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Carbon-13, Phosphorus-31, and Proton NMR Studies of the Interactions of the Carbonylbis(triphenylphosphine)rhodium(I) Cation with Base Pairs of 6-Mercaptoguanosine and 8-Mercaptoguanosine with Cytidine

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The interactions of the electrophile $[(PPh_3)_2(CO)Rh]^+$ (denoted as Rh(I)) with the base pairs 6-mercaptoguanosine–cytidine and 8-mercaptoguanosine–cytidine in neutral and basic dimethyl-d_6 sulfoxide solutions have been investigated by using ^{13}C, ^1H, and $^{31}P\{^1H\}$ NMR spectroscopy. The addition of Rh(I) to the s^{6}Guo–Cyd mixture leads to both the s^{6}Guo–Rh(I) and the Cyd–Rh(I) interactions. However, the addition of Rh(I) to the s^{8}Guo–Cyd mixture produces only the Cyd–Rh(I) interaction. When triethylamine (TEA) is added to the s^{6}Guo–Cyd–Rh(I) mixture, s^{6}Guo is deprotonated at N(1), forming the s^{6}Guo$^-$ anion and leading to the s^{6}Guo$^-$–Rh(I) interaction as the only detectable interaction. The addition of TEA to the s^{8}Guo–Cyd–Rh(I) mixture produces the s^{8}Guo$^-$–Rh(I) interaction, where s^{8}Guo has been deprotonated at N(7), the Cyd–Rh(I) interaction, and uncomplexed Cyd. These interactions are discussed in terms of their possible relevance to hydrogen-bond disruption, base mispairing, and antitumor activity of thiolated guanine derivatives.

Introduction

It was first shown many years ago that 6-mercaptopurine and some of its derivatives exhibit anticarcinogenic activity toward selected types of tumors.[1-5] It has since been suggested that this activity could result from the incorporation of 6-mercaptopurine derivatives into nucleic acids.[6-8] The secondary and tertiary structures of nucleic acids are dictated by base-stacking and hydrogen-bonding phenomena. It has been previously reported that hydrogen-bonded nucleic base pairs involving thiolated bases have different dimensions than their nonthiolated analogues that could cause distortions in the nucleic acid structure and alter the biological behavior of the nucleic acid.[9] It is possible that such alterations are fundamental to the anticarcinogenic behavior of active mercaptopurine derivatives.

It has been further noted that metal complexes of 6-mercaptopurine derivatives often exhibit anticarcinogenic behavior, and in some cases the presence of the metal leads to enhanced activity.[1,10,11] The interactions of metal ions with nonthiolated nucleosides have received considerable attention; however, the interactions of metals with thiolated nucleosides have been less thoroughly investigated. In view of the biological activity of mercaptopurine derivatives in both the presence and absence of metal ions, further studies directed at understanding the effects that sulfur substituents have on base stacking and hydrogen-bonding interactions are warranted.

We have previously investigated the interaction of the rhodium electrophile $[(PPh_3)_2(CO)Rh]^+$ with 6-mercaptoguanosine (s^{6}Guo) and 8-mercaptoguanosine (s^{8}Guo) in $(CD_3)_2SO$ solutions.[12] The electrophile (abbreviated as Rh(I)) was found to coordinate at the sulfur of both s^{6}Guo and s^{8}Guo. The acidities of the N(1)–H in s^{6}Guo and N(7)–H in s^{8}Guo were found to increase as a result of coordination at the sulfur atoms. Changes in the acidities of thiolated nucleosides upon metal complexation undoubtedly affect the nature of hydrogen-bonding interactions involving the thiolated nucleosides and could play a significant role in the metal-enhanced antitumor activity of 6-mercaptopurine derivatives.

In our continuing efforts to interpret differences in the behavior of thiolated and nonthiolated nucleic bases with metal ions, we report here the results of studies involving interactions of $[(PPh_3)_2(CO)Rh]^+$ with base pairs containing cytidine (Cyd) and the thiolated nucleosides s^{6}Guo and s^{8}Guo.

