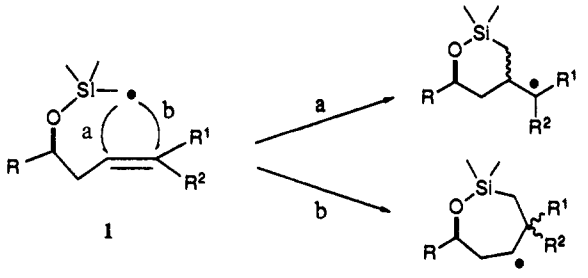
Scheme I



relative stability of the transition state C over A or B.

The high degree of regio- and stereocontrol demonstrated in this novel type of free-radical-mediated chirality transmission process in nonrigid, acyclic systems suggests the suitability of this approach as a general method for the hydroxy-directed 1,3-asymmetric induction at an sp^2 center. The stereoselective 6-exo α-silyl radical cyclization in combination with the facility of subsequent oxidative cleavage allows convenient access to branched-chain 1,4-diols.

Acknowledgment. This work was supported by the National Institutes of Health (Grant No. DK30025).

Supplementary Material Available: Complete spectroscopic characterization of all new compounds described in this paper including IR and ^1H and ^{13}C NMR spectral data and combustion and/or high-resolution mass spectral analyses of the molecular formula (13 pages). Ordering information is given on any current masthead page.

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Stereochemically Controlled Ligands Influence Atropisomerization of Pt(II) Nucleotide Complexes. Evidence for Head-to-Head and Stable Λ Head-to-Tail Atropisomers

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The remarkable effectiveness of Pt(II) anticancer drugs containing cis amines has prompted studies that demonstrate the need for at least one NH on each amine for reasonable activity.[1] The role such NH groups play in drug binding to DNA, the likely molecular target, is a central issue.[2] The drugs selectively cross-link adjacent guanine (G) residues by the N7s.[3] Selective binding of coordinating agents to target biomolecules and the contributions of H-bonding and steric effects in such binding are fundamentally important subjects.

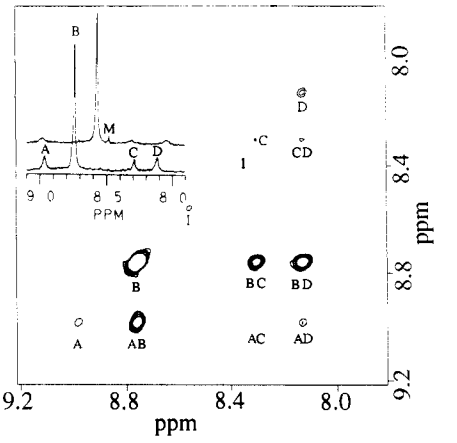

Figure 1. 2D EXSY spectrum (360 MHz, 22 °C, 360 ms mixing time, pH 3) of the products formed in a solution of 5′-GMP/(*R,S,S,R*)-LPt = 2:1. A, D, B, and C are H8 signals for HH, HH, HT(major), and HT(minor), respectively, in both 2D and 1D (insert) spectra. In the 2D spectrum, A is less intense than D as a result of magnetization transfer to NCH_3. Cross peaks are denoted by two letters. Insert: The upper spectrum in the insert is from the analogous (*S,R,R,S*)-LPt experiment. Minor peaks: M, residual 1:1 complex; I, minor impurities or noise.

X-ray and NMR studies of Pt oligonucleotide adducts with adjacent G residues cross-linked at N7 reveal that the two six-membered rings are on the same side of the Pt coordination plane (head-to-head, HH, conformation).[4] In the solid state, the large majority of cis bis complexes of 6-oxopurine bases, nucleosides, and nucleotides with several metal centers adopt the head-to-tail (HT) conformation, with the six-membered rings on opposite sides of this plane.[5] In only four cases, all from Lippert's laboratory and all Pt(II) complexes with 9-ethylguanine, was an HH conformation found.[5a]

In solution, *cis*-$[PtA_2(\text{nucleos(t)ide})_2]^{x(+\text{or}-)}$ complexes (where A = an amine or one-half of a diamine chelate) usually exhibit free rotation about the Pt–N7 bond.[6-9] In a pioneering study, Cramer demonstrated that guanosine rotation can be slowed sufficiently to detect atropisomers on the NMR time scale, if A_2

