Contribution from the Department of Chemistry,
Emory University, Atlanta, Georgia 30322

First Definitive Demonstration of Ortho Shielding Effects on ^{195}Pt NMR Signals. Dependence of Shift on Heterocyclic Ligand Basicity and Ortho Substituents in Four Series of Complexes with Chloro, Dimethyl Sulfoxide, and Pyridine Ligands

Luigi G. Marzilli,* Yuiko Hayden, and Michael D. Reily

Received October 28, 1985

As a first step in addressing the problem of assigning nucleobase metal binding sites by ^{195}Pt NMR shifts, we measured ^{195}Pt NMR chemical shifts of four closely related series of complexes of the types *trans*-[Pt(Xpy)(Me_2SO)Cl_2], *cis*-[Pt(Xpy)(Me_2SO)Cl_2], *cis*-[Pt(Xpy)(Me_2SO)$_2$Cl]$^+$, and *cis*-[Pt(Xpy)$_2$(Me_2SO)Cl]$^+$ where Xpy = pyridine (X = H) or a substituted pyridine. The solvent was dimethyl-d_6 sulfoxide, and 90 individual complexes were studied. When Xpy was py or a 4-substituted py ranging in basicity from 4-CN-py (pK_a = 1.9) to 4-$(CH_3)_2$N-py (pK_a = 9.7), a small, linear dependence of shift on pK_a was observed. For the one trans series, the increase in basicity led to slight deshielding (downfield shift). For the three cis series, shielding was observed as ligand pK_a was increased. Contrary to previous findings that increasing ligand steric size resulted in deshielding, substitution at the 2-position of the pyridine with $-NH_2$, $-NHCH_3$, or $-O^-$ led to a pronounced shielding. This is the first clear example of such an ortho shielding effect. When the 2-position of the pyridine contained C_6H_5, (C_6H_5)C(O), or 3-thienyl, a large deshielding effect was observed. When substituents (X = or ≠ X′) were present at both the 2- and the 6-positions of pyridine, the shielding and deshielding effects observed were in the same directions expected from substitution of X or X′ above but were not quantitatively additive. Thus, the shielding effect order in the trans series was 2-NH_2-6-NH_2-py > 2-NH_2-py > 2-NH_2-6-CH_3-py since the effects of $-NH_2$ and $-CH_3$ were opposite. In general, the following order appears to hold for 2-substituent effects (shielding to deshielding): O^- > NHR > CH_3O > $HOCH_2$ ~ CH_3 ~ C_2H_5 ~ *n*-C_3H_7 > HC(O) > (C_6H_5)C(O) ~ 3-thienyl > C_6H_5 > CN. Although current theory cannot deal adequately with an atom as large as Pt, these results offer hope that empirical relationships may be found that will allow assignment of binding sites and signals in more complex molecules such as adducts of Pt anticancer compounds to nucleic acid components.

Introduction

^{195}Pt NMR spectroscopy of Pt amine complexes can be an invaluable tool in the assessment of the nature of the coordinated ligands.[1] The method has been used to evaluate both the solution chemistry of Pt anticancer agents and the reaction products between these very important drugs and biomolecules.[2-13] ^{195}Pt NMR spectroscopy has proved useful in coordination chemistry and organometallic chemistry, and many examples are detailed in a recent review.[1]

There have been, however, relatively few systematic studies on the relationship of ^{195}Pt chemical shift in a given coordination environment to the electronic and steric properties of the attached ligands.[1] Our interest in pursuing this subject arose during studies aimed at evaluating the products formed between mononucleotides and Pt anticancer agents.[13] A qualitative rule, first suggested by Reedijk,[14] is that Pt coordinated to N1 of a purine (adenine or guanine) is ca. 40 ppm upfield to Pt coordinated to N7 of the same purine. What is the origin of such a "rule"? Even such a relatively simple spectral dependence as the relationship of shift to basicity of heterocyclic ligands has been studied in only one series of compounds, namely *trans*-[PtL(C_2H_2)Cl_2].[15] When L = Xpy (pyridine or substituted pyridine), an increase in basicity led to a downfield shift (i.e. deshielding). Since N1 of adenine or guanine (deprotonated at N1) is more basic than N7, the only published systematic study would have predicted the opposite "rule"! Therefore, we undertook a study to determine the nature of such a dependence.