Experimental Section

Materials. Cytidine, 6-mercaptoguanosine, and 8-mercaptoguanosine were obtained from Sigma Chemical Corp. and were used without further purification. The cation $[(PPh_3)_2(CO)Rh]^+$ was added to $(CD_3)_2SO$ solutions of the nucleosides in the form of $[Rh(PPh_3)_2(CO)_3]PF_6$, which loses two carbon monoxide molecules when placed in solution with the bases. $[Rh(PPh_3)_2(CO)_3]PF_6$ was prepared according to the method of Schrock and Osborn.[13]

Methods. The ^{13}C, ^1H, and $^{31}P\{^1H\}$ NMR spectra were obtained on a JEOL FX90Q Fourier transform spectrometer. The ^{13}C NMR spectra were measured at 22.51 MHz, with $(CH_3)_4Si$ as the internal standard. The ^1H NMR spectra were obtained at 89.55 MHz with $(CH_3)_4Si$ as the internal standard, and the $^{31}P\{^1H\}$ NMR spectra were measured at 36.19 MHz with 85% H_3PO_4 as the external standard. All spectra were obtained at ambient temperatures. The ^{13}C NMR peak assignments were made according to the literature.[14,15]

Sample Preparation. NMR solutions for the mixture studies were prepared by dissolving the appropriate quantities of nucleosides and $[Rh(PPh_3)_2(CO)_3]PF_6$ in 2.5 mL of $(CD_3)_2SO$ to give the desired nucleoside:nucleoside and rhodium:nucleoside ratios based on a nucleoside concentration of 0.15 M. For basic solutions, approximately 125 μL of triethylamine was added to the appropriate solution.

Results and Discussion

6-Mercaptoguanosine–Cytidine Mixtures. Previous reports have demonstrated the utility of ^1H NMR studies in assessing the extent of hydrogen bonding in nucleic base pairs.[16-20] By

(1) Kirschner, S.; Wei, Y.; Francis, D.; Bergman, J. G. *J. Med. Chem.* **1966**, *9*, 369.
(2) Montgomery, J. A.; Schabel, F. M., Jr.; Skipper, H. *Cancer Res.*, **1962**, *22*, 504.
(3) Schabel, F. M.; Montgomery, J. A.; Skipper, H. E.; Laster, W. R., Jr.; Thomson, J. R. *Cancer Res.* **1961**, *21*, 690.
(4) Fox, J. J.; Wempen, I.; Hampton, A.; Doerr, I. L. *J. Am. Chem. Soc.* **1958**, *80*, 1669.
(5) Hitchings, G. H.; Rhoads, C. P. *Ann. N.Y. Acad. Sci.* **1954**, *60*, 183.
(6) (a) Balis, M. E. "Antagonists and Nuclei Acids"; Elsevier: New York, 1968; pp 167-169. (b) LePage, G. A.; Howard, N. *Cancer Res.* **1963**, 23, 622. (c) LePage, G. A.; Junga, I. G. *Cancer Res.* **1963**, 23, 739. (d) LePage, G. A. *Cancer Res.* **1960**, 20, 403. (e) Kaplan, H. S.; Smith, K. C.; Tomlin, P. *Nature (London)* **1961**, 190, 794. (f) Adams, D. H. *Biochem. J.* **1963**, 89, 240.
(7) Weigent, D. A.; Nelson, J. A. *Cancer Res.* **1980**, *40*, 4381.
(8) Harris, B. A.; Weigent, D. A.; Nelson, J. A. *Biochem. Pharmacol.* **1979**, *28*, 1169.
(9) Bugg, C. E.; Thewalt, U. *J. Am. Chem. Soc.* **1970**, *92*, 7441.
(10) Hansen, H. J.; Bennett, S. J.; Nadler, S. B. *Arch. Biochem. Biophys.* **1962**, *98*, 379.
(11) (a) Maeda, M.; Abiko, N.; Sasaki, T. *J. Med. Chem.* **1981**, *24*, 167. (b) Skinner, S. M.; Lewis, R. W. *Res. Commun. Chem. Pathol. Pharmacol.* **1977**, *16*, 183. (c) Skinner, S. M.; Swatzell, J. M.; Lewis, R. W. *Ibid.* **1978**, *19*, 165. (d) Kanzawa, F.; Maeda, M.; Sasaki, T.; Hoshi, A.; Kuretani, K. *J. Natl. Cancer Inst. (U.S.)* **1982**, *68*, 287.
(12) Abbott, D. W.; Woods, C. *Inorg. Chem.* **1983**, *22*, 1918.
(13) Schrock, R. R.; Osborn, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 2397.
(14) Jones, A. J.; Grant, D. M.; Winkley, M. W.; Robins, R. K. *J. Am. Chem. Soc.* **1970**, *92*, 4079.
(15) Jennette, K. W.; Lippard, S. J.; Ucko, D. A. *Biochim. Biophys. Acta* **1975**, *402*, 403.
(16) Wang, S. M.; Li, N. C. *J. Am. Chem. Soc.* **1968**, *90*, 5069.
(17) Kan, L. S.; Li, N. C. *J. Am. Chem. Soc.* **1970**, *92*, 281.

