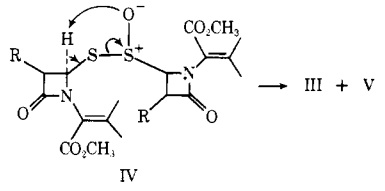
fluxing benzene for 1 h and evaporating the solvent afforded the thione VI as a yellow gum: IR ($CHCl_3$) 1825 cm^{-1}; NMR ($CDCl_3$) δ 5.86 (s, 1 H), 5.43 (s, 1 H), 5.21 (m, 2 H), and 1.92 (s, 3 H). Thione VI was obtained in comparable yield to thione V. However, it was less stable than V, and, consequently, purification was achieved by removing the pentyl sulfide byproduct through the used of cellulose preparative thin layer chromatography.

The thione functionality adds a new dimension to β-lactam chemistry. The utilization of the thioxo-β-lactam in the construction of new penicillins and cephalosporins is currently under investigation.

Acknowledgment. The authors wish to express their gratitude to Dr. Jack Baldwin for useful discussions during the preparation of this manuscript and to Mr. J. R. Burgtorf for technical assistance.

References and Notes

(1) T. S. Chou, *Tetrahedron Lett.*, 725 (1974); T. S. Chou, J. R. Burgtorf, A. L. Ellis, S. R. Lammert, and S. P. Kukolja, *J. Am. Chem. Soc.*, **96**, 1609 (1974).
(2) R. D. G. Cooper, L. D. Hatfield, and D. O. Spry, *Acc. Chem. Res.*, **6**, 32 (1973).
(3) R. Lattrell, *Angew. Chem.*, 925 (1973).
(4) The ready dimerization of sulfenic acid to thiosulfinate is well documented; see J. R. Shelton and K. E. Davies, *J. Am. Chem. Soc.*, **89**, 718 (1967).
(5) This is in line with the finding by E. Block that the S–S bond of thiosulfinate is unusually weak and the acidity of hydrogen on carbon bonded to sulfur is enhanced; see E. Block, *J. Am. Chem. Soc.*, **94**, 642 (1972).
(6) In theory, one could expect only a 50% yield of thione V by pyrolysis of the thiosulfinate IV. However, the 67% yield of thione V can be rationalized by β-elimination of IV giving the thione and regeneration of III (R_2 = H). Sulfenic acid III could subsequently undergo dimerization and β-elimination or simply dehydration to give more thione V.



IV

(7) The chirality of V as reflected at C_3 is the same as C_6 of the starting penicillin. This contention is supported by optical rotation of V: $[\alpha]^{25}_D = -18.2°$ (*c* 0.01, benzene:ethanol = 1:1).
(8) G. C. Levy, G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972, p 133.
(9) The mass spectrum of V (R_1 = CH_3) gave the molecular ion peak at *m/e* 358 and other fragments at *m/e* 330 ($M^+ - CO$), 315 ($M^+ - CO - CH_3$), 299 ($M^+ - CO_2CH_3$), 271 ($M^+ - CO_2CH_3 - CO$), 203 ($C_8H_4NO_2CH{=}C{=}S^+$), and 187 ($C_8H_4NO_2CH{=}C{=}O^+$).
(10) The disulfide VII was obtained by heating penicillin sulfoxide I (R = CH_3) in neat *n*-pentylmercaptan at 105 °C under N_2 for 16 h. The exclusive formation of the β,γ-unsaturated ester disulfide was in contrast to the report of Barton and co-workers in which penicillin V sulfoxides reacted with isobutylmercaptan to give the α,β-unsaturated ester disulfide; see D. H. R. Barton, P. G. Sammes, and M. V. Taylor, *Chem. Commun.*, 1137 (1971).
(11) The thiosulfinate VIII was obtained as a mixture of diastereomers. Exclusive oxidation of the pentyl sulfur was probably the result of the deactivation of azetinone sulfur electronically through induction and sterically by the phthalimido moiety which prevents oxidation of that sulfur.

