Interligand Hydrogen Bonding in Metal–Purine Complexes: The Crystal Structure of *cis*-[Theophyllinatochlorobis(ethylenediamine)cobalt(III)] Perchlorate*

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cis-[Theophyllinatochlorobis(ethylenediamine)cobalt(III)]perchlorate,$[Co(C_2N_2H_8)_2Cl(C_7N_4O_2H_7)]ClO_4$, crystallizes in the monoclinic system, space group $P2_1/n$, with $a = 14.878$ (9), $b = 9.108$ (4), $c = 14.286$ (7) Å, $\beta = 93.91$ (5)°, $V = 1934.8$ Å^3, $Z = 4$, $D_m = 1.68$ (2), $D_c = 1.69$ g cm^{-3}. Intensities for 2381 independent reflections with $I > \sigma(I)$ were used in the structural solution and refinement. The final R value, weighted R value and goodness-of-fit are 0.111, 0.084 and 1.8, respectively. The coordination sphere about the cobalt is approximately octahedral with the two bidentate ethylenediamine ligands in *cis* positions. The chloride ligand and N(7) of the theophylline group complete the coordination sphere. The complex exhibits interligand hydrogen bonding between the ethylenediamine ligands and the carbonyl group, C(6)–O(6), on theophylline. The perchlorate anion is ion-paired with the complex cation in the solid.

Introduction

We have undertaken this structural analysis for the following reasons: (1) we wished to examine the strength of the interligand hydrogen bonds in the *cis*-versus the *trans*-isomer (Marzilli, Kistenmacher & Chang, 1973; Kistenmacher, 1975); (2) we wanted to see if the different steric requirements for interligand hydrogen bonding in the two isomers caused any significant changes in the expected molecular conformation or dimensions; (3) because the *cis*-isomer is a better representation of the polyamine ligand arrangement in the triethylenetetramine complexes we have used in solution binding selectivity experiments (Marzilli, Kistenmacher, Darcy, Szalda & Beer, 1974).

Experimental

We were able to separate *cis*-[Co(C$_2$N$_2$H$_8$)$_2$Cl(C$_7$N$_4$O$_2$H$_7$)]Cl from the same reaction mixture that yielded the *trans*-isomer (Marzilli & Chang, 1973, private communication; Kistenmacher, 1975). Suitable crystals of the chloride salt could not be grown. We obtained single crystals from aqueous solution with the perchlorate anion as the counter ion. Preliminary photographs indicated a monoclinic lattice. Unit-cell dimensions were derived from the 2θ, ω and χ values for 14 reflections. Complete crystal data are given in Table 1.

Intensity data were collected on a Syntex $P\bar{1}$ computer-controlled diffractometer equipped with an incident-beam, graphite-monochromator crystal. The crystal used in data collection was a monoclinic prism, [101] as the prism axis, with dimensions: $0.10 \times 0.10 \times$

Table 1. *Crystal data*

$$cis\text{-}[Co(C_2N_2H_8)_2Cl(C_7N_4O_2H_7)]^+\,Cl_4^-$$

$a = 14.878$ (9) Å	Space group $P2_1/n$
$b = 9.108$ (4)	$Z = 4$
$c = 14.286$ (7)	$D_m = 1.68$ (2) g cm^{-3}
$\beta = 93.91$ (5)°	$D_c = 1.69$
$V = 1934.8$ Å^3	$\mu = 12.4$ cm^{-1}
M.W. 493.2	λ(Mo $K\alpha$) = 0.71069 Å

0.25 mm. Intensity data were collected with Mo $K\alpha$ radiation by the θ–2θ scan technique; individual scan speeds were determined by a rapid scan at the calculated Bragg peak, and the rate of scanning varied from 2 to 24° min^{-1}. Three standards were measured after every 100 reflections, and their intensities showed no unusual fluctuations or decay with time. A total of 3394 independent reflections in the hkl and $hk\bar{l}$ octants were surveyed and assigned observational standard deviations based on the equation: $\sigma^2(I) = S + (B_1 + B_2)\,(T_S/2T_B)^2 + (pI)^2$, where S, B_1 and B_2 are the scan and background counts, T_S and T_B are the scan and individual background counting times ($T_B = \frac{1}{4}T_S$ for all reflections) and p was taken to be 0.03 and represents the expected error proportional to the diffracted beam intensity (Busing & Levy, 1957). Because of a large number of very weak reflections, only the 2381 reflections with $I > \sigma(I)$ were used in the structural solution and refinement. These intensities and their standard deviations were corrected for Lorentz and polarization effects, but no correction for absorption was applied ($\mu = 12.4$ cm^{-1}). The structure factor amplitudes were placed on an approximately absolute scale by the method of Wilson (1942).