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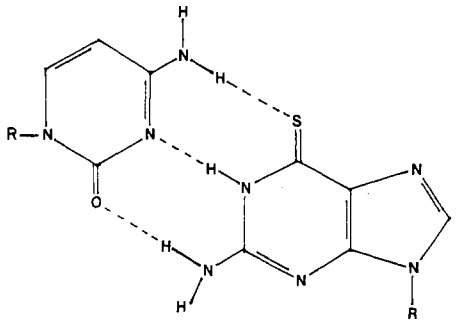
Table I. ^1H NMR Chemical Shifts for Mixtures of Cytidine, 6-Mercaptoguanosine, 8-Mercaptoguanosine, and the Carbonylbis(triphenylphosphine)rhodium(I) Cation[a]

	δ[b]						
	mercaptoguanosine				cytidine		
	H(7)	H(1)	H(8)	$-NH_2$	H(6)	$-NH_2$	H(5)
Cyd					7.86	7.18	5.72
s^6Guo		11.96	8.16	6.83			
s^6Guo–Cyd		12.03	8.17	6.93	7.89	7.26	5.80
s^6Guo–Cyd–Rh(I)		*c*	8.17	6.93	*d*	7.17	5.80
s^8Guo	12.91	11.05		6.54			
s^8Guo–Cyd	12.94	11.91		6.96	7.93	7.42	5.72
s^8Guo–Cyd–Rh(I)	12.98	11.15		6.62	*d*	7.20	5.74

[a] Abbreviations: Rh(I) = $[(PPh_3)_2(CO)Rh]^+$; s^6Guo = 6-mercatoguanosine; Cyd = cytidine. The solutions are 0.15 M in $(CD_3)_2SO$. [b] Chemical shifts are measured from $(CH_3)_4Si$ internal standard at 89.55 Hz. [c] Not observed due to exchange broadening. [d] Masked by the triphenylphosphine peaks.

analogy with the Guo–Cyd base pair, the hydrogen atoms expected to be involved in the hydrogen bonding between s^6Guo and Cyd are H(1), $-NH_2$ on s^6Guo and $-NH_2$ on Cyd.



The ^1H NMR data in Table I show that the proton NMR peaks of s^6Guo and Cyd are relatively unshifted in 1:1 mixtures of s^6Guo–Cyd. The lower electronegativity of sulfur and greater internuclear hydrogen-bond distances[21] contribute to weakening the hydrogen-bonding interactions between s^6Guo and Cyd as compared to those between Guo and Cyd, thus, the negligible shifts for the proton NMR peaks. Previous studies involving nucleoside base pairs in $(CD_3)_2SO$ have shown that the ^{13}C NMR peaks of the nucleosides are not sensitive to hydrogen-bonding interactions.