We selected a Pt coordination system that has been explored in depth in this laboratory.[16] In particular, we have examined four closely related series of compounds, *trans*-[Pt(Xpy)(Me_2SO)Cl_2], *cis*-[Pt(Xpy)(Me_2SO)Cl_2], *cis*-[Pt(Xpy)(Me_2SO)$_2$Cl]$^+$, and *cis*-[Pt(Xpy)$_2$(Me_2SO)Cl]$^+$ (where Xpy = a mono- or disubstituted py). We selected Xpy for the initial study since many compounds are available that differ greatly in bulk and basicity. This study has allowed us to identify the relative contribution of nonbonded and through-bond effects on the shifts. We have greatly extended the range of known nonbonded contributions of N donor ligands and found clear evidence for an ortho shielding effect (i.e. upfield shifts for some ortho substituents).

Experimental Section

Reagents. *cis*-[Pt(Me_2SO)$_2Cl_2$][17] and K[Pt(Me_2SO)Cl_3][18] were prepared by known methods from $K_2[PtCl_4]$. All pyridine ligands were obtained from Aldrich or Sigma and used without further purification.

Instrumentation. All ^{195}Pt NMR spectra were obtained on an IBM WP-200 FT NMR spectrometer, operating at 42.93 MHz. A pulse width of 19.0 μs, corresponding to a 30° tip angle, was used with a relaxation delay of 0.4 s. The spectral window was 50 000-62 500 Hz in most cases, with 8K or 16K (real and imaginary) data points. Typically 1000-10 000 transients were averaged, and the resulting FID was multiplied by an exponential function (LB = 50 Hz) prior to Fourier transformation. All ^{195} Pt NMR chemical shifts were determined in Me_2SO-d_6 solution by using 0.1 M $Na_2[PtCl_6]$ in D_2O as an external reference.

^{1}H NMR spectra were obtained on a Nicolet 360NB FT NMR spectrometer, described previously.[16] The solvent used was Me_2SO-d_6, and all chemical shifts were referenced to Me_4Si. Typical Pt concentrations used were 0.1 and 0.02 M for ^{195}Pt and ^{1}H NMR spectroscopic measurements, respectively.

Methods. In order to obtain spectra of transient *trans*-[Pt(Xpy)(Me_2SO)Cl_2] compounds, a weighed amount of *cis*-[Pt(Me_2SO)$_2Cl_2$] was added to a stoichiometric amount of ligand in solution and the initial spectrum was quickly taken (usually 5 and 2 min after mixing for the ^{195}Pt and ^{1}H NMR experiments, respectively). The decrease of an initial new peak and increase of a second new peak were observed with time in

(1) Pregosin, P. S. *Coord. Chem. Rev.* **1982**, *44*, 247.
(2) Boreham, C. J.; Broomhead, J. A.; Fairlie, D. P. *Aust. J. Chem.* **1981**, *34*, 659.
(3) Ismail, I. M.; Kerrison, S. J. S.; Sadler, P. J. *Polyhedron* **1982**, *1*, 57.
(4) Gill, D. S.; Rosenberg, B. *J. Am. Chem. Soc.* **1982**, *104*, 4598.
(5) Kuroda, R.; Ismail, I. M.; Sadler, P. J. *J. Inorg. Biochem.* **1984**, *22*, 103.
(6) Lippard, S. J. *Science (Washington, D.C.)* **1982**, *218*, 1075.
(7) Hollis, L. S.; Amundsen, A. R.; Stern, E. W. *J. Am. Chem. Soc.* **1985**, *107*, 274.
(8) Kerrison, S. J. S.; Sadler, P. J. *J. Chem. Soc., Chem. Commun.* **1977**, 861.
(9) Hollis, L. S.; Lippard, S. J. *J. Am. Chem. Soc.* **1983**, *105*, 3494.
(10) Woollins, A.; Rosenberg, B. *J. Inorg. Biochem.* **1984**, *20*, 23.
(11) Appleton, T. G.; Hall, J. R.; Ralph, S. F. *Inorg. Chem.* **1985**, *24*, 673.
(12) Clore, G. M.; Gronenborn, A. M. *J. Am. Chem. Soc.* **1982**, *104*, 1369.
(13) Miller, S. K.; Marzilli, L. G. *Inorg. Chem.* **1985**, *24*, 2421.
(14) Dijt, F. J.; Canters, G. W.; den Hartog, J. H. J.; Marcelis, A. T. M.; Reedijk, J. *J. Am. Chem. Soc.* **1984**, *106*, 3644.
(15) Motschi, H.; Sze, S. N.; Pregosin, P. S. *Helv. Chim. Acta* **1979**, *62*, 2086.
(16) Reily, M. D.; Wilkowski, K.; Shinozuka, K.; Marzilli, L. G. *Inorg. Chem.* **1985**, *24*, 37.
(17) Price, J. H.; Williamson, A. N.; Schramm, R. F.; Wayland, B. B. *Inorg. Chem.* **1972**, *11*, 1280.
(18) Kuskushkin, Y. N.; Vyazmenskii, Y. E.; Zorina, L. I. *Russ. J. Inorg. Chem. (Engl. Transl.)* **1968**, *13*, 1573.

