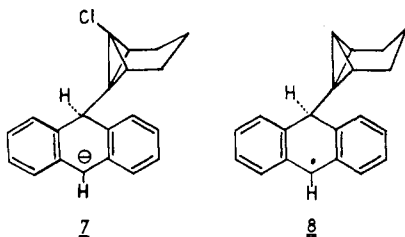


126.61 (d), 128.65 (d), 132.33 (d), 134.66 (s), 143.25 (s), 144.70 (s).

It is interesting to note that the adduct **3** contains the structural unit of a [4.1.1]propellane.⁹ This system is now easily accessible via the procedure outlined above. Judging from molecular models, the bicyclobutane bridgehead carbon atoms C-11 and C-17 in **3** are positioned outside the tetrahedron formed by the four corresponding substituents, C-10, C-12, C-16, C-17 for C-11, and C-9, C-11, C-12, C-16 for C-17.^{10,11}

The formation of the Diels–Alder adduct **3** can be regarded as unequivocal proof for the existence of **2** as an intermediate only, if one were able to exclude alternative routes from **1** to **3** under the experimental conditions employed. This is, however, not the case. The bridgehead bicyclobutyl anion derived from **1** might add to anthracene, the intermediate **7**, after



electron transfer from the carbanionic center to the halogen, might lose the chloride anion, and might form the diradical **8** that could close the ring.

Experiments to differentiate between these mechanistic possibilities are in progress.

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References and Notes

- G. Szeimies, J. Harnisch, and O. Baumgärtel, *J. Am. Chem. Soc.*, **99**, 5183 (1977).
- G. Szeimies, F. Philipp, O. Baumgärtel, and J. Harnisch, *Tetrahedron Lett.*, 2135 (1977).
- The yield was not optimized.
- The values of combustion analysis and of osmometric molecular weight determination are consistent with C₂₂H₁₈.
- For a recent example of a thermal retro-carbene ring opening of a bicyclo[1.1.0]butane system, see G. Szeimies, J. Harnisch, and K.-H. Stadler, *Tetrahedron Lett.*, 243 (1978).
- For a recent review on transition metal ion catalyzed isomerizations of strained hydrocarbons, see K. C. Bishop III, *Chem. Rev.*, **76**, 461 (1976).
- In addition to **5** a second, not yet identified, isomer was formed in 11% yield.
- G. Szeimies, A. Schloßer, F. Philipp, P. Dietz, and W. Mickler, *Chem. Ber.*, **111**, 1922 (1978).
- D. Ginsburg, "Propellanes: Structure and Reactions", Verlag Chemie, Weinheim/Bergstr., 1975.
- For examples of molecules with "inverted tetrahedron", see K. B. Wiberg, G. J. Burgmaier, K. W. Shen, S. J. La Placa, W. C. Hamilton, and M. D. Newton, *J. Am. Chem. Soc.*, **94**, 7402 (1972), and references therein.
- After submission of this manuscript the x-ray structure of **3** has been determined by J.-P. Declercq, G. Germain, and M. Van Meerssche (University of Louvain, Belgium) which confirms the proposed structure for **3** and the "inverted tetrahedron" for C-11 and C-17. We thank Professor Van Meerssche for communicating these results to us prior to publication.

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Metal Ion Binding to Cytidine in Solution. Compelling Raman and Carbon-13 Nuclear Magnetic Resonance Spectral Evidence for Coordination to the Exocyclic Oxygen at Position 2

Sir:

Diverse electrophiles (H⁺, Pt^{II}, Hg^{II} compounds), which bind to N(3) of cytosine derivatives,¹ cause characteristic Raman difference spectra in the 1100–1400-cm⁻¹ region in aqueous^{2,3} and dimethyl sulfoxide-*d*₆⁴ solutions. We observe a new type of difference spectrum which can be attributed to the binding of hard metal ions to O(2) of cytidine in Me₂SO-*d*₆. Definitive evidence for O(2) binding in solution is lacking but such binding occurs frequently in solids.⁵⁻⁷ The problem in distinguishing O(2) and N(3) binding sites in solution can be appreciated when it is realized that the sites are strongly coupled electronically and that the expected metal–O(2)–C(2) angle⁸ places the metal ion at a position close to that expected for an N(3) bound metal atom.

