14 and N31–C32–C33–C34, N21–C22–C23–C24 and N41–C42–C43–C44, being 51.8° and 28.7°, respectively while planes of two ligands coordinating to the same vanadium atom (COO^-, O^- and N, COO^- coordination) are close to perpendicular to each other (89° and 78° at V1, V3 and V2, V4, respectively). The diameter of the cavity in the structure is approximately 4.5 Å. Solvent water molecules form an extensive H-bond network in the structure shown in Fig. 3. Table 3 lists the distance and angle data of these H-bonds.

Interestingly, the basic arrangement of the ligand molecules in the solid state proved to be identical with that assumed to be formed in aqueous solution and also proposed on the basis of molecular modeling and the EPR parameters (see above). The ligands behave as bridging units between the VO(IV) centres, the carboxylate being the bridging donor group, and the configuration is always *cis*, with one water molecule in the equatorial plane of each VO(IV). Several extra water molecules are also present in the lattice, in hydrogen-bonding with the equatorially coordinated water molecules. This is in agreement with the analytical results, which indicated the presence of several molecules of crystal water. Elemental analysis indicated 7 water molecules in the amorf complex prepared, while X-ray analysis suggested 9 in the single crystal in a strong hydrogen-bonding network (vide supra).

This is an interesting example, where the complex has the same donor atom arrangements in the solid state and in solution: the (eq–eq, eq–ax) *cis* arrangement of the ligands is a steric requirement and a water molecule can occupy a strong equatorial site in the VO(IV) coordination sphere, several extra solvent molecules being included through hydrogen-bonding. At lower pH, when the phenolic-OH groups are still in non-coordinating protonated form, although the group arrangement is mostly *cis* in solution, the solid neutral complex which precipitates out $(VO(3HPA)_2H)_2)$ contains the four coordinating donors $2 \times (N, COO^-)$ in a *trans* arrangement. Our attempts to isolate this complex in a

Table 2
Selected bond lengths (Å) and angles (°) or their range of VO(V) and VO(IV) complexes of picolinic acid derivatives

	$K_2[VO(O_2)_2(PA)]\cdot 2H_2O$	$K_2[VO(O_2)_2(3HPA)]\cdot 3H_2O$	bpV(2,4-pdc)	bpV(3-acetpic)	$[VO(3HPA)(H_2O)]_4\cdot 9H_2O$
Bond lengths					
V–N	2.123(5)	2.137(2)	2.144(11)	2.179(4)	2.124–2.152
V=O	1.599(4)	1.606(2)	1.622(9)	1.621(3)	1.584–1.608
$V-O_{carb1}$	2.290(4)	2.314(2)	2.299(8)	2.190(6)	1.963–1.986
$V-O_{carb2}$					2.119–2.154
$V-O_{water}$					2.034–2.073
$V-O_{phen}$					1.935–1.986
Bond angles					
O=V–N	93.6(2)	94.92(7)	93.1(4)	93.39(16)	91.9–95.9
$O=V-O_{carb}$	166.7(2)	168.73(7)	166.3(4)	166.04(15)	158.2–160.7
$O=V-O_{carb}$					96.7–98.4
$N-V-O_{carb2}$	73.1(2)	73.(6)	73.7(6)	72.7(4)	73.3–74.4
$N-V-O_{carb1}$					85.0–90.1
Reference	[23]	[23]	[24]	[24]	this work

solid form suitable for X-ray determination were unsuccessful.

3.3. Biological studies

The insulin-mimetic activity, pharmacokinetic features and organ distribution of bis complexes of the picolinic acid derivatives were studied in detail by Sakurai et al. [13]. They found a close relationship between the in vitro insulin-mimetic activity, the in vivo antidiabetic action and the disposition in the blood. CL_{tot} was considered as the most important metallokinetic parameter, determining the blood concentration–time profiles of the vanadium(IV) complexes. The most noteworthy finding was the significant positive correlation between CL_{tot} (total body clearance) and IC_{50} (50% inhibitory concentration of the complex on fatty acid release) for the VO(IV) picolinato complexes with $VO(N_2O_2)$ coordination mode. On the basis of these results, it was concluded that the in vitro insulin-mimetic activity, the metallokinetic character and the in vivo antidiabetic action of the VO(IV)–picolinato complexes are closely related to their chemical structures.

On the other hand, our earlier speciation studies [9,12,26,27] strongly suggested that on dissolution in water the above complexes undergo considerable transformations and there are important differences between the solid-state structures of these complexes and their solution states under physiological conditions (biospeciation). 3HPA is a noteworthy example of how significantly the structure of a solid compound, $[VO(3HPA)_2H_2]$, may change simply when it is dissolved in water. Interestingly, the tetranuclear complex $[VO(3HPA)]_4$ is neutral, in contrast with the mononuclear bis complex, which exists as a 1- complex $[VO(3HPA)_2H]$, at neutral pH (Fig. 1). This change in