0020-1669/86/1325-0974$01.50/0

Table I. ^{195}Pt NMR Chemical Shifts of Species Formed in the Reaction between *cis*-$[Pt(Me_2SO)_2Cl_2]$ and Pyridine or Nonbulky Pyridines[a]

substituent	pK_a[b]	*cis*-$[Pt(Xpy)(Me_2SO)Cl_2]$	*trans*-$[Pt(Xpy)(Me_2SO)Cl_2]$	*cis*-$[Pt(Xpy)_2(Me_2SO)Cl]^+$	*cis*-$[Pt(Xpy)(Me_2SO)_2Cl]^+$
4-$(CH_3)_2N$	9.7	−2868	−3016	−2983	−3379
4-CH_3	6.1	−2859	−3020	−2964	−3360
4-H	5.25	−2856	−3018	−2957	−3355
4-C_2H_3	5.6	−2855	−3018	−2956	−3357
4-HC(O)	4.5	−2844	−3016	−2932	−3342
4-CN	1.9	−2843	−3021	−2931	−3339

[a] Shifts in ppm relative to external 0.1 M $Na_2[PtCl_6]$. [b] pK_a values obtained from ref 21.

Table II. ^{195}Pt NMR Chemical Shifts of Species Formed in the Reaction between *cis*-$[Pt(Me_2SO)_2Cl_2]$ and Substituted Pyridines[a]

substituent	pK_a[b]	*cis*-$[Pt(Xpy)(Me_2SO)Cl_2]$	*trans*-$[Pt(Xpy)(Me_2SO)Cl_2]$	*cis*-$[Pt(Xpy)_2(Me_2SO)Cl]$	*cis*-$[Pt(Xpy)(Me_2SO)_2Cl]^+$
2-NH_2, 6-NH_2	8.3	−3004	−3051		−3422
2-$NHCH_3$	(8.1)	−2936	−3039	−3007	−3394
2-NH_2, 6-CH_3	7.4	−2945	−3022	−3042	−3384
2-NH_2	6.8	−2941	−3043	−3023	−3401
2-NH_2, 5-NO_2	2.4	−2927	−3051	−3002[c]	−3370
2-CH_3, 6-CH_3	6.7	−2860			−3326
2-*n*-C_3H_7	6.0	−2853	−2996	−2893	−3341
2-CH_3	5.9	−2871	−3005	−2932	−3356
2-C_2H_5	5.9	−2859	−2998	−2896	−3342
2-$CH_3C(O)$	(3.9)				−3249[d]
2-HC(O)	3.8	−2830[c]	−2995[c]		−3285
2-$(C_6H_5)C(O)$	(3.6)	−2784	−2923[c]		−3284
2-O	0.75 (1)	−2910		−2986	−3416
	11.65 (2)				
2-C_6H_5	4.5	−2743[c]	−2916[c]		−3251
2-(3-thienyl)	(4.7)	−2757[c]	−2925[c]		−3265
2-$HOCH_2$	(5.6)	−2880	−3010	−2876	−3346
2-CH_3O	3.2	−2883	−3003	−2950	−3372
2-CN	−0.26				−3228
3-CH_3, 5-CH_3	6.2	−2863	−3017	−2985	−3372
3-HC(O)	3.7	−2850	−3026	−2934	−3343

[a] Shifts in ppm from external 0.1 M $Na_2[PtCl_6]$. [b] pK_a values obtained from ref 21; values in parentheses were estimated from similar compounds. [c] Weak signals. [d] Several additional unidentified signals were observed for this solution, 3 weeks after the addition of $AgNO_3$.

both types of experiment. Consistent with previous assignments,[16] the former and the latter peaks were assigned to *trans*-$[Pt(Xpy)(Me_2SO)Cl_2]$ and *cis*-$[Pt(Xpy)(Me_2SO)Cl_2]$, respectively.