The ^{13}C NMR spectral data (Table II) of a 1:1:1 mixture of s^6Gu–Cyd–Rh(I) reveal a set of peaks that can be attributed to the s^6Guo–Rh(I) interaction[12] and a set of peaks that can be attributed to the Cyd–Rh(I) interaction.[20] A number of ^{13}C NMR peaks that match some of those of uncomplexed Cyd are also observed. The ^1H NMR spectrum of the 1:1:1 s^6Guo–Cyd–Rh(I) mixture shows that the H(1) peak of s^6Guo disappears when Rh(I) is added to a 1:1 mixture of s^6Guo–Cyd. The disappearance of the H(1) peak is indicative of an increase in the acidity of H(1) and subsequent exchange broadening of the H(1) peak due to complexation of Rh(I) at S(6).[12]

The $^{31}P\{^1H\}$ NMR spectrum of the 1:1:1 mixture of s^6Guo–Cyd–Rh(I) is shown in Figure 1. This spectrum is interpreted as the overlap of a broad singlet resulting from the s^6Guo–Rh(I) interaction and a doublet resulting from the Cyd–Rh(I) interaction. In addition to the $^{31}P\{^1H\}$ NMR data (Table III) being consistent with the ^{13}C NMR results, they are also consistent with data from previous studies[12,20] that show that ligand exchange occurs in the s^6Guo–Rh(I) system

Table II. ^{13}C NMR Chemical Shifts for Various Mixtures of 6-Mercaptoguanosine, 8-Mercaptoguanosine, Cytidine, Triethylamine, and the Carbonylbis(triphenylphosphine)rhodium(I) Cation[a]

obsd interactions	δ(base carbon atoms)[b]				
	C(2)	C(4)	C(5)	C(6)	C(8)
	Nucleosides				
s^6Guo	152.9	147.8	128.2	175.0	138.3
s^8Guo	150.8	149.4	104.0	153.4	165.6
Cyd	155.4	165.5	93.8	141.5	
	1:1:1 s^6Guo–Cyd–Rh(I)				
s^6Guo–Rh(I)[c]	154.7	145.6	127.3	171.9	140.1
Cyd–Rh(I)[c]	151.3	163.4	92.9 (?)	141.1	
Cyd		164.8	94.1	141.9	
	1:1:1 s^8Guo–Cyd–Rh(I)				
s^8Guo	150.9	149.5	104.1	153.5	165.6
Cyd–Rh(I)[c]	151.2	163.4	92.9	141.0	
	1:1:1:xs s^6Guo–Cyd–Rh(I)–TEA				
s^6Guo–Rh(I)–TEA[c]	161.3	146.6	129.3	175.6	138.5
Cyd	155.7	165.6	94.0	141.5	
	1:1:1:xs s^8Guo–Cyd–Rh(I)–TEA				
s^8Guo–Rh(I)–TEA[c]	152.8	150.7	109.8	153.6	161.8
Cyd–Rh(I)[c]	151.0	163.6	92.9	141.6	
Cyd	155.9	165.8	94.5	141.0	

[a] Abbreviations: s^6Guo = 6-mercaptoguanosine; s^8Guo = 8-mercaptoguanosine; Cyd = cytidine, Rh(I) = $[(PPh_3)_2(CO)Rh]^+$, TEA = triethylamine, xs = excess. Concentration ratios are based on 0.15 M solutions in $(CD_3)_2SO$. [b] Chemical shifts are measured from $(CH_3)_4Si$ internal standard at 22.51 MHz. [c] For shifts of isolated two-component mixtures, see ref 14 (mercaptoguanosine mixtures) and 22 (cytidine mixtures).

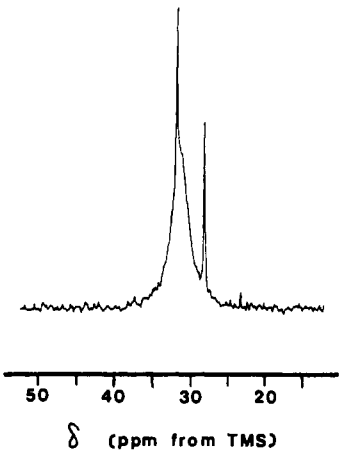
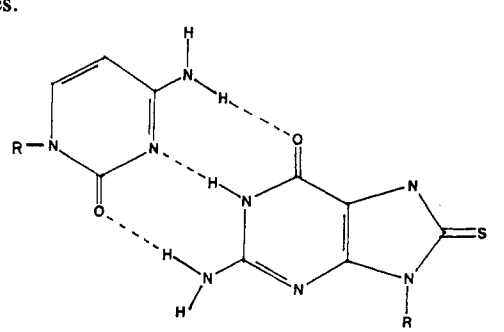


Figure 1. $^{31}P\{^1H\}$ NMR spectrum of the 1:1:1 mixture of 6-mercaptoguanosine, cytidine, and the carbonylbis(triphenylphosphine)rhodium(I) cation.

but not in the Cyd–Rh(I) system.