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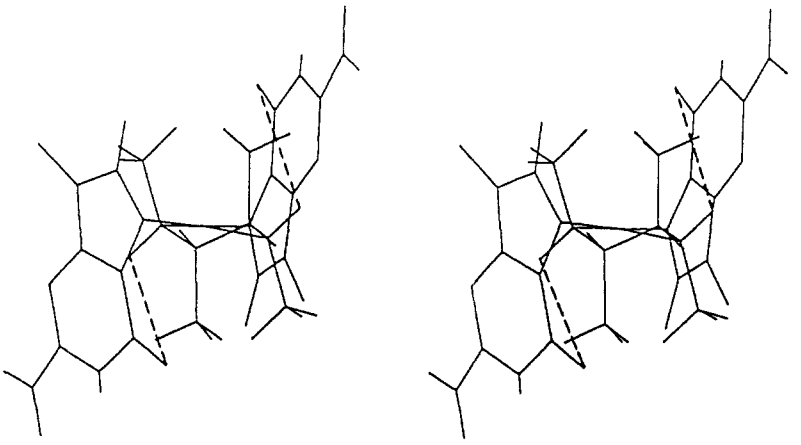

Figure 2. Stereoview of (*R,S,S,R*)-LPt(5′-GMP)$_2$ ΔHT atropisomer. For clarity, the sugar and phosphate moieties are not shown.

is a sufficiently bulky chelate.[6] Two GH8 signals were detected. In an insightful analysis, it was shown that the asymmetric sugar led to two possible HT atropisomers, each with one H8 signal, when the *cis*-PtA$_2$ moiety had local C_2 symmetry. Two signals are also expected for the nonequivalent GH8s in the HH atropisomer. The observation of only two of four possible signals could be best explained with the two HT atropisomers. In a clever experiment, Reedijk and co-workers used a non-C_2 *cis*-PtA$_2$ moiety to establish that only HT isomers were found in solution,[7] consistent with most crystallographic results.[5] The bulky A$_2$ ligand(s) often lacked NH groups. Although *N,N*′-dimethylethylenediamine (*N,N*′-Me$_2$en) complexes also formed HT atropisomers, the broad guanosine H8 signals revealed a fast rotation rate.[8]

Since the role of the NH groups is of central importance in understanding the Pt class of drugs, we have designed a ligand system that would allow us to stereospecifically control NH orientation. Thus, we have prepared several isomers of LPt(H$_2$O)SO$_4$, where L = *N,N*′-dimethyl-2,3-diaminobutane (see supplementary material). The *C*-methyl groups simultaneously control the N stereochemistry (and hence the orientation of the NH), limit ligand flexibility, and increase ligand bulk compared to *N,N*′-Me$_2$en. We focus this report on the (*R,S,S,R*)-L complexes, where the configurations at the four asymmetric centers are *R*, *S*, *S*, and *R* at N, C, C, and N, respectively.

The treatment of (*R,S,S,R*)-LPt(H$_2$O)SO$_4$ with 2 equiv of 5′-dGMP or 3′- or 5′-GMP gave four H8 product NMR signals. These 1D and a series of 2D ^{1}H NMR spectra are quite revealing. In an exchanging system, the typical NOESY (nuclear Overhauser effect spectroscopy) experiment is often called an EXSY (exchange spectroscopy)/NOESY experiment because both exchange and NOE cross peaks are observed. We focus on the 5′-GMP studies (Figure 1). First, connectivities are revealed between all four H8 signals (Figure 1), demonstrating that these arise from all three possible atropisomers in slow chemical exchange, even at room temperature. Thus, the added bulk in the ethylene group decreases rotation about Pt–N7 relative to *N,N*′-Me$_2$en complexes.[8] Second, in the 1D spectrum, H8 signals A and D have equal intensity and must arise from the HH atropisomer. This is the first unambiguous evidence for such an isomer for a Pt bis(nucleotide) complex.[10] Third, the large (B) and one small (C) H8 signals are for the HT atropisomers. On the basis of signal intensity, the order of stability is HT(major) $\gg$ HH > HT(minor). This predominance of one atropisomer contrasts with previous studies in which the HT atropisomers had similar abundances and no HH atropisomer was observed.[6-8,11] Fourth, in the EXSY/NOESY spectrum the ratio of the H8/NCH$_3$ NOE cross peak to the H8/NH cross peak unambiguously defines the G orientation. On the basis of the known absolute configuration of 2,3-diaminobutane,[12] the HT(major) species has the ΛHT configuration (Figure 2).[6,8] Although the solution chirality of atropisomers has not been determined previously, the ΔHT atropisomer has been found in the solid state in all complete X-ray structural reports for 6-oxopurine nucleos(t)ide complexes with several metal centers.[5] Fifth, when the same experiment shown in Figure 1 was carried out at 2 °C, cross peaks involving double rotation (HT(major) → HT(minor), BC; exchange between the downfield and upfield H8 signals of the HH isomer, AD) lost relative intensity much more than the others, which arose from HT → HH single rotations. As predicted,[8] double rotations are probably energetically very unfavorable; the double-rotation cross peaks observed likely result from two sequential rotations during the long mixing times required for a good signal-to-noise ratio. The presence of the NOE cross peaks complicates a quantitative rate analysis. Sixth, the greater stability of the ΛHT atropisomer suggests strongly that O6···HN H bonding predominates over PO···HN H bonding. Indeed, the 3′-GMP product has a similar isomer distribution and chemical shift pattern, but the 3′-phosphate group is too remote to participate in NH H-bonding. Seventh, in the (*S,R,R,S*)-L series, the NOE data are consistent with predominance of the ΔHT atropisomer. In this case, the major HT atropisomer is even more favored (Figure 1 insert), consistent with the solid-state results which typically reveal the Δ configuration.