Except for uridine (thymidine) and N(1) of guanosine, similar complexes are formed between metal ions and nucleosides in water and in Me₂SO.^{1,9} The high solubilities obtainable in Me₂SO permit weak interactions to be observed. The existence of such interactions for alkaline earth metal ions is the subject of both intense interest and controversy.^{1,10-12} For example, the nature of the interaction of Mg²⁺ with the adenine ring in the Mg²⁺–ATP complex is unclear.¹³

We showed that the ~1-ppm shifts observed in the ¹H NMR spectrum of guanosine (in Me₂SO) upon addition of alkaline earth chloride salts¹¹ were largely due to hydrogen-bonding interactions with the chloride counterion.¹² A large chloride ion effect is also observed for cytidine.^{10,14,15} The relatively small but reproducible ¹³C shifts observed for cytidine in Me₂SO-*d*₆ on addition of alkaline earth chloride salts¹⁰ cannot be attributed to the chloride ion effect.^{10,16} In general, the changes in shifts of ligand resonances induced by metal coordination are difficult to interpret. Thus, it was reported¹⁰ that alkaline earth salts caused *downfield* shifts in the C(2) resonance of cytidine in Me₂SO-*d*₆, whereas HgCl₂ which binds to N(3) causes large *upfield* shifts and ZnCl₂ (also believed to bind at N(3))¹⁷ causes small upfield shifts of this resonance. Most metal species induce upfield shifts of C(4), but the alkaline earth cations were reported to have a diversity of effects.^{10,18} Electrophiles known to bind to N(3) cause upfield shifts in both the C(2) and the C(4) of cytidine in Me₂SO¹⁶ and aqueous solutions.² Results that we have obtained with nitrate salts are given in Table I.

Raman difference spectroscopy is much less subject than NMR spectroscopy to environmental effects.¹⁻³ The Raman results have been readily interpretable because diverse N(3) bound electrophiles, such as HgCl₂, H⁺, and Pt^{II} complexes, cause similar difference spectra.¹⁻³ The effects of HgCl₂ and H⁺ (not shown) on the Raman spectrum of cytidine are similar

Table I. Metal Ion Induced ¹³C NMR Shifts in Cytidine^a

Salt (M)	C-2	C-4	C-5	C-6	C-1'
HgCl ₂ (0.5)	+2.7	+2.2	-1.7	-0.9	-0.6
Zn(NO ₃) ₂ (0.5)	+0.2	+1.2	-1.3	-0.6	+0.1
Ba(NO ₃) ₂ (0.5)	-0.8	+0.5	-0.6	-0.1	+0.3
La(NO ₃) ₃ (0.47)	-0.8	+0.5	-1.0	-0.1	+0.5
Pr(NO ₃) ₃ (0.46)	+10.1	+2.1	-1.4	+0.7	+1.1
Corrected	+10.9	+1.6	-0.4	+0.8	+0.6

^a 0.2 M in Me₂SO-*d*₆, in parts per million, Me₄Si reference, upfield shifts from free ligand values positive, Varian CFT-20 instrument. Shifts for the metal free solutions were as follows: C-2 (155.4), C-4 (165.5), C-5 (93.8), C-6 (141.4), and C-1' (89.2). See ref 16 for assignments.

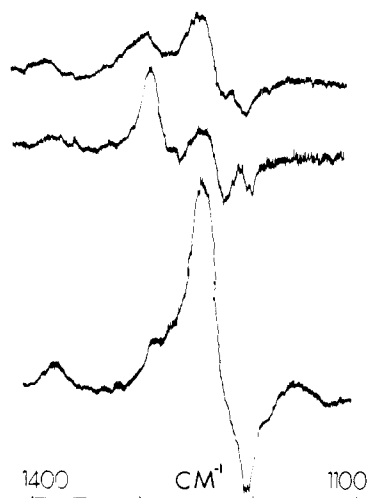


Figure 1. Raman difference spectra (in $\text{Me}_2\text{SO}-d_6$) obtained by subtracting the Raman spectrum of cytidine 0.7 M in the absence of metal salts from the spectrum of similar solutions containing 0.7 M salt: HgCl_2 (bottom), $\text{Ba}(\text{NO}_3)_2$ (middle), $\text{Zn}(\text{NO}_3)_2$ (top). A Spex Ramalog instrument interfaced with a Nicolet 1180 computer was used. All spectra were the results of four scans. The solutions were 0.1 M in NaClO_4 which served as an intensity standard. The spectra are corrected for the metal salt plus solvent and are displayed with the same vertical scale.