Solution and refinement of the structure

The positions of the cobalt atoms and the six atoms of its primary coordination sphere were derived from a three-dimensional Patterson synthesis. A structure

factor Fourier calculation $(R = \sum ||F_o| - |F_c||/\sum |F_o| = 0\cdot40)$ allowed the positioning of 17 of the remaining heavy atoms; the oxygen atoms on the perchlorate group were difficult to locate accurately. A second structure factor Fourier map $(R = 0\cdot29)$ permitted acceptable positioning of the oxygen atoms of the perchlorate group. Six cycles of isotropic least-squares refinement, minimizing $\sum w(|F_o| - |F_c|)^2$ with $w = 1/\sigma^2(F_o)$, reduced the R value to $0\cdot14$; by this stage the isotropic temperature parameters of the four perchlorate oxygens had reached values ranging from 16–22 Å^2, giving further indication of the very high thermal motion (disorder) of the anion. The high thermal parameter on the chlorine atom of this group, $B = 9$ Å^2, suggests that the disorder has translational as well as rotational components. A difference Fourier map was computed and showed large anisotropy, particularly along the y axis, associated with the perchlorate group. Several attempts were made to postulate disorder models that might account for the residual density. These attempts were unsuccessful, and it was decided to let the perchlorate group refine in the normal way acknowledging the fact that the resultant anisotropic thermal parameters would be without physical significance. The difference map was, however, of sufficient quality to allow the positioning of the 23 hydrogen atoms in the asymmetric unit. The hydrogen atoms were assigned the isotropic temperature factor of the atom to which they were attached, except for the methyl hydrogens for which B was set equal to $7\cdot0$ Å^2. No attempt has been made to refine any of the hydrogen atom positional or thermal parameters.

After the addition of the hydrogen atoms, four further cycles of least-squares were calculated with all the heavy atoms allowed to refine anisotropically. In the last cycle of refinement no shift/error exceeded $0\cdot6$. The final values for R, the weighted R $\{[\sum w(F_o - F_c)^2/\sum wF_o^2]^{1/2}\}$, and the goodness-of-fit $\{[\sum w(F_o - F_c)^2/(n - p)]^{1/2}\}$, where $n = 2381$ and $p = 253$ parameters, were $0\cdot111$, $0\cdot084$ and $1\cdot8$, respectively. The scattering factors for all of the heavy atoms were taken from the compilation of Hanson, Herman, Lea & Skillman (1964). The scattering curve for H was that of Stewart, Davidson & Simpson (1965). The real parts of the scattering factors for Co and Cl were corrected for anomalous dispersion effects (Cromer, 1965). Final atomic parameters for the heavy atoms are collected in Table 2, while those for the hydrogen atoms are given in Table 3.*

For the structure factor and Fourier calculations, the X-RAY 67 series of programs (Stewart, 1967) was used; the least-squares refinements were performed using an extensively modified version of ORFLS (Busing, Martin & Levy, 1962); the best plane calculations were by the program of Pippy & Ahmed (1968); the illustrations were prepared with the aid of ORTEP (Johnson, 1965). All remaining calculations were done with locally written programs.

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* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30606 (18 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 2. *Final heavy-atom parameters and their estimated standard deviations* ($\times 10^4$)

The form of the anisotropic ellipsoid is $\exp[-(B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + 2B_{12}hk + 2B_{13}hl + 2B_{23}kl)]$.