Finally, an unusual but characteristic feature of GpG species cross-linked at N7 by Pt(II) is a large difference ($\sim$1 ppm) in the HH signals with the 3′-G downfield in single strands. The HH complexes studied here exhibit the same remarkable difference. In a gedanken experiment, we constructed GpG moieties from our bis(nucleotide) complexes. For these, the "3′-G" H8 signal is downfield when the normal anti configuration about the glycosyl bond is presumed. This result suggests that the interligand interactions in the coordination sphere may be dictating the guanine orientations in single-stranded PtGpG adducts. However, the nucleotides are not tethered, and the previous analyses suggesting that the guanine orientations dictated by the sugar phosphate backbone are responsible for the shift differences require reexamination.[13]

The controlled stereochemistry approach we have demonstrated here, namely, the inversion of chirality of the HT atropisomers, holds promise for the controlled design of uniquely distorted DNA and RNA conformations, such as may occur for genetic signaling and in ribozymes.[14]

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Supplementary Material Available: General description for the preparation of compounds, elemental analyses, and figures showing a different perspective to that in Figure 2 and part of the EXSY spectrum of (*S,R,R,S*)-LPt(5′-GMP)$_2$ (3 pages). Ordering information is given on any current masthead page.

Dithiolene Coordination in the Molybdopterin Cofactor of DMSO Reductase: In Situ Evidence from Resonance Raman Spectroscopy

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We present resonance Raman (RR) spectra of DMSO reductase (DR) from *Rhodobacter sphaeroides*[1,2] which strongly support the view[3-6] that its Mo atom is bound to pterin via a dithiolene chelate. DMSO reductase is a member of a class of redox enzymes that contain an extractable molybdopterin cofactor that is able to reconstitute nitrate reductase activity in a cofactor-minus mutant, Nit-1, of *Neurospora crassa*.[7] The extracted cofactor is labile and has so far eluded direct structural characterization.[6] On the basis of persuasive chemical evidence, however, the structure shown in Figure 1 was proposed for the Mo cofactor in hepatic sulfite oxidase and milk xanthine oxidase. The major features of the structure of molybdopterin were confirmed by structural studies on the carboxamidomethyl derivative.[6] More recently, the Mo cofactor of DR has been shown to contain an extended form of molybdopterin, molybdopterin guanine dinucleotide, in which the pterin is attached to 5′-GMP through a pyrophosphate linkage.[8] DR is an attractive vehicle for in situ characterization of the cofactor by RR spectroscopy, because of its rich electronic spectrum, also shown in Figure 1, which is unobscured by other chromophores, i.e., Fe–S clusters and flavin, or heme, that are present in most Mo enzymes.[9] Reported RR spectra of xanthine oxidase are dominated by Fe–S cluster modes.[10]