in Me_2SO (Figure 1). However, although $\text{Ba}(\text{NO}_3)_2$ and HgCl_2 have similar effects on the Raman spectrum in most spectral regions, $\text{Ba}(\text{NO}_3)_2$ produces a new difference spectrum in the 1100–1400- cm^{-1} region (Figure 1). Several lines of evidence lead us to suggest that the $\text{Ba}(\text{NO}_3)_2$ spectrum is a consequence of binding to O(2).

First, cytosine and cytidine experience similar chemical shifts on addition of $\text{Ba}(\text{NO}_3)_2$. The ribose sugar is evidently not involved in complex formation.

Second, when O(2) of cytosine is replaced with the soft sulfur atom, no evidence was found for complex formation with either $\text{Sr}(\text{NO}_3)_2$ or $\text{Ba}(\text{NO}_3)_2$. A complex is formed between 2-thiocytosine and HgCl_2 as expected. A solution 0.2 M in both reagents leads to an upfield shift for C(2) of 12 ppm, whereas C(4) is unshifted.

Third, $\text{La}(\text{NO}_3)_3$ produces diamagnetic shifts which are almost identical with those produced by $\text{Ba}(\text{NO}_3)_2$ at ~ 0.5 M (Table I). The lanthanides have a well-known preference for oxygen donors and the paramagnetic members of the group are useful shift reagents. Thus, $\text{Pr}(\text{NO}_3)_3$ causes paramagnetic shifts of ~ 11 ppm (upfield) in the C(2) resonance and an ~ 1.6 -ppm shift in the C(4) resonance (Table I). Such paramagnetic shifts are wholly consistent with O(2) binding.

Fourth, the majority of x-ray structures of metal complexes containing cytosine derivatives are found to contain some interaction between the metal and O(2).⁶ Although these interactions are usually weaker than N(3) interactions, in a Mn^{2+} -CMP complex the O(2) is the exclusive base binding site.¹⁹ The Mn^{2+} is a hard metal ion but even the soft Ag^+ ion has been found to interact with O(2).⁷

We have extensively evaluated the role the exocyclic groups on nucleic acid bases play in determining both the structure and stability of metal complexes.⁵ Steric hindrance plays a crucial role and there is currently no example of an octahedral metal ion bound to the sterically crowded N(3) site of cytosine. However, the Mn^{2+} -CMP compound cited above,¹⁹ which is the only example of exclusive O(2) base binding, is octahedral. Models suggest that O(2) binding has minimal steric requirements and the high coordination number metal ions that we have used, in addition to having a chemistry which prefers oxygen donors, would have steric difficulty accommodating N(3) coordination.

Fifth, unlike every other metal salt that we have studied which induces an appreciable Raman difference spectrum, $\text{Zn}(\text{NO}_3)_2$ causes almost a negligible shift in the C(2) resonance (Table I). In contrast, $\text{Zn}(\text{NO}_3)_2$ causes a larger shift in the C(4) resonance than does $\text{Ba}(\text{NO}_3)_2$. The Raman difference spectrum (Figure 1) for $\text{Zn}(\text{NO}_3)_2$ is intermediate to that found for HgCl_2 and $\text{Ba}(\text{NO}_3)_2$. The Zn^{2+} ion has an affinity for both oxygen and nitrogen donors and can achieve low coordination numbers. The shifts in the ^{13}C resonances and the Raman difference spectrum of cytidine induced by $\text{Zn}(\text{NO}_3)_2$ can readily be rationalized if this metal ion forms two types of complexes involving O(2) binding and N(3) binding, respectively. These two complexes would cause the C(2) resonance to shift in opposite directions (leading to a small overall shift) but the C(4) resonance to shift upfield in both cases.