8-Mercaptoguanosine–Cytidine Mixtures. On the basis of the ^1H NMR data (Table I), the hydrogen-bonding interactions illustrated for s^8Guo and Cyd are as strong as those previously observed for Guo and Cyd through ^1H NMR studies.



(18) Newmark, R. A.; Cantor, C. R. *J. Am. Chem. Soc.* **1968**, *90*, 5010.
(19) Katz, L.; Penman, S. *J. Mol. Biol.* **1966**, *15*, 220.
(20) Abbott, D. W.; Woods, C. *Inorg. Chem.* **1983**, *22*, 2918.
(21) Thewalt, U.; Bugg, C. E. *J. Am. Chem. Soc.* **1972**, *94*, 8892.

Table III. ^{31}P NMR Chemical Shifts and Coupling Constants for Various Mixtures of 6-Mercaptoguanosine, 8-Mercaptoguanosine, Cytidine, Triethylamine, and the Carbonylbis(triphenylphosphine)rhodium(I) Cation[a]

obsd interactions[b]	δ[c]	J_{Rh-P}, Hz
1:1:1 s^{6}Guo-Cyd-Rh(I)		
Cyd-Rh(I)	31.47	126.96
s^{6}Guo-Rh(I)	30.96	*d*
1:1:1:xs s^{6}Guo-Cyd-Rh(I)-TEA		
e	30.13	126.95
s^{6}Guo-TEA-Rh(I)	20.97	*d*
e	8.73	87.89
1:1:1 s^{8}Guo-Cyd-Rh(I)		
Cyd-Rh(I)	31.48	126.95
1:1:1:xs s^{8}Guo-Cyd-Rh(I)-TEA		
Cyd-Rh(I)	31.48	126.95
s^{8}Guo-TEA-Rh(I)	29.05	136.72

[a] Abbreviations: Rh(I) = $[(PPh_3)_2(CO)Rh]^+$; s^{6}Guo = 6-mercaptoguanosine; s^{8}Guo = 8-mercaptoguanosine; Cyd = cytidine; TEA = triethylamine; xs = excess. Concentration ratios are based on a concentration of 0.15 M in $(CD_3)_2SO$. [b] For shifts of isolated two-component mixtures, see ref 14 (mercaptoguanosine mixtures) and 22 (cytidine mixtures). [c] Chemical shifts are measured from 85% H_3PO_4 external standard at 36.19 MHz. [d] Singlet. [e] This interaction cannot be assigned with certainty.

This is not surprising since the components involved in hydrogen bonding are the same in both cases and since the sulfur atom in s^{8}Guo is well removed from the atoms involved in hydrogen bonding with Cyd. The H(1) and $-NH_2$ resonances of s^{8}Guo in the 1:1 s^{8}Guo–Cyd mixture are shifted downfield by 0.86 and 0.42 ppm, respectively, from their free nucleoside positions, while the $-NH_2$ resonance of Cyd is shifted downfield by 0.24 ppm. Again, hydrogen-bonding effects are not evident from the ^{13}C NMR spectrum of the mixture.

The ^{13}C NMR spectrum of a 1:1:1 mixture of s^{8}Guo–Cyd–Rh(I) contains peaks that correspond to those of uncomplexed s^{8}Guo and a set of peaks that indicate the presence of the Cyd–Rh(I) interaction. The preference of Rh(I) for Cyd is somewhat surprising since s^{8}Guo contains the soft sulfur atom and since it is known from previous studies[12] that Rh(I) will coordinate at S(8) of s^{8}Guo. It has also been shown that Rh(I) prefers to bind at S(8) rather than O(6) of s^{8}Guo, even though Rh(I) interactions at O(6) of Guo have been shown to occur.[22] However, in 1:1:1 mixtures of Guo–Cyd–Rh(I), some interaction at O(6) of Guo is detectable in addition to the Cyd–Rh(I) interaction,[20] while the 1:1:1 mixtures of s^{8}Guo–Cyd–Rh(I) show only the Cyd–Rh(I) interaction.