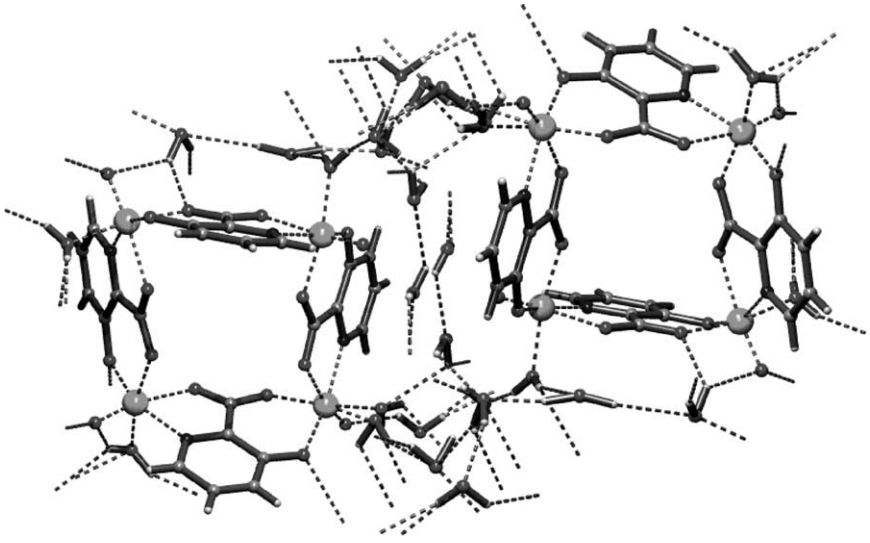

Fig. 3. H-bond scheme of $[VO(3HPA)(H_2O)]_4\cdot 9H_2O$ showing the layered structure, H-bonded water molecules and direction of ligand planes.

Table 3
Hydrogen bonds in $[VO(3HPA)(H_2O)]_4 \cdot 9H_2O$

Nr	Donor–H···acceptor	ARU	D–H	H···A	D···A	D–H···A
1	O(1W)–H(2W)–O(8W)	2566.09	0.88(6)	2.35(6)	2.920(19)	123(6)
2	O(2W)–H(3W)–O(7W)		0.98(7)	2.20(7)	3.16(3)	164(8)
3	O(2W)–H(4W)–O(5W)		0.94(6)	2.12(7)	2.994(14)	155(6)
4	O(3W)–H(5W)–O(4W)		0.78(8)	2.38(7)	2.92(2)	128(7)
5	O(3W)–H(6W)–O(45)	1545.01	0.83(6)	2.05(7)	2.60(2)	124(7)
6	O(4W)–H(7W)–O(25)		0.88(6)	2.43(8)	2.902(18)	114(7)
7	O(4W)–H(7W)–O(34)	1545.01	0.88(6)	2.27(8)	2.786(13)	113(6)
8	O(4W)–H(8W)–O(1W)		0.97(6)	2.29(6)	2.840(18)	115(5)
9	O(5W)–H(9W)–O(35)	1645.01	0.85(7)	2.05(6)	2.854(11)	159(8)
10	O(5W)–H(10W)–O(24)	1655.01	0.89(7)	2.43(7)	3.098(12)	133(6)
11	O(6W)–H(11W)–O(33)	1546.01	0.93(7)	1.98(6)	2.876(8)	163(6)
12	O(6W)–H(12W)–O(41)	2666.01	0.91(7)	2.16(7)	2.899(8)	138(6)
13	O(6W)–H(12W)–O(44)	2666.01	0.91(7)	2.56(7)	3.244(10)	132(6)
14	O(7W)–H(14W)–O(44)	1545.01	0.93(6)	2.22(6)	2.92(2)	131(6)
15	O(15)–H(15A)–O(1W)	2666.02	0.79(12)	1.91(12)	2.595(16)	146(11)
16	O(15)–H(15B)–O(9W)		0.78(11)	2.53(10)	3.274(13)	160(10)
17	O(15)–H(15B)–O(23)	1655.01	0.78(11)	2.55(11)	2.872(11)	106(9)
18	O(8W)–H(15W)–O(1W)	2566.02	0.94(8)	2.34(8)	2.920(19)	120(7)
19	O(8W)–H(16W)–O(1W)	2566.02	0.96(5)	2.59(7)	2.920(19)	100(4)
21	O(8W)–H(16W)–O(7W)	2666.08	0.96(5)	2.25(6)	3.15(3)	157(7)
22	O(9W)–H(17W)–O(2W)		1.00(6)	1.77(6)	2.762(15)	167(8)
23	O(9W)–H(18W)–O(6W)	2666.07	1.02(7)	2.55(6)	3.437(14)	145(6)
24	O(25)–H(25B)–O(7W)	1455.08	1.06(14)	1.91(16)	2.48(2)	109(12)
25	O(35)–H(35A)–O(5W)	1465.06	0.69(11)	2.31(12)	2.854(11)	136(13)
26	O(35)–H(35B)–O(6W)	2566.07	0.96(10)	1.77(10)	2.664(11)	153(9)
27	O(45)–H(45A)–O(2W)	1565.03	0.82(11)	1.86(11)	2.625(14)	154(11)
28	O(45)–H(45B)–O(3W)	1565.04	0.58(14)	2.03(15)	2.60(2)	173(18)

Translation of ARU-code to equivalent position code: [1465] = $-1+x, 1+y, z$; [1565] = $x, 1+y, z$; [2666] = $1-x, 1-y, 1-z$; [1655] = $1+x, y, z$; [1455] = $-1+x, y, z$; [2566] = $-x, 1-y, 1-z$; [1545] = $x, -1+y, z$; [1645] = $1+x, -1+y, z$; [1546] = $x, -1+y, 1+z$.

the charge conditions will significantly affect its membrane transport ability and hence its absorption properties.

4. Conclusions

All these results suggest that the solution structures and solution speciation of these insulin-mimetic complexes have more important effects on their physiological activity than do their solid-state structures, as little part of the complexes remains intact on dissolution, their entry into the organism, and their transport to the cells.

5. Supplementary data

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 181333. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1 EZ (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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