	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Co	392 (1)	1612 (2)	165 (1)	38 (1)	72 (2)	24 (1)	−0 (1)	9 (1)	0 (1)
Cl(1)	−911 (2)	861 (4)	955 (2)	61 (2)	142 (5)	40 (2)	−12 (2)	1 (1)	−8 (2)
Cl(2)	1893 (5)	1270 (6)	4849 (3)	171 (5)	229 (10)	61 (3)	51 (6)	−42 (3)	−7 (4)
O(2)	3528 (5)	2507 (8)	−1777 (5)	48 (4)	149 (12)	40 (14)	10 (6)	29 (3)	12 (6)
O(6)	2670 (5)	1167 (9)	1093 (5)	55 (4)	189 (15)	36 (4)	42 (6)	17 (3)	38 (6)
O(10)	2736 (20)	1618 (44)	4453 (21)	275 (28)	1265 (133)	276 (31)	−58 (57)	65 (24)	−120 (51)
O(11)	1707 (15)	123 (20)	4329 (12)	295 (23)	406 (39)	144 (14)	0 (24)	−102 (14)	−57 (20)
O(12)	2105 (16)	1105 (18)	5681 (10)	454 (31)	420 (38)	78 (10)	145 (26)	−90 (15)	−3 (16)
O(13)	1377 (16)	2334 (19)	4599 (11)	367 (26)	418 (38)	143 (13)	279 (27)	13 (14)	82 (18)
N(1)	3059 (5)	1826 (10)	−364 (5)	36 (5)	104 (14)	39 (5)	5 (7)	15 (4)	12 (7)
N(3)	2103 (5)	3076 (9)	−1463 (5)	44 (5)	103 (14)	30 (5)	−10 (7)	14 (4)	5 (6)
N(7)	783 (5)	2470 (9)	469 (5)	28 (4)	107 (13)	26 (4)	−10 (6)	12 (3)	−2 (6)
N(9)	602 (6)	3549 (10)	−960 (5)	49 (5)	88 (13)	35 (5)	−4 (7)	12 (4)	4 (7)
N(10)	24 (5)	643 (10)	2796 (6)	38 (5)	138 (16)	42 (5)	−17 (7)	17 (4)	6 (7)
N(11)	945 (6)	−288 (9)	1381 (6)	60 (6)	95 (13)	35 (5)	4 (7)	9 (4)	−2 (7)
N(12)	−149 (5)	3462 (10)	1995 (5)	49 (5)	106 (13)	38 (4)	−7 (7)	14 (4)	15 (7)
N(13)	1470 (6)	2362 (10)	2329 (5)	57 (6)	122 (14)	23 (5)	24 (7)	8 (4)	−8 (6)
C(1)	3940 (7)	1209 (15)	−158 (7)	42 (7)	262 (29)	50 (7)	20 (11)	24 (5)	47 (11)
C(2)	2919 (7)	2495 (12)	−1238 (7)	48 (7)	87 (16)	43 (6)	4 (9)	24 (5)	−2 (8)
C(3)	1944 (7)	3872 (13)	−2381 (7)	54 (7)	200 (23)	29 (6)	34 (10)	7 (5)	26 (9)
C(4)	1443 (7)	3043 (10)	−826 (7)	37 (6)	69 (16)	40 (6)	−3 (7)	6 (5)	1 (7)
C(5)	1575 (6)	2371 (11)	41 (6)	34 (6)	76 (14)	24 (5)	−14 (7)	11 (4)	8 (7)
C(6)	2425 (7)	1753 (12)	332 (6)	46 (6)	80 (15)	32 (6)	17 (8)	7 (4)	−1 (8)
C(8)	223 (6)	3157 (11)	−157 (6)	31 (5)	106 (17)	29 (5)	−5 (8)	10 (4)	6 (8)
C(10)	126 (8)	−985 (12)	2684 (8)	70 (8)	74 (16)	48 (7)	−14 (9)	3 (6)	14 (8)
C(11)	956 (8)	−1246 (11)	2229 (7)	75 (8)	75 (17)	44 (7)	−3 (9)	9 (6)	19 (8)
C(12)	458 (8)	4264 (13)	2674 (7)	60 (8)	118 (18)	37 (6)	−10 (10)	9 (6)	−8 (8)
C(13)	1385 (8)	3985 (13)	2402 (8)	57 (7)	131 (18)	40 (6)	−33 (9)	−0 (5)	−20 (9)

Table 3. *Coordinates* ($\times 10^3$) *and isotropic*
temperature parameters of the hydrogen atoms

	x	y	z	B*
H(1) [N(10)]	−54	85	288	3·5
H(2) [N(10)]	36	94	328	3·5
H(3) [C(10)]	−37	−136	231	3·8
H(4) [C(10)]	16	−144	328	3·8
H(5) [C(11)]	99	−225	205	3·9
H(6) [C(11)]	146	−102	264	3·9
H(7) [N(11)]	63	−71	92	3·9
H(8) [N(11)]	149	−15	123	3·9
H(9) [N(12)]	−66	329	224	3·2
H(10) [N(12)]	−25	400	149	3·2
H(11) [C(12)]	39	392	329	3·7
H(12) [C(12)]	33	529	264	3·7
H(13) [C(13)]	181	436	287	3·8
H(14) [C(13)]	148	443	182	3·8
H(15) [N(13)]	153	198	289	3·0
H(16) [N(13)]	194	215	203	3·0
H(17) [C(8)]	−39	336	−5	3·1
H(18) [C(3)]	135	453	−247	7·0
H(19) [C(3)]	270	342	−268	7·0
H(20) [C(3)]	125	317	−271	7·0
H(21) [C(1)]	394	41	30	7·0
H(22) [C(1)]	423	181	23	7·0
H(23) [C(1)]	441	139	−69	7·0

* The hydrogen atoms have been assigned the isotropic
temperature factor of the atom to which they are attached,
except for the methyl hydrogens where B was set equal to
7·0 $Å^2$.

Discussion

(a) *Molecular conformation and the interligand hydrogen bonds*

The molecular conformation of the *cis*-[theophyllin-atochlorobis(ethylenediamine)cobalt(III)]$^+$ cation is illustrated in Fig. 1. The crystal contains a racemic mixture of $\Delta\lambda\lambda$† and $\Delta\delta\delta$ complex cations due to the centrosymmetric space group. The overall molecular geometry is quite similar to that observed in the *cis*-[adeninatochlorobis(ethylenediamine)cobalt(III)]$^+$ cation (Kistenmacher, Marzilli & Chang, 1973; Kistenmacher, 1974). The interligand hydrogen-bond system in the *cis*-adenine complex [N(11)–H···N(3)···H–N(13)] has been supplanted here by the N(11)–H···O(6)···H–N(13) interligand bonds. The two O(6)···H distances, Fig. 1, at 1·99 and 2·14 Å are within the acceptable range for N–H···O hydrogen bonds (< 2·2–2·4 Å). Also, the interligand hydrogen-bond distances are nearly equivalent to the N–H···O distances from O(2) of a symmetry-related complex to hydrogens on N(10) and N(12) (Fig. 2).