The ^1H NMR data are consistent with the ^{13}C NMR results in that the H(7) peak and the H(1) peak are observed in the ^1H NMR spectrum (Table I). It has been previously shown[12] that coordination of Rh(I) at S(8) of s^{8}Guo leads to disappearance of the H(7) peak as a result of exchange broadening. The presence of the H(7) peak in 1:1:1 s^{8}Guo–Cyd–Rh(I) mixtures suggests a lack of coordination of Rh(I) to s^{8}Guo in this mixture. The $^{31}P\{^1H\}$ NMR spectrum (Table III) exhibits a doublet with a chemical shift and coupling constant characteristic of the Cyd–Rh(I) interaction. These data are further evidence that coordination of Rh(I) does not occur with s^{8}Guo in the 1:1:1 mixture.

Basic 6-Mercaptoguanosine–Cytidine Mixtures. It has been shown that addition of Rh(I) to a mixture of s^{6}Guo and triethylamine (TEA) leads to the binding of Rh(I) at S(6) of s^{6}Guo with concomitant deprotonation at N(1).[12] The ^{13}C NMR spectrum of a 1:1:1:xs (xs = excess) mixture of s^{6}Guo–Cyd–Rh(I)–TEA exhibits two sets of peaks. One set is characteristic of the s^{6}Guo–Rh(I)–TEA interaction for binding of Rh(I) at S(6) and deprotonation at N(1).[12] The second set of peaks corresponds to those of uncomplexed Cyd. The lack of ^{13}C NMR peaks due to the Cyd–Rh(I) interaction indicates that although the Cyd–Rh(I) interaction is observed for s^{6}Guo–Cyd–Rh(I) mixtures, the addition of TEA favors the s^{6}Guo–Rh(I)–TEA interaction through the formation of the 6-mercaptoguanosinate anion and reduces the Cyd–Rh(I) interaction to the point that it is no longer detectable by ^{13}C NMR chemical shift studies.

The $^{31}P\{^1H\}$ NMR spectrum (Table III) of this mixture shows as its major peak a broad singlet at a chemical shift characteristic of the s^{6}Guo–Rh(I)–TEA interaction;[12] however, the spectrum also exhibits two doublets, centered at 30.13 and 8.73 ppm. The origins of these doublets are unknown. The $^{31}P\{^1H\}$ NMR spectrum, however, does agree with the ^{13}C NMR results in that it demonstrates that the major interaction present is the s^{6}Guo–Rh(I)–TEA interaction.

Basic 8-Mercaptoguanosine–Cytidine Mixtures. In a previous study we noted that the addition of TEA to s^{8}Guo–Rh(I) mixtures, where Rh(I) binds to S(8), results in deprotonation of s^{8}Guo at N(7).[12] The ^{13}C NMR spectrum (Table II) of a 1:1:1:xs mixture of s^{8}Guo–Cyd–Rh(I)–TEA exhibits three sets of peaks. One set of ^{13}C NMR peaks corresponds to the s^{8}Guo–Rh(I)–TEA interaction. The second and third sets of peaks correspond to the Cyd–Rh(I) interaction and to uncomplexed Cyd. Since no s^{8}Guo–Rh(I) interaction was observed in the neutral 1:1:1 s^{8}Guo–Cyd–Rh(I) mixture, the addition of TEA to this mixture increases the interaction of Rh(I) with s^{8}Guo. This interaction occurs at S(8) and is accompanied by deprotonation at N(7), resulting in formation of s^{8}Guo$^-$.[12] The $^{31}P\{^1H\}$ NMR spectrum (Table III) contains two doublets, one with spectral parameters characteristic of the s^{8}Guo–Rh(I)–TEA interaction and one with spectral parameters characteristic of the Cyd–Rh(I) interaction.