The evidence which we have presented, that the different metal ion dependent patterns in both the Raman difference and C-13 spectra are a consequence of O(2) binding, is compelling. Theoretical studies have predicted that hard metal ions will bind preferentially to O(2) over N(3) but that simultaneous N(3), O(2) coordination is most preferred.²⁰ We cannot exclude simultaneous binding of one metal to both sides with differing degrees of interaction dependent on the metal center. Such simultaneous interactions are known,^{5,6} particularly for Cu^{2+} , and we are continuing our studies to further clarify this point.

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References and Notes

- (1) L. G. Marzilli, *Prog. Inorg. Chem.*, **23**, 255 (1977).
- (2) G. Y. H. Chu, R. E. Duncan, and R. S. Tobias, *Inorg. Chem.*, **16**, 2625 (1977).
- (3) S. Mansy, T. E. Wood, J. C. Sprowles, and R. S. Tobias, *J. Am. Chem. Soc.*, **96**, 1762 (1974).
- (4) L. G. Marzilli and C. P. Van Vuuren, unpublished results.
- (5) L. G. Marzilli and T. J. Kistenmacher, *Acc. Chem. Res.*, **10**, 146 (1977).
- (6) D. Hodgson, *Prog. Inorg. Chem.*, **23**, 211 (1977).
- (7) L. G. Marzilli, T. J. Kistenmacher, and M. Rossi, *J. Am. Chem. Soc.*, **99**, 2797 (1977).
- (8) J. S. Kwiatkowski and B. Pullman, *Adv. Heterocycl. Chem.*, **18**, 199 (1975); R. Bonaccorsi, A. Pullman, E. Scrocco, and J. Tomasi, *Theoret. Chim. Acta (Berlin)*, **24**, 51 (1972).
- (9) Y. H. Chao and D. R. Kearns, *J. Am. Chem. Soc.*, **99**, 6425 (1977).
- (10) T. Yokono, S. Shimokawa, and J. Sohma, *J. Am. Chem. Soc.*, **97**, 3827 (1975).
- (11) S. Shimokawa, H. Fukui, J. Sohma, and K. Hotta, *J. Am. Chem. Soc.*, **95**, 1777 (1973).
- (12) C. H. Chang and L. G. Marzilli, *J. Am. Chem. Soc.*, **96**, 3656 (1974).
- (13) A. Szent-Györgyi, "Bioenergetics", Academic Press, New York, N.Y., 1957, pp 64–73.
- (14) L. G. Marzilli, W. C. Trogler, D. P. Hollis, T. J. Kistenmacher, C. H. Chang, and B. E. Hanson, *Inorg. Chem.*, **14**, 2568 (1975).
- (15) A. C. Plaush and R. R. Sharp, *J. Am. Chem. Soc.*, **98**, 7973 (1976).
- (16) K. W. Jennette, S. J. Lippard, and D. A. Ucko, *Biochem. Biophys. Acta*, **402**, 403 (1975); F. Coletta, R. Ettore and A. Gambaro, *J. Magn. Reson.*, **22**, 453 (1976). For some complementary studies using aqueous solutions see ref 2 and D. J. Nelson, P. L. Yeagle, T. L. Miller, and R. B. Martin, *Bioinorg. Chem.*, **5**, 353 (1976).
- (17) S. M. Wang and N. C. Li, *J. Am. Chem. Soc.*, **88**, 4592 (1966).
- (18) The effects of chloride and nitrate salts are similar. All of the alkaline earth nitrates cause shifts in the same direction and we have concentrated on $\text{Ba}(\text{NO}_3)_2$ which causes the largest shifts. The differences reported earlier¹⁰ for the alkaline earth chlorides is probably the result of using the solvent signal (which shifts) as a reference.
- (19) K. Aoki, *J. Chem. Soc., Chem. Commun.*, 748 (1976).
- (20) D. Perahia, A. Pullman, and B. Pullman, *Theoret. Chim. Acta (Berlin)*, **43**, 207 (1977).

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