As noted for the *trans*-[theophyllinatochlorobis-(ethylenediamine)cobalt(III)]$^+$ cation (Kistenmacher, 1975) the Co–N(7)–C(5,8) angles are markedly different (Table 4): Co–N(7)–C(5), 131·8 (5)°, and Co–N(7)–C(8), 123·3 (5)° in the *cis*-theophylline cation; 132·1 (2)° and 124·9 (2)° in the *trans*-theophylline cation. The two analogous angles in the *cis*-adenine com-

plex (Kistenmacher, 1974) are, however, reasonably equivalent: Co–N(9)–C(4), 127·7 (2)°, and Co–N(9)–C(8), 128·3 (2)°. As we have noted previously, the dissymmetry is probably due to the increase of the interligand hydrogen-bond system from a five-membered ring in the adenine complex to a six-membered ring in the two theophylline complexes (Marzilli, Kistenmacher & Chang, 1973).

Table 4. *Heavy-atom interatomic bond lengths and*
angles

Estimated standard deviations: Co–Cl 0·003, Co–N 0·008,
N(O)–C 0·012 Å, angles 0·5–0·7°. Cl–O 0·06 Å, O–Cl–O 4°
(perchlorate anion).

(a) Coordination sphere about the cobalt atom

Co–Cl(1)	2·225 Å	Co–N(11)	1·966 Å
Co–N(7)	1·984	Co–N(12)	1·945
Co–N(10)	1·969	Co–N(13)	1·940

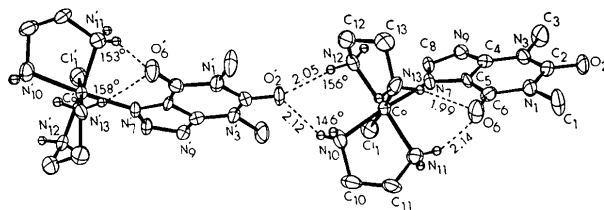| Cl(1)–Co–N(7)	92·2°	N(7)—Co–N(12)	91·4°
Cl(1)–Co–N(10)	87·2	N(7)—Co–N(13)	90·3
Cl(1)–Co–N(11)	90·3	N(10)–Co–N(11)	85·0
Cl(1)–Co–N(12)	90·9	N(10)–Co–N(12)	92·0
Cl(1)–Co–N(13)	175·2	N(10)–Co–N(13)	90·6
N(7)–Co–N(10)	176·5	N(11)–Co–N(12)	176·7
N(7)–Co–N(11)	91·7	N(11)–Co–N(13)	93·7
		N(12)–Co–N(13)	84·9

Fig. 1. A perspective view of two symmetry-related *cis*-[theophyllinatochlorobis(ethylenediamine)cobalt(III)]$^+$ cations. Note in particular the two interligand and the two inter-molecular hydrogen bonds. The thermal ellipsoids are drawn at the 40% probability level.
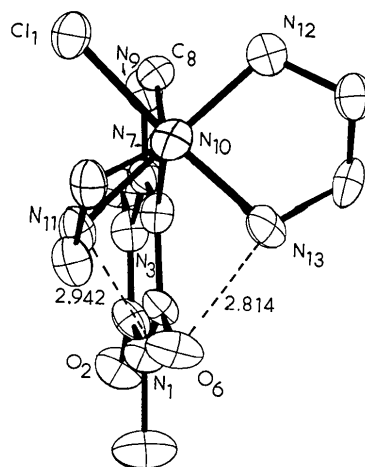

Fig. 2. A projection view of the complex cation down the N(10)–Co bond. The thermal ellipsoids are drawn at the 40% probability level.

† For details concerning the notation of the conformation of the ethylenediamine rings, see *Inorg. Chem.* (1970). **9**, 1–5.

Table 4 (cont.)

(b) Ethylenediamine chelate rings

N(10)-C(10)	1·500 Å	N(12)-C(12)	1·473 Å
C(10)-C(11)	1·454	C(12)-C(13)	1·480
C(11)-N(11)	1·492	C(13)-N(13)	1·488

Co—N(10)-C(10)	108·6°	Co—N(12)-C(12)	110·5°
N(10)-C(10)-C(11)	107·7	N(12)-C(12)-C(13)	106·4
C(10)-C(11)-N(11)	107·7	C(12)-C(13)-N(13)	105·9
C(11)-N(11)-Co	109·7	C(13)-N(13)-Co	108·3