T. S. Chou,* G. A. Koppel, D. E. Dorman, J. W. Paschal
The Lilly Research Laboratories, Eli Lilly and Company
Indianapolis, Indiana 46206
Received August 24, 1976

Molecular Structure of μ-(9-Methyladenine-N^1,N^7)-bis(diisopropyl sulfoxide-*S*)-*trans*-dichloroplatinum(II)[1]

Sir:

The anticarcinogenic chemotherapeutic effect of platinum(II) complexes is thought to be associated, in vivo, with the direct complexation of the platinum complex with the purine and pyrimidine bases of deoxyribonucleic acid.[2,3] Recent experiments have suggested that complexation with the purine bases is more important than with pyrimidine bases.[4]

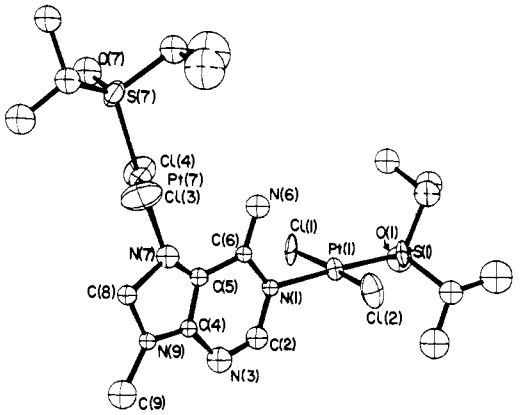


Figure 1.

On the basis of spectroscopic results, it has been suggested that platinum complexes can coordinate to one of the N7, N1, or NH_2-6 positions of adenosine[5,6] and coordination at N7 has been confirmed by x-ray crystallography.[7] In addition, it has been suggested that N1 and N7 positions can be coordinated simultaneously by two different platinum atoms.[6] We report here x-ray crystallographic evidence that confirms this suggestion.

Yellow crystals of the title compound were prepared by the stoichiometric reaction of $K[PtCl_3(\{(CH_3)_2CH\}_2SO)]$[8] with 9-methyladenine in water, the product being crystallized from acetone solution by evaporation at room temperature. Satisfactory analyses were obtained for C, H, S, N, and Cl.

Crystal data: $C_{18}H_{35}Cl_4N_5O_2Pt_2S_2$; M 949.6; monoclinic; space group $P2_1/c$; a = 15.620 (8), b = 17.357 (5), c = 14.05 (2) Å; β = 104.8 (1)°; Z = 4; d_c = 1.71 g cm^{-3}. Intensity data were collected using a Syntex $P\bar{1}$ diffractometer with Mo Kα radiation. The two crystallographically independent platinum atoms were located by direct methods. (The pseudosymmetry between the coordinates of the two platinum atoms precluded a unique solution to the Patterson map.) The other atoms were located by successive electron density difference syntheses. Full-matrix least-squares refinement, with anisotropic temperature factors for Pt, Cl, and S atoms, converged to a conventional R value of 0.069 for 1344 reflections with $I > 3\sigma(I)$.

The molecule is shown in Figure 1. The arrangement of ligand atoms about each platinum atom is essentially a square, the Pt-Cl (Pt(1)-Cl(1), 2.29 (1); Pt(1)-Cl(2), 2.31 (1); Pt(7)-Cl(3), 2.30 (1); Pt(7)-Cl(4), 2.30 (1)), Pt-N (Pt(1)-N(1), 2.08 (3); Pt(7)-N(7), 2.07 (3)); and Pt-S (Pt(1)-S(1), 2.23 (1); Pt(7)-S(7), 2.25 (1)) distances, bond lengths within the bis(isopropyl) sulfoxide group and all angles do not differ significantly from values we have found previously for a similar platinum complex of 1-methylcytosine.[8] Bond lengths and angles within the 9-methyladenine group do not differ significantly from the average values listed by Voet and Rich.[9]