In only a few cases were *cis*-$[Pt(Xpy)(Me_2SO)_2Cl]^+$ and *cis*-$[Pt(Xpy)_2(Me_2SO)Cl]^+$ observed during the course of the reactions.[16] Therefore, these species were usually generated in situ by adding 0.9 equiv of $AgNO_3$ to the reaction mixture (Pt:Xpy = 1:1) for *cis*-$[Pt(Xpy)(Me_2SO)_2Cl]^+$, and an additional 1 equiv of Xpy was added subsequently to generate *cis*-$[Pt(Xpy)_2(Me_2SO)Cl]^+$.[16]

For some Xpy, the ^1H NMR spectra of *cis*-$[Pt(Xpy)(Me_2SO)Cl_2]$ and *trans*-$[Pt(Xpy)(Me_2SO)Cl_2]$ overlapped and, therefore, *trans*-$[Pt(Xpy)(Me_2SO)Cl_2]$ was prepared as a solid from the reaction of $K[Pt(Me_2SO)Cl_3]$ and the ligand in aqueous solution.[19] NMR spectra of these *trans*-$[Pt(Xpy)(Me_2SO)Cl_2]$ complexes were taken immediately after dissolution. This procedure does not give analytically pure materials but is known to give predominantly the desired complex.[16]

When Xpy = 2-, 2,5-, or 2,6-substituted pyridines, longer times were required for the formation of the complexes. Typically, 18–24 h elapsed before appreciable buildup of *trans*-$[Pt(Xpy)(Me_2SO)Cl_2]$ was observed in the 1:1 reaction. The isomerization to *cis*-$[Pt(Xpy)(Me_2SO)Cl_2]$ was also much slower, and usually 1–2 weeks at 25 °C was required for this product to predominate. Upon addition of $AgNO_3$, the mixtures were allowed to stand at room temperature in the dark until no additional AgCl was produced (typically 1 day to 1 week). Upon removal of the AgCl, ^{195}Pt NMR spectroscopy revealed nearly quantitative conversion of all Pt species to *cis*-$[Pt(Xpy)(Me_2SO)_2Cl]^+$. When the 2-substituent was very large (e.g. benzoyl, 3-thienyl, acetyl, phenyl, etc.), only 5–20% of *cis*-$[Pt(Me_2SO)_2Cl_2]$ was converted to *trans*- and *cis*-$[Pt(Xpy)(Me_2SO)Cl_2]$. Even in these cases, we observed nearly 100% conversion of all Pt species to *cis*-$[Pt(Xpy)(Me_2SO)_2Cl]$. Of all the 2-substituted Xpy compounds studied, only when X = $HOCH_2$, CH_3O, NHR, or alkyl were *cis*-$[Pt(Xpy)_2(Me_2SO)Cl]^+$ species observed.

Results

A total of 90 different Pt complexes were studied. The data for py and 4-substituted pyridine complexes in all four series are given in Table I. The data for 2-substituted- and 2,6- or 2,5-disubstituted-pyridine coordination compounds in all four series are given in Table II along with data for the complexes of 3-CH_3-5-CH_3-py and 3-HC(O)-py. The results in Table II are grouped according to substitutent type and, within groups, according to Xpy pK_a values.

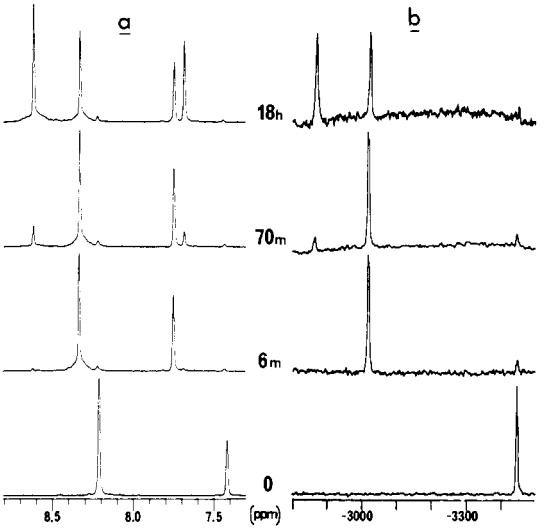

Figure 1. Changes in the (a) ^1H and (b) ^{195}Pt NMR spectra during the 1:1 reaction of 3-CH_3-5-CH_3-py and *cis*-$[Pt(Me_2SO)_2Cl_2]$ in Me_2SO-d_6. Bottom traces: (a) 0.1 M 3-CH_3-5-CH_3-py; (b) 0.1 M *cis*-$[Pt(Me_2SO)_2Cl_2]$. Upper traces: spectra recorded at times indicated after the addition of (a) *cis*-$[Pt(Me_2SO)_2Cl]$ and (b) 3-CH_3-5-CH_3-py. Times indicate elapsed time from addition of the second reactant to the midpoint of acquisition. Typically, total acquisition times were 30 s and 10 min for ^1H and ^{195}Pt NMR spectra, respectively. Solution and spectral conditions are listed in the Experimental Section.