(c) Comparison of the bond lengths and angles in the theophylline moieties in the cis- and trans-complexes* and theophylline†

	cis	trans	theo
N(1)-C(1)	1·438 Å	1·455 Å	1·468 Å
N(1)-C(2)	1·392	1·398	1·404
N(1)-C(6)	1·418	1·400	1·387
N(3)-C(2)	1·343	1·359	1·359
N(3)-C(3)	1·503	1·461	1·473
N(3)-C(4)	1·384	1·375	1·376
N(7)-C(5)	1·367	1·404	1·373
N(7)-C(8)	1·366	1·346	1·332
N(9)-C(4)	1·335	1·341	1·354
N(9)-C(8)	1·360	1·342	1·334
C(2)-O(2)	1·228	1·228	1·215
C(4)-C(5)	1·384	1·379	1·370
C(5)-C(6)	1·420	1·413	1·421
C(6)-O(6)	1·243	1·245	1·217
C(1)-N(1)-C(2)	115·7°	116·7°	116·4°
C(1)-N(1)-C(6)	118·6	117·2	117·3
C(2)-N(1)-C(6)	125·7	126·1	125·9
C(2)-N(3)-C(3)	119·0	119·4	120·3
C(2)-N(3)-C(4)	120·3	120·3	119·7
C(3)-N(3)-C(4)	120·5	120·2	120·0
Co—N(7)-C(5)	131·8	132·1	†
Co—N(7)-C(8)	123·3	124·9	†
C(5)-N(7)-C(8)	104·4	102·8	106·5
C(4)-N(9)-C(8)	103·1	102·4	103·7
N(1)-C(2)-N(3)	117·7	116·7	117·8
N(1)-C(2)-O(2)	119·6	120·8	120·6
N(3)-C(2)-O(2)	122·7	122·5	121·5
N(3)-C(4)-N(9)	126·8	125·6	127·5
N(3)-C(4)-C(5)	122·3	122·3	121·2
N(9)-C(4)-C(5)	110·8	112·1	111·3
N(7)-C(5)-C(4)	107·3	106·4	105·3
N(7)-C(5)-C(6)	132·3	132·9	131·7
C(4)-C(5)-C(6)	120·4	120·6	122·8
N(1)-C(6)-C(5)	113·4	113·7	112·5
N(1)-C(6)-O(6)	117·6	118·9	121·2
C(5)-C(6)-O(6)	128·9	127·4	126·3
N(7)-C(8)-N(9)	114·3	116·2	113·2

(d) Perchlorate anion

| Cl(2)-O(10) | 1·45 Å | Cl(2)-O(12) | 1·22 Å |
| Cl(2)-O(11) | 1·30 | Cl(2)-O(13) | 1·28 |

O(10)-Cl(2)-O(11)	96°	O(11)-Cl(2)-O(12)	119°
O(11)-Cl(2)-O(12)	104	O(11)-Cl(2)-O(13)	111
O(10)-Cl(2)-O(13)	104	O(12)-Cl(2)-O(13)	119

* Estimated standard deviations: N(O)-C 0·004 Å, angles 0·3-0·5°.

† There is a hydrogen atom off N(7) in theophylline. Estimated standard deviations: C-N 0·008 Å, angles 0·4°.

Fig. 2 is a conformational view of the cis-theophylline complex down the N(10)-Co bond. The theophylline ring sits nearly symmetrically between the Co-Cl(1)···

Co-N(12) and the Co-N(11)····Co-N(13) bonds. There is, as found in the trans-theophylline and the cis-adenine complexes, some inequality in the donor····acceptor distances, and a tilting of the purine ring is evident. Crystal packing may play some role in the tilting of the ring. However, it should be noted, as in the cis-adenine complex (Kistenmacher, 1974), that there is a short contact between the hydrogen atom off C(8) and the coordinated chloride ligand: H···Cl distance, 2·83 Å, C(8)-H···Cl angle = 108°. The effect of this interaction would appear to be larger in the cis-adenine complex than in the cis-theophylline complex [N(12)-Co-N(7)-C(8) torsion angle (a positive value corresponds to a right-handed screw) equal to −53·2 (4)°; N(12)-Co-N(9)-C(8) torsion angle in the cis-adenine cation equal to −62·4 (2)°], and may contribute to the inequivalence of the NH···O distances.

(b) Bond distances and angles

Heavy-atom distances and angles are summarized in Table 4. Estimated standard deviations for the bond lengths and angles in the coordination complex are: Co-Cl 0·003, Co-N 0·008, N(O)-C 0·012 Å, 0·5-0·7° for the heavy-atom bond angles. The bond lengths and angles in the perchlorate anion are also given in Table 4. The anion has very large standard deviations associated with its bond lengths and angles: Cl(2)-O about 0·06 Å with Cl(2)-O(10) reaching 0·10 Å, bond angle e.s.d.'s about 4°.