Summary. Relative nucleoside stabilities with the carbonylbis(triphenylphosphine)rhodium(I) electrophile have been determined and were found to be s^{6}Guo(S(6)) ≥ Cyd(N(3)) > s^{8}Guo(S(8)). In a previous study[12] we determined that the relative order for those nucleosides studied was Cyd(N(3)) > Guo(O(6)) > Ado(N(1)) >> Thd, Urd. The substitution of sulfur for O(6) of Guo leads to an increase in strength of the interaction of the electrophile with the guanosine derivative when compared to Cyd. This increased interaction is probably due to the greater affinity of the "class b" metal has for the softer sulfur atom over the oxygen atom. The overall nucleoside stability order then becomes s^{6}Guo(S(6)) ≥ Cyd(N(3)) > Guo(O(6)) ≥ s^{8}Guo(S(8)) > Ado(N(1)) > Thd, Urd. When the sulfur atom is incorporated into the guanosine at position 8, the interaction of the Rh(I) species at S(8) is not strong enough to compete with the interaction of Rh(I) at N(3) of Cyd. It is possible that a stronger interaction of Rh(I) at S(8) is precluded by steric interference of the Rh(I) moiety with the ribose group of s^{8}Guo and/or by a decrease in nucleophilicity of the S(8) site compared to the S(6) site of s^{6}Guo.

The addition of base to mixtures of Cyd and the thiolated nucleosides leads to deprotonation of s^{6}Guo at N(1) and s^{8}Guo at N(7). The formation of the thiolated guanosinate ions shifts the interaction of Rh(I) away from Cyd in favor of interaction with the thiolated guanosinate ions. The interaction of Rh(I) with the 8-mercaptoguanosinate ion is equal to or greater than that with Cyd. This behavior is different from that observed in the 1:1:1 Cyd–s^{8}Guo–Rh(I) mixture, where the Rh(I) interacts only with Cyd. When the results of this study are combined with previous results,[20] the nucleoside stability order for the Rh(I) electrophile may be expressed as s^{6}Guo(S(6))$^-$ > Guo(O(6))$^-$ ≃ s^{8}Guo(S(8))$^-$ > Guo(O(6)) ≥ Ado(N(1))

(22) Abbott, D. W.; Woods, C. *Inorg. Chem.* **1983**, *22*, 597.

≫ Thd, Urd. This order of interaction is probably the result of a combination of several factors, including site nucleophilicity, "class b" acid–base interactions, and steric interactions.

The results presented here demonstrate that metal interactions with thiolated guanosine derivatives can significantly alter the acidities of protons bonded to ring nitrogen atoms. These perturbations could have drastic effects on the extent to which thiolated nucleic acid derivatives are involved in hydrogen bonding when incorporated in nucleic acids and could readily lead to base mispairing. The phenomena discussed here could be important in defining the role of thiolated guanine derivatives as antitumor agents.

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Nitrogen-15 and Cobalt-59 NMR Study of the Bent Nitrosyl Ligand in Cobalt Complexes

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The strongly bent nitrosyl ligand, with an MNO angle around 120°, differs markedly from the linear ligand in spectroscopic properties. ^{15}N shifts are reported for 5-coordinate cobalt(III) complexes with Schiff base (salen, acacen, benacen, ketox, salox) or dithiocarbamato basal ligands and bent apical nitrosyl ligands. As in *C*-nitroso groups, the nitrogen is strongly deshielded (by 500–800 ppm) relative to comparable linear nitrosyls. The ^{15}NO and ^{59}Co shielding tends to decrease with a decrease in the MNO angle and in the energy of the longer wavelength electronic absorption. The relatively low cobalt shielding is consistent with other evidence that the strongly bent nitrosyl is a weaker ligand than linear nitrosyl. Nitrosyls with intermediate angles appear to have intermediate properties.

Introduction

The bent nitrosyl ligand in transition-metal complexes has been more elusive than might have been expected, on the analogy of the main-group XNO compounds, since NOX angles between 105 and 120° are found for *C*- or *N*-nitroso compounds, nitrites, thionitrites, nitrosyl halides, and so on. Most transition-metal nitrosyls[1] have nearly linear MNO groups, in which the ligand is formally NO^+, isoelectronic with CO. Back-bonding then gives an M=N=O contribution reminiscent of the bonding in N_2O and NO_2^+, which are linear; indeed, the linear nitrosyl ligand heads the "spectrochemical series" (based on IR spectroscopy) of π-acceptor ligands.[2] This property can be linked with the relatively low energy of the $\pi^*(NO)$ orbital, arising from the electronegativity of nitrogen and oxygen.