(19) Kong, P.-C.; Iyamuremye, D.; Rochon, F. D. *Bioinorg. Chem.* **1976**, *6*, 83.

In most cases, it was possible to unambiguously assign shifts, since conditions were established previously[16] to maximize the relative amounts of each of the related compounds. Solutions were also examined by ^{1}H NMR spectroscopy (360 MHz) although ^{195}Pt NMR spectral changes were more informative. A correlation of ^{1}H NMR results with ^{195}Pt NMR results is given in Figure 1.

For compounds with amino groups, the coordination site could be either the exocyclic NH_2 group or the endocyclic N. However, the binding of the amino group in these cases can be excluded on the basis of several of the following criteria. First, preliminary studies with aniline suggest that binding via the amino group will give much higher ^{195}Pt upfield shifts than observed with all the aminopyridine compounds, except 2-NH_2-6-NH_2-py in the trans series. Second, 2-(methylamino)pyridine gave results which were very similar to those for 2-aminopyridine. The methyl group on the amino group in the former compound would have an appreciable deshielding effect on the ^{195}Pt NMR signal,[20] if the ligand were coordinated via the exocyclic N. Third, the 2,6-diaminopyridine compound will have a symmetrical ^{1}H NMR spectrum if coordinated by the endocyclic N whereas a more complex pattern will result from amino group binding since all ring H's will be inequivalent. A simple pattern was observed. Fourth, single amino signals were observed for the complexes *trans*-[Pt(Xpy)(Me_2SO)Cl_2], *cis*-[Pt(Xpy)(Me_2SO)Cl_2], and *cis*-[Pt(Xpy)(Me_2SO)$_2$Cl]$^+$, when Xpy = 2,6-diaminopyridine; furthermore, the relative chemical shifts of these NH_2 resonances follow the same trend as observed[16] for the analogous cytidine and 5-methylcytidine complex (which are bound through N3); i.e., NH_2 signals appear to higher field in the series *cis*-[PtL(Me_2SO)$_2$Cl]$^+$ < *cis*-[PtL(Me_2SO)Cl_2] < *trans*-[PtL(Me_2SO)Cl_2]. Fifth, *cis*-[Pt(Xpy)$_2$(Me_2SO)Cl]$^+$ complexes could not be formed with any 2,6-disubstituted species. If amino group binding were occurring, these compounds should have been formed since *cis*-[Pt($C_6H_5NH_2$)$_2$(Me_2SO)Cl]$^+$ forms readily. Steric factors influencing binding should be similar for the amino-group-bound aminopyridines and anilines. Finally, a totally consistent picture emerges as to factors influencing shift and the ^{195}Pt NMR results are not nearly as well explained if amino group to Pt binding is invoked. These additional pieces of evidence will be pointed out in the Discussion. The situation with regard to 2-O-py$^-$ is less clear-cut, since base must be added to induce coordination (vide infra).

Although the emphasis of this study was to examine the effects of Xpy complexes, a few observations on substituting Cl by Me_2SO are worth noting. Comparison of the shifts for a given Xpy in the two series *cis*-[Pt(Xpy)(Me_2SO)$_2$Cl]$^+$ and *cis*-[Pt(Xpy)(Me_2SO)Cl_2] leads to differences in shifts of ca. 475 ± 50 ppm. The shielding effect of substituting Cl by Me_2SO in going from [Pt(Me_2SO)Cl_3]$^-$ to *cis*-[Pt(Me_2SO)$_2Cl_2$] is 491 ppm (−2959 to −3450 ppm, respectively). Treatment of *cis*-[Pt(Me_2SO)$_2Cl_2$] with either $AgNO_3$ or $AgClO_4$ gives the same species, presumably [Pt(Me_2SO)$_4$]$^{2+}$, with a ^{195}Pt NMR signal at −3231 ppm. This shift is actually downfield to that of *cis*-[Pt(Me_2SO)$_2Cl_2$]. One likely explanation for this result is that two of the Me_2SO ligands in [Pt(Me_2SO)$_4$]$^{2+}$ are O- rather than S-bonded. This conclusion agrees with previous binding assignments.[17] Interestingly, an attempt to prepare [Pt(Me_2SO)$_3$Cl]$^+$ in situ by adding 1 equiv of $AgNO_3$ to *cis*-[Pt(Me_2SO)$_2Cl_2$] led to only a 50:50 mixture of [Pt(Me_2SO)$_4$]$^{2+}$ and *cis*-[Pt(Me_2SO)$_2Cl_2$], as judged by ^{195}Pt NMR spectroscopy.