As is evident from the above, the experimental data for the cis-theophylline crystal are of considerably lower quality than those for the trans-isomer (Kistenmacher, 1975), owing to our inability to provide a suitable model for the disordered perchlorate anion. Accordingly, we shall limit our discussion of bond lengths and angles to general trends. The Co-Cl bond length is reasonably well known, and the observed value of 2·225 (3) Å is shorter by 0·03 Å than was found in the cis-adenine and the trans-theophylline complexes, 2·255 (1) and 2·259 (1) Å, respectively. The average Co-N(ethylenediamine) distance, 1·955 (7) Å, is in good agreement with average values in the cis-adenine and in the trans-theophylline complex. The Co-N(7) distance, 1·984 (8) Å, is slightly longer than in the trans-isomer, 1·956 (2) Å; the shortening of the Co-Cl and the lengthening of the Co-N(7) bonds may be related to the different steric properties of the cis- and trans-isomers (see below).

The parameters in the coordinated theophylline are given in part (c) of Table 4. The high e.s.d.'s associated with these parameters preclude any lengthy comparison with those found in the trans-complex or in theophylline (also given in part (c) of Table 4). The C(3)-N(3) and N(7)-C(5) distances in the cis-complex are closer to the values observed in theophylline (Shefter, 1969) than the trans-complex, possibly indicating that the electronic effects due to the formation of the coordination bond in the trans-isomer are larger than those in the cis-isomer, consistent with the shorter Co-N(7) bond

in the *trans*-complex. The larger C(5)–N(7)–C(8) bond angle in the *cis*-isomer *vs.* the *trans*-isomer may again be related to the weaker coordination bond in the *cis*-isomer. The C(6)–O(6) bond length shows the same lengthening (about 0·03 Å) as the *trans*-complex *versus* the value in theophylline, in accord with about the same degree of interligand hydrogen bonding in each case.

As is typical (Sletten & Jensen, 1969; Voet & Rich, 1970), the nine-atom framework of the theophylline anion is significantly non-planar (Table 5). The degree of non-planarity is somewhat less than in the *trans*-complex. In particular, the pyrimidine portion of the molecule is quite planar. The imidazole and pyrimidine rings are tilted about the C(4)–C(5) bond with a dihedral angle of 2·4° (2·3° in the *trans*-isomer). It was noted in the *trans*-complex that the Co atom was about 0·04 Å out of the equatorial plane away from the chloride ligand. In the *cis*-isomer, the cobalt also lies 0·04 Å out of the plane defined by Cl(1), N(11–13) [plane (*d*), Table 5] toward the coordination site occupied by the coordinated theophylline anion. The lengthening of the Co–N(7) bond and the shortening of the Co–Cl(1) bond probably result from the larger steric factors associated with the formation of the interligand hydrogen bonds in the *cis*-isomer.

Table 5. *Some least-squares planes and deviations*

In each of the equations of the planes, the *X*, *Y* and *Z* are coordinates (Å) referred to the orthogonal axes *a*, *b* and *c**. The atoms used to define the planes have been equally weighted.

(*a*) Theophylline nine-atom framework
$$(-0{\cdot}2795X - 0{\cdot}8764Y - 0{\cdot}3922Z = -2{\cdot}5585 \text{ Å})$$

N(1)	0·022 Å	C(4)	−0·031 Å
N(3)	0·007	C(5)	−0·011
N(7)	0·012	C(6)	−0·026
N(9)	−0·014	C(8)	0·029
		C(2)	0·012

Deviations of substituent atoms from the plane

Co	0·231	C(1)	0·039
O(2)	0·035	C(3)	−0·074
O(6)	−0·065	H(8)	−0·031

(*b*) Theophylline pyrimidine ring
$$(-0{\cdot}2941X - 0{\cdot}8747Y - 0{\cdot}3852Z = -2{\cdot}6152 \text{ Å})$$

N(1)	0·011	C(4)	−0·011
N(3)	0·005	C(5)	0·016
C(2)	−0·006	C(6)	−0·015

Deviations of substituent atoms from the plane

O(2)	−0·002	C(1)	0·010
O(6)	−0·052	C(3)	−0·082

(*c*) Theophylline imidazole ring
$$(-0{\cdot}2589X - 0{\cdot}8758Y - 0{\cdot}4073Z = -2{\cdot}5250 \text{ Å})$$

N(7)	−0·007	C(5)	0·004
N(9)	−0·005	C(8)	0·008
		C(4)	0·000

(*d*) 'Pseudo-equatorial plane [Cl(1), N(11)–N(13)]'
$$(0{\cdot}3380X + 0{\cdot}3867Y - 0{\cdot}8580Z = -1{\cdot}3573 \text{ Å})$$

Cl(1)	0·003	N(12)	−0·004
N(11)	−0·003	N(13)	0·004

Deviations of other atoms from the plane

Co	0·049	N(7)	2·032
		N(10)	−1·916

The perchlorate anion and its associated thermal ellipsoids are illustrated in Fig. 3. The Cl(2)–O distances range from 1·22 (6) Å, Cl(2)–O(12), to 1·45 (10) Å, Cl(2)–O(10); the O–Cl(2)–O bond angles range from 96 (4)° to 119 (4)° (Table 4). The chlorine atoms show significant thermal motion which is principally in the direction of the Cl(2)–O(10) bond; this may account for the fact that only the Cl(2)–O(10) bond is in agreement with the accepted Cl–O bond length of 1·438 (3) Å (Olovsson, 1968). We have not attempted to correct the bond lengths or angles for the apparent thermal motion (by employing the Schomaker & Trueblood (1968) method, for example), since we have little reason to believe that the refined anisotropic temperature parameters are physically reasonable.