Much less is known about the bent nitrosyl ligand, and a purpose of the present work has been to use ^{15}N and ^{59}Co NMR, in conjunction with electronic spectroscopy, to make comparisons with better known ligands. A strongly bent nitrosyl (with IrNO angle 124°) was characterized by X-ray crystallography in 1968;[3] strong MNO bending in $[Co(NO)(S_2CNMe_2)_2]$ was indicated earlier[4] and has since been confirmed.[5] A dozen or so such $\{MNO\}^8$ complexes have now been characterized with square-pyramidal or octahedral coordination. They can be described in terms of a lone pair on the nitrogen and a d^6 metal, so that the ligand is formally NO^-. The $\langle MNO\rangle^n$ description is useful for partially bent nitrosyls with a less obvious distribution of n_N and d electrons, as in mononitrosyls with an odd n_N electron and dinitrosyls with distorted NMN and MNO angles.[1]

The ease of bending of MNO, in contrast to MCO or MN_2, can also be related to the low energy of the $\pi^*(NO)$ orbital, which is comparable with the energies of the d orbitals with which it overlaps.[6] The bending, as an intramolecular redox process, has mechanistic and catalytic significance, since the shift of a d-electron pair onto nitrogen can allow nucleophilic attack on the metal and electrophilic attack on the nitrosyl.[7]

Many problems have arisen in the characterization of bent nitrosyls. This is a very labile group so there are preparative difficulties, crystallographic (rotational) disorder is common, and thermal motions are particularly large for the oxygen. The structure may change from solid to solution (the energy barrier being small),[8] and there is a sizeable overlap of NO stretching frequencies for bent and linear MNO.[9]

The gap can now be filled by ^{15}N NMR spectroscopy. It has long been known that nitrogen carrying a lone pair of electrons in a delocalized system, as in main-group nitroso and nitrosyl compounds, is deshielded by low-energy $n_N \rightarrow \pi^*$ circulations in the magnetic field.[10] The deshielding of 300 ppm or more from NNO to R_2NNO, or from NO_2^+ to RONO,[10] suggested a nitrogen NMR criterion for MNO bending. A dramatic dependence of the nitrogen shift on the MNO angle was found, with deshieldings of up to 800 ppm for strongly bent compared with linear cobalt nitrosyls[11] and intermediate deshieldings for intermediate MNO angles in dinotrosyls.[12] Such deshielding can also be used as a criterion

(1) Enemark, J. H.; Feltham, R. D. *Coord. Chem. Rev.* **1974**, *13*, 339. Feltham, R. D.; Enemark, J. H. (vol. 12 in *Top. Stereochem.* **1981**, *12*, 155 and references therein.
(2) Horrocks, W. D.; Taylor, R. C. *Inorg. Chem.* **1963**, *2*, 723.
(3) Hodgson, D. J.; Ibers, J. A. *Inorg. Chem.* **1968**, *7*, 2345.
(4) Alderman, P. R. H.; Owston, P. G.; Rowe, J. M. *J. Chem. Soc.* **1962**, 668.
(5) Enemark, J. H.; Feltham, R. D. *J. Chem. Soc., Dalton Trans.* **1972**, 718.
(6) Hoffmann, R.; Chem, M. M. L.; Elian, M.; Rossi, A. R.; Mingos, D. M. P. *Inorg. Chem.* **1974**, *13*, 2666 and references therein.
(7) McCleverty, J. A. *Chem. Rev.* **1979**, *79*, 53.
(8) Bell, L. K.; Mason, J.; Mingos, D. M. P.; Tew, D. G. *Inorg. Chem.* **1983**, *22*, 3497, and work to be submitted for publication.
(9) Connelly, N. G. *Inorg. Chim. Acta Rev.* **1972**, *6*, 47.
(10) Mason, J. *Chem. Rev.* **1981**, *81*, 205.
(11) Bell, L. K.; Mingos, D. M. P.; Tew, D. G.; Larkworthy, L. F.; Povey, D. C.; Sandell, B.; Mason, J. *J. Chem. Soc., Chem. Commun.* **1983**, 125.

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