Figure 2 shows a portion of the high-frequency RR spectra of DR in oxidized [DRox] and reduced [DRred] form, excited at 676.4 nm. This wavelength is near the lowest energy electronic absorption bands, 720 and 640 nm, for DRox and DRred. The RR band at 1575 cm^{-1} in DRox and 1568 cm^{-1} in DRred is in the C=C stretching region. Its assignment to the dithiolene C=C stretch is supported by the down shift upon reduction from Mo(VI) to Mo(IV), due to redistribution of electron density in the dithiolene ring. The direction of the redox-associated frequency shift is not easily predictable. The C=C bond order should be decreased by electron donation from the dithiolene π system to the metal. For Mo(IV) the C=C bond order may also be decreased by back-donation from the metal d_π to the dithiolene. The net effect is to produce a slight (7 cm^{-1}) down shift in ν(C=C) upon reduction. The frequency is higher in DRred than it is in the oxo-Mo(IV) bis-dithiolene complex, $MoO(S_2C_2(CO_2Me)_2)_2^{2-}$,[11] 1535 cm^{-1}, possibly reflecting the increased competition between two dithiolene ligands for the Mo(IV) acceptor d_π orbitals.

Figure 3 shows RR spectra in the 200–500-cm^{-1} region, where Mo–ligand stretching modes are expected. Comparison of the spectra with those of enzyme extracted from bacteria grown on ^{34}S shows isotope-sensitive bands, which are attributable to Mo–S stretching. DRred shows two ^{34}S-sensitive bands, at 352 and 383 cm^{-1}, and so does DRox, at 350 and 370 cm^{-1}. In addition, the DRox bands have shoulders at 336 and 377 cm^{-1}, which also appear to shift on ^{34}S substitution, as do the weak 368-, 417-, and

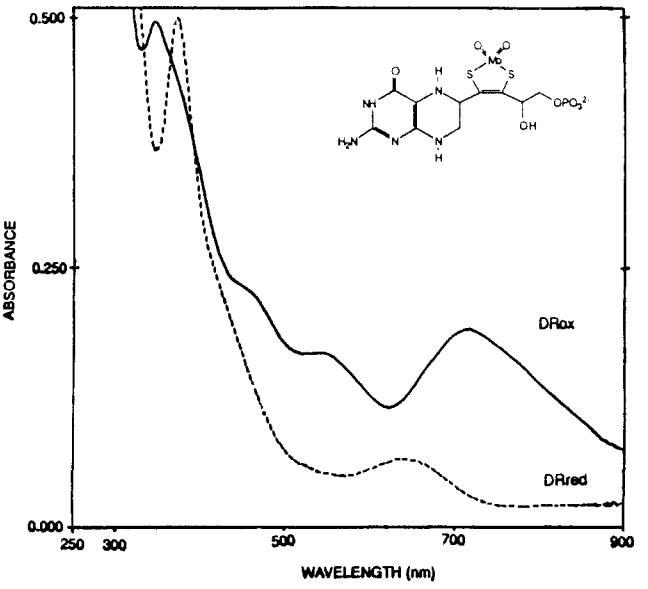

Figure 1. Absorption spectra of DR (7.9 mg/mL, 0.096 mM) prepared from *Rh. sphaeroides* by a modification[2] of the method of Satoh and Kurihara.[1] The enzyme as isolated was in the oxidized form, Mo(VI), and was reduced with sodium dithionite. Excess dithionite was removed by anaerobic gel (PD-10) chromatography. The enzyme appeared as a single band on SDS–PAGE gels. Its activity (16 μmol of DMSO oxidized/(min·mg)) was established by monitoring the substrate-dependent oxidation of dithionite-reduced benzyl viologen in 50 mM Tris·HCl, pH = 7.5. The structure of the molybdopterin moiety of molybdopterin guanine dinucleotide, which is proposed[6] on the basis of chemical evidence, is shown in the inset.

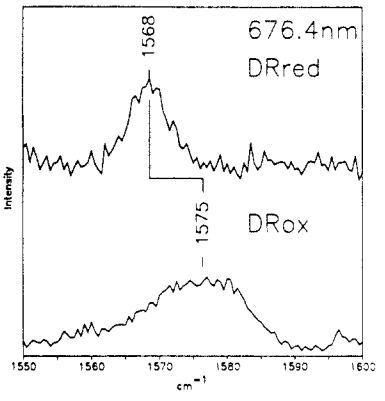

Figure 2. RR spectrum, 676.4-nm excited, of oxidized and reduced DR (0.91 mM) in the C=C stretching region. The spectra were obtained from frozen solution on a cold finger cooled to 77 K.[18] DRred was loaded onto the sample cell in an O_2-free glove box. Excitation was from a Kr^+ laser. The scattered light was scanned with a Spex 1401 double monochromator equipped with photon counting electronics. Conditions: 200-mW output laser power; 6-cm^{-1} slit width; 0.5-cm^{-1} steps; 1 s/step.

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