(*c*) *Crystal packing and intermolecular hydrogen bonding*

A packing diagram of the unit cell viewed down the *c** axis is illustrated in Fig. 4. There is an extensive array of inter-cation hydrogen bonds, Fig. 4, Table 6. The N(10)–H···O(2)···H–N(12) hydrogen-bond system serves to tie together the complex cations in a
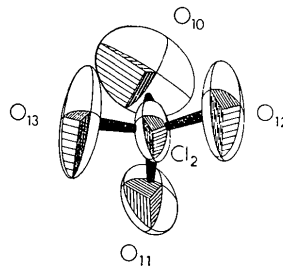

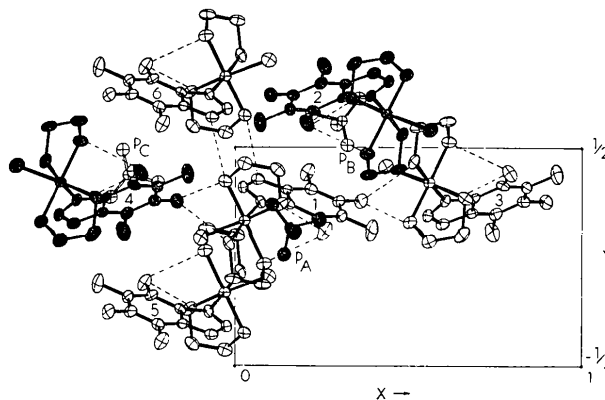Fig. 3. A perspective view of the perchlorate anion. The thermal ellipsoids are drawn at the 30% probability level.

Fig. 4. A view down the *c** axis of the crystal packing. The dashed lines indicate hydrogen bonds. The labeled cations and anions (*P*) have the following coordinate transformations relative to Table 2: (1) *x*,*y*,*z*; (2) ½−*x*,½+*y*,½−*z*; (3) ½+*x*,½−*y*,−½+*z*; (4) −½+*x*,½−*y*,½+*z*; (5) −*x*,−*y*, −*z*; (6) −*x*,1−*y*,−*z*; (*P_A*) *x*,*y*,*z*; (*P_B*) ½−*x*,½+*y*,½−*z*; (*P_C*) −½+*x*,½−*y*,−½+*z*.

head-to-tail fashion along [100]. Cross-linkages between the cations are accomplished by the N(12)–H⋯N(9) hydrogen bonds across centers of symmetry, Fig. 4. The perchlorate anion forms essentially an ion pair with a single cation, with the seven shortest O(perchlorate)⋯H–N(C) contacts with a single complex, Table 6. The weak interactions observed for the perchlorate anions are consistent with its associated high thermal motion (disorder).

(d) Summary

We have demonstrated here and in previous papers (Kistenmacher, Marzilli & Chang, 1973; Kistenmacher, 1974,1975) that coordinated purines are capable of forming hydrogen bonds with other ligands in the coordination sphere of a transition metal complex. These results are not without some precedent. At least three previous instances of interligand hydrogen bonds, involving unidentate ligands as opposed to the chelate complexes we have been studying, have been reported: (1) Taylor (1973) has observed an interligand hydrogen bond between the exocyclic amine group, $-N(10)H_2$, on a protonated adenine and a chloride ligand in the complex trichloroadeniniumzinc(II); (2) Clark & Orbell (1974) have shown that in a nickel(II) complex containing inosine-5′-monophosphate that an interligand hydrogen bond exists between a coordinated water molecule and O(6) of the hypoxanthine moiety; (3) similarly, Sletten (1971) has observed an interligand hydrogen bond from a coordinated water molecule and O(6) in the complex [bis-(9-methyl-6-oxopurine)-copper(II)] dichloride. In each of these complexes, as well as the two theophylline complexes we have studied, the site of coordination is through N(7). In each case, the angles M–N(7)–C(5) and M–N(7)–C(8) are quite dissymmetric as we have observed – about 132° and 120°, respectively. Furthermore, Heitner & Lippard (1974) have reported a structural study of a palladium complex with 6-mercapto-9-benzylpurine

as a chelate ligand–metal binding at N(7) and the exocyclic sulfur S(6). The requirements of chelate formation have produced dramatically different Pd–N(7)–C(5) and Pd–N(7)–C(8) angles – 110° and 146°. These findings suggest that in N(7)–coordinated purines there is extreme variability of the exocyclic angles at N(7), either in response to chelate formation or interligand hydrogen bonding.

The formation of interligand hydrogen bonds noted above surely plays an important role in the stabilization of these complexes. Also, the ability of the nucleic acid bases to form such interactions may influence the site at which metal coordination takes place. The variety of exocyclic functions displayed by the four common purine and pyrimidine bases may, therefore, be employed to direct metal binding to a specific site by a suitable choice of other ligands in the coordination sphere.