Discussion

The only other study of the effects of pyridine ligands on ^{195}Pt NMR shifts has been reported by Motschi et al.[15] These workers examined the system *trans*-[Pt(Xpy)(C_2H_4)Cl_2] in $CDCl_3$ at −50 °C and found a small shift dependence on pK_a such that the ^{195}Pt signal moved downfield 12 ppm as the Xpy basicity increased from 4-CN-py (pK_a = 1.9)[21] to 4-$(CH_3)_2$N-py (pK_a = 9.7).[21]

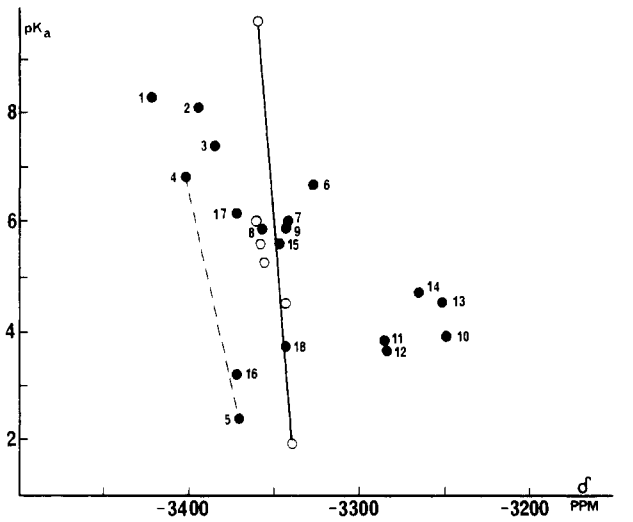

Figure 2. Plot of pK_a vs. ^{195}Pt chemical shift for the series *cis*-[Pt(Xpy)(Me_2SO)$_2$Cl]$^+$. Chemical shifts are relative to external 0.1 M $Na_2[PtCl_6]$; solution conditions are described in the Experimental Section. Open circles represent Xpy = pyridine or 4-substituted pyridines, and the line connects 4-CN-py and 4-$(CH_3)_2$N-py. Closed circles represent other substituted pyridines that are numbered as follows: (1) 2-NH_2, 6-NH_2; (2) 2-$NHCH_3$; (3) 2-NH_2, 6-CH_3; (4) 2-NH_2; (5) 2-NH_2, 5-NO_2; (6) 2-CH_3, 6-CH_3; (7) 2-*n*-C_3H_7; (8) 2-CH_3; (9) 2-C_2H_5; (10) 2-CH_3C(O); (11) 2-HC(O); (12) 2-(C_6H_5)C(O); (13) 2-C_6H_5; (14) 2-(3-thienyl); (15) 2-$HOCH_2$; (16) 2-CH_3O; (17) 3-CH_3, 5-CH_3; (18) 3-HC(O). The dashed line connects 2-NH_2-5-NO_2-py and 2-NH_2-py. See Tables I and II for ligand pK_a values.

The data we have gathered are best appreciated and interpreted on the basis of plots of pK_a vs. shift. Typical results were obtained in the series *cis*-[Pt(Xpy)(Me_2SO)$_2$Cl]$^+$ (Figure 2). In this figure, we have drawn a line between the points for 4-CN-py and 4-$(CH_3)_2$N-py.

From Figure 2, it is clear that all 4-substituted pyridine complexes fall in a narrow shift range of ca. 25 ppm. Furthermore, there is an upfield shift as the basicity of the pyridine *increases*. This result is in contrast with the one previous study in which the opposite trend was observed. This basicity vs. shift trend in Figure 2 is also found for the *cis*-[Pt(Xpy)(Me_2SO)Cl_2] and *cis*-[Pt(Xpy)$_2$(Me_2SO)Cl]$^+$ series but is opposite to that found in the *trans*-[Pt(Xpy)(Me_2SO)Cl_2] series. The trend for the latter agrees with that published previously.[15] *Again*, we emphasize that the effect of basicity here is *small*, ranging from 4 to 50 ppm in the series *trans*-[Pt(Xpy)(Me_2SO)Cl_2] and *cis*-[Pt(Xpy)$_2$(Me_2SO)Cl]$^+$, respectively. If we accept that basicity of the donor atom N has a well-defined influence, then we must attribute to steric or remote effects the observation that points for all 2- and 2,6-substituted species lie off the line in Figure 2, with the exception of the points for the 2-alkyl-py species.

Several types of 2-substituents are present in these complexes—amine groups, alkyl groups, alkoxy groups, and unsaturated groups. In Figure 2, we have also connected the points for 2-NH_2-py and 2-NH_2-5-NO_2-py. There appears to be a slightly greater dependence of shift on basicity for these compounds. The five 2-amino-substituted pyridine complexes all have shifts upfield to that expected on the basis of ligand pK_a. On this basis, we believe that 2-amino substituents have either a remote nonbonded effect or a steric effect on the shift. The ortho effect is shielding (i.e. causes an upfield shift). The point for 2-NH_2-6-NH_2-py is more shielded, and thus both −NH_2 groups are contributing to the shift. This finding, as mentioned above, is another of the pieces of evidence supporting endocyclic pyridine binding. Similarly, the signal for the 2-NH_2-6-CH_3-py complex is deshielded relative to that for 2-NH_2-py. as also found for 2-CH_3-6-CH_3-py, the 6-CH_3 group is deshielding. Since the

(20) Pregosin, P. S.; Sze, S. N.; Salvadori, P.; Lazzaroni, R. *Helv. Chim. Acta* **1977**, *60*, 2514.

(21) Perrin, D. D. "Dissociation Constants of Organic Bases in Aqueous Solution"; Butterworths: London, 1965.

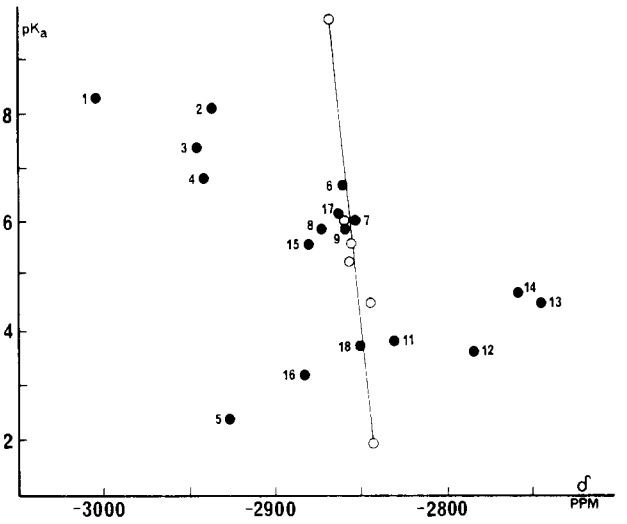

Figure 3. Plot of pK_a vs. ^{195}Pt chemical shift for the series *cis*-[Pt(Xpy)(Me_2SO)Cl_2]. Open circles represent Xpy = pyridine or 4-substituted pyridines, and the line connects 4-CN-py and 4-$(CH_3)_2$N-py. Closed circles represent other substituted pyridines. See caption for Figure 2 for the numbering scheme.

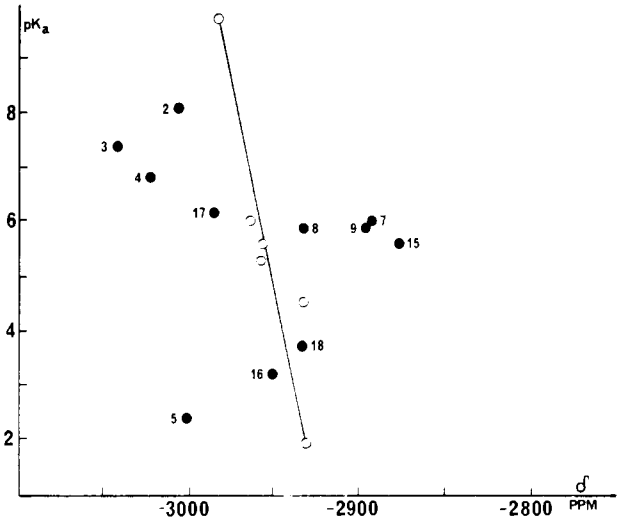

Figure 4. Plot of pK_a vs. ^{195}Pt chemical shift for the series *cis*-[Pt(Xpy)$_2$(Me_2SO)Cl]$^+$. Open circles represent Xpy = pyridine or 4-substituted pyridines, and the line connects 4-CN-py and 4-$(CH_3)_2$N-py. Closed circles represent other substituted pyridines. See caption for Figure 2 for the numbering scheme.

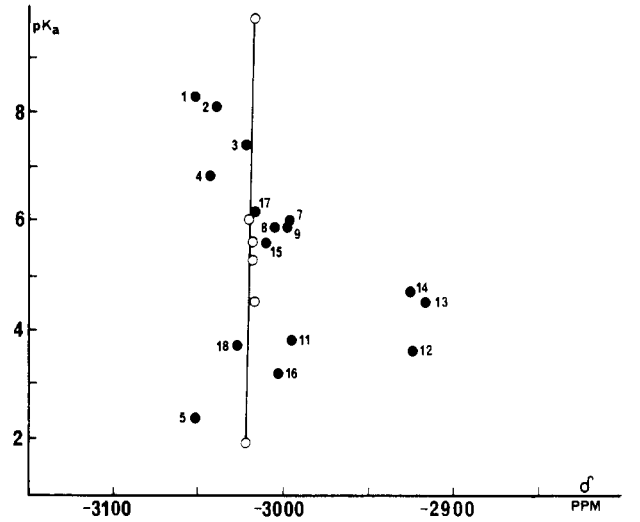

Figure 5. Plot of pK_a vs. ^{195}Pt chemical shift for the series *trans*-[Pt(Xpy)(Me_2SO)Cl_2]. Open circles represent Xpy = pyridine or 4-substituted pyridines, and the line connects 4-CN-py and 4-$(CH_3)_2$N-py. Closed circles represent other substituted pyridines. See caption for Figure 2 for the numbering scheme.

greater basicity of 2-NH_2-6-CH_3-py compared to that of 2-NH_2-py should have resulted in a slight shielding, this comparison is further evidence for endocyclic N binding.

The shifts in the *cis*-[Pt(Xpy)(Me_2SO)$_2$Cl]$^+$ series are only modestly influenced by 2-alkyl substituents. Again, since the point for 2-CH_3-6-CH_3-py is somewhat more deshielded, the alkyl substituent effect is also additive. The most consistently deshielding 2-substituents are phenyl, benzoyl, and 3-thienyl, which shift the resonance by ca. 60–90 ppm from the value expected from the line for 4-substituted pyridine compounds. The formyl group is also deshielding, but the magnitude of this effect is smaller than that of phenyl and appears to be dependent on the series being investigated (vide infra). The alkoxy substituents, $HOCH_2$ and CH_3O, have only a small effect on this series.

In anticipation of further discussion, we can establish an order for 2-substituents (shielding to deshielding) as follows: $O^- > NHR > CH_3O \sim HOCH_2 \sim CH_3 \sim C_2H_5 \sim n\text{-}C_3H_7 > HC(O) > (C_6H_5)C(O) \sim$ 3-thienyl $> C_6H_5$. This order applies almost unchanged to the series *cis*-[Pt(Xpy)(Me_2SO)Cl_2] (Figure 3). Relative to the line, the 2-formyl group is still deshielding but much less so than the 2-phenyl group. In addition, the 2-alkyl compounds have almost no effect, and 2-methyl may actually be shielding (but the effect, if real, is very small). The 2-amino group is even more shielding than in the *cis*-[Pt(Xpy)(Me_2SO)$_2$Cl]$^+$ series. However, the position of the line for the 4-substituted species in Figure 3 is simply in a different position relative to the above 2-substituent-effect trend as compared to the *cis*-[Pt(Xpy)(Me_2SO)$_2$Cl]$^+$ series (Figure 2). Similarly, in the *cis*-[Pt(Xpy)$_2$(Me_2SO)Cl]$^+$ series (Figure 4), the same trends hold but with the "pK_a line" being somewhat more shielding than in the other two cis series.

The general remote effect found for the different 2-substituents also holds for the *trans*-[Pt(Xpy)(Me_2SO)Cl_2] series (Figure 5). *However*, the dependence in donor group basicity is very small and opposite to that of the three cis series. Furthermore, the effects across the series 2-NH_2 → 2-C_6H_5 are smaller than in the three cis series.

The deshielding effect of substituting H by CH_3, CH_3 by CH_2CH_3, etc. has been observed for both N and P ligands.[1] It has been stated, "There is no clear suggestion connecting chemical shift theory to this observation...".[1] It was concluded that such effects could be applied empirically without a fundamental knowledge of theory. It was implied that an adequate theoretical description is unlikely to be available for such large atoms in the forseeable future.[1]

Our demonstration here that amino groups are unusual in inducing upfield shifts shifts suggests that the origin of the 40 ppm "rule of thumb" for assigning Pt binding sites to N1 or N7 for adenine derivative could be a consequence of the ortho effect of the amino substituent for the Ni-bound species. For guanine derivatives, the situation is