Significant features of the structure are the large dihedral angles between the plane of the 9-methyladenine and the plane of each platinum atom and its four bonded atoms. The adenine-Pt(7) plane angle is 61° and the adenine-Pt(1) plane angle is 89°. Similar large angles have been observed for a platinum-1-methylcytosine complex (84°)[8] and a platinum-2,6-lutidine complex (81°).[10] These large angles are caused by the steric requirements of the groups attached to the carbon atoms adjacent to the bound nitrogen atom, and similar large dihedral angles will occur in any square planar platinum-DNA-base complex. This will undoubtedly cause a marked distortion in a coiled DNA chain, when platinum complexes are bound to the bases. This distortion may well be the reason

why *cis*-dichlorodiammineplatinum(II), in addition to being a useful anticancer agent, is an activator of other anticancer drugs.[11]

The title molecule is of further interest in that recent studies have shown that $K(PtCl_3Me_2SO)$ complexes directly and efficiently to the base functions of denatured DNA.[12] One to one complexation is observed with cytosine, guanine, and thymine bases, while 1:2 complexation is observed for the adenine bases. This difference in the complexation behavior of the adenine bases is clearly consistent with the structure reported here and provides a potentially useful method for sequencing the adenine bases in DNA using electron microscopy.[12]

References and Notes

(1) Supported by the National Research Council of Canada and McMaster University Science and Engineering Research Board.
(2) J. J. Roberts and J. M. Pascoe, *Nature (London)*, **235**, 282 (1972).
(3) M. J. Cleare, *Coord. Chem. Rev.*, **12**, 349 (1974).
(4) A. J. Thomson, "Platinum Coordination Complexes in Cancer Chemotherapy", T. A. Connors and J. J. Roberts, Ed., Springer-Verlag, New York, N.Y., 1974, p 38; A. B. Robins, *ibid.*, p 63.
(5) S. Mansy, B. Rosenberg and A. J. Thomson, *J. Am. Chem. Soc.*, **95**, 1633 (1973).
(6) P.-C. Kong and T. Theophanides, *Inorg. Chem.*, **13**, 1981 (1974).
(7) A. Terzis, N. Hadjiliadis, R. Rivest, and T. Theophanides, *Inorg. Chim. Acta*, **12**, L5–L6 (1975).
(8) C. J. L. Lock, R. A. Speranzini, and J. Powell, *Can. J. Chem.*, **54**, 53 (1976).
(9) D. Voet and A. Rich, *Prog. Nucl. Acid Res. Mol. Biol.*, **10**, 183 (1970).
(10) R. Melanson and F. D. Rochon, *Can. J. Chem.*, **54**, 1002 (1976).
(11) J. J. Roberts, private communication to B. Rosenberg, 1974.
(12) F. P. Ottensmeyer and R. Whiting, *Biochim. Biophys. Acta*, in press.

Colin James Lyne Lock,* Robert Anthony Speranzini Graham Turner

Institute for Materials Research, McMaster University Hamilton, Ontario, Canada L8S 4M1

John Powell

Lash-Miller Chemical Laboratories, University of Toronto Toronto, Ontario, Canada M5S 1A1

Received August 16, 1976

Resonance Raman Spectra of Liganded and Unliganded Carp Hemoglobin in Both R and T States

Sir:

Unliganded mammalian hemoglobins (Hb) adopt a thermodynamically stable conformation exhibiting a low ligand affinity, denoted the T state. The binding of oxygen and other ligands or oxidation is usually accompanied by a transition to a different, high affinity, conformation, denoted the R state, and the cooperative ligand-binding properties of hemoglobin are a consequence of the reversible transition between these two forms.[1] The nature of the transduction mechanism whereby ligation or oxidation of the pentacoordinate ferroheme controls this conformational equilibrium, and reciprocally, whereby the protein conformation determines the apparent ligand affinity at the heme, is a matter of keen interest.[2]

The most widely known and completely articulated proposal is the "trigger mechanism" elaborated by Perutz[1,3] following suggestions of Williams[4] and Hoard.[5] It includes a proposed coupling between protein conformation and the spin state and position of iron: the five-coordinate high-spin Fe(II) of an unliganded heme in Hb lies substantially out of the mean porphyrin plane and is considered to be held in a stressed state by tension exerted through the protein. Upon oxygenation, the Fe atom becomes low spin and moves into the porphyrin plane with a concomitant release to tension. However, this mechanism has been seriously questioned, and other views of the nature of the stresses (forces) on the heme group and resulting strains (deformations) have been presented.[2,6] We here report a resonance Raman (RR) spectroscopic study of deoxy- and cyanomet-Hb from the carp which shows no evidence of heme strain upon changing protein conformation.

At neutral pH, carp (*cyprinus carpio*) hemoglobin shows cooperative effects characteristic of a T $\rightleftarrows$ R switch upon ligation. However, at low pH, particularly in the presence of organic phosphates, both unliganded and liganded forms remain in the T state, whereas at high pH, both forms adopt the R conformation.[7] Therefore, it is possible to induce a change between T and R merely by changing the pH, providing a unique opportunity to examine in both low and high affinity conformations the properties of both liganded and unliganded hemes.

Resonance Raman spectroscopy provides a particularly sensitive probe of heme properties. A number of vibrational bands have been correlated to heme spin and oxidation state.[8] The underlying cause of observed variations in vibrational frequencies is perturbations in the porphyrin structure, variously considered to be doming occurring upon motion of the metal-atom[8] and changes in the diameter of the porphyrin "central hole".[9] In either case, these "structure-sensitive" Raman bands provide a means of investigating whether changes in protein conformation can indeed induce strains in the heme prosthetic group.

We have obtained[10] RR spectra of carp deoxy-Hb in the T state, pH 5.8 with 4mM inositol hexaphosphate (IHP), and in the R state, pH 8.8, usually at 4° in order to improve protein stability. Figure 1 presents the high-frequency region of the RR spectra obtained with laser frequencies near the visible (5145 Å) and Soret (4579 Å) heme absorptions; Table I lists the frequencies of the structure-sensitive bands for both the

Table I. Frequencies of Structure-Sensitive RR Bands for Hb and Cyanomet-Hb

Deoxy-Hb			Cyanomet-Hb		
	Carp[b,c]			Carp[c]	
Human[a]	T state[d]	R state[e]	Human[a]	T state[d]	R state[e]
1358 (p) vs	1354 (B,Q)	1355 (B,Q)	1374 (p) vs	1372 (B,Q)	1371 (B,Q)
1473 (p) m	1471 (B,Q)	1469 (B,Q)	1508 (p) m	1504 (B,Q)	1505 (B,Q)
1546 (dp) m	1545 (Q)	1544 (Q)	1564 (dp) m	1560 (Q)	1561 (Q)
1552 (ap) s	1557 (Q)[f]	1559 (Q)[f]	1588 (ap) s	1590 (Q)	1588 (Q)
1565 (p) m	1564 (B)	1565 (B)	1583 (p) m	1584 (B)	1586 (B)
1607 (dp) s	1604 (B,Q)	1603 (B,Q)	1642 (dp) vs	1642 (B,Q)	1641 (B,Q)

[a] Vs = very strong, s = strong, m = medium, p = polarized, dp = depolarized, ap = anomalously polarized; ref 8a. [b] Spectra taken at 4 °C. [c] B = 4579-Å excitation; Q = 5145-Å excitation; vs and s bands—estimated reproducibility, ±1 cm^{-1}; m bands—estimated reproducibility, ±2 cm^{-1}. [d] ~1.2 mM in heme, 0.1 M phosphate-citrate, pH 5.8, plus 4 mM IHP. [e] ~1.2 mM in heme, 0.1 M Tris, pH 8.8. [f] This feature appears as a shoulder in spectra with the abscissa expanded, and is clearly resolved from the adjacent (1545 cm^{-1}) peak in successive spectra taken with parallel and perpendicular orientation of the polaroid analyzer.