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Table 6. Hydrogen bonds and close contacts of the type D–H⋯A

D	H	A	H⋯A	D⋯A	∠D–H⋯A	(∠H–D⋯A)
(a) Interligand hydrogen bonds						
N(11)	H(8)	O(6)[a]	2·14 Å	2·942 Å	153°	(19°)
N(13)	H(16)	O(6)[a]	1·99	2·814	158	(15)
(b) Intermolecular hydrogen bonds						
N(10)	H(1)	O(2)[b]	2·12	2·890	146	(24)
N(12)	H(9)	O(2)[b]	2·05	2·864	156	(17)
N(12)	H(10)	N(9)[d]	2·41	3·149	143	(33)
(c) Close contacts involving the perchlorate oxygens						
N(13)	H(15)	O(10)[a]	2·8	3·53	143	
C(8)	H(17)	O(10)[c]	2·8	3·71	154	
N(10)	H(2)	O(11)[a]	2·5	3·25	140	
N(13)	H(15)	O(11)[a]	2·7	3·51	164	
N(10)	H(2)	O(13)[a]	2·7	3·51	170	
N(13)	H(15)	O(13)[a]	2·5	3·26	147	

(a) $x,\quad y,\quad z$ (c) $-\frac{1}{2}+x, \frac{1}{2}-y, -\frac{1}{2}+z$
(b) $-\frac{1}{2}+x, \frac{1}{2}-y, \frac{1}{2}+z$ (d) $-x, 1-y,\quad -z$

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The Crystal Structure of Procaine Dihydrogen Orthophosphate

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The crystal structure of the dihydrogen phosphate salt of procaine was determined by use of three-dimensional X-ray diffractometer data. Crystals of the salt are triclinic, space group $P\bar{1}$, with $a = 8\cdot029$ (2), $b = 8\cdot384$ (1), $c = 13\cdot839$ (1) Å, $\alpha = 72\cdot37$ (3), $\beta = 83\cdot50$ (3) and $\gamma = 71\cdot94$ (3)°. The structure was solved by the heavy-atom method and refined by least-squares calculations. Difference Fourier maps suggest that there may be a partially substituted water site, and the refined occupancy of this site is $0\cdot050$ (4). The final R index, based upon 2793 reflections, is $0\cdot040$. The procaine conformation is like that found in crystal structures of other procaine salts, except for several large differences involving torsion angles within the diethylamino groups. Unlike other crystal structures of procaine salts, the carbonyl oxygen atom, O(7), is a hydrogen-bond acceptor. The procaine cation hydrogen-bonds to phosphate ions through its tertiary and p-amino groups, resulting in an arrangement similar to that postulated for the binding of procaine to the phospholipids of nerve membranes.

Introduction

Procaine, an ester of p-aminobenzoic acid, is a useful local anesthetic (Keys, 1945). Its exact mechanism of action is not known (Ritchie & Greengard, 1966), but there is evidence that the compound interacts with the membranes of nerve fibers (Toman, 1952; Skou, 1954; Shanes, 1958, 1963; Condouris, 1961, 1963; Buchi & Perlia, 1960; Shanes, Freygang, Grundfest & Amatniek, 1959; Thimann, 1943; Kuperman, Okamoto, Beyer & Volpert, 1969; Eckert, 1962a,b; Agin, 1965; Weidmann, 1955), thereby interfering with the ion-conduction processes required for nerve impulses (Skou, 1954; Shanes, 1958, 1963; Condouris, 1961, 1963). The biological effects of procaine, which forms reversible complexes with various phospholipids *in vitro* (Feinstein, 1964; Goldman, 1964), have been attributed to interactions between the anesthetic and the phospholipids of nerve membranes. One would expect the procaine cation to interact with the phosphate moieties of phospholipids. A model for the type of interaction that might occur has been postulated by Feinstein (1963, 1964). According to this model, procaine binds simultaneously to two phosphate groups from neighboring phospholipid molecules: to one through the terminal tertiary amino group, and to the other through the p-amino group of the phenyl moiety.

We determined the crystal structure of the dihydrogen phosphate salt of procaine to obtain information about the possible factors involved in procaine interactions with phosphates.

Experimental

Transparent plates of procaine phosphate were obtained by slowly evaporating an aqueous solution containing equimolar quantities of procaine and phosphoric acid. Weissenberg and oscillation photographs showed the unit cell to be triclinic, dictating space group $P1$ or $P\bar{1}$. A crystal fragment, with approximate dimensions of $0\cdot05 \times 0\cdot13 \times 0\cdot14$ mm, was cut from a larger plate and mounted on a Picker FACS-1 X-ray diffractometer with its a axis slightly inclined to the ϕ axis of the diffractometer. The angular settings for 12 high-angle (Cu $K\alpha_1$, $\lambda = 1\cdot54051$ Å) reflections were measured and the unit-cell parameters were obtained from a least-squares analysis of these measurements. Crystal data are listed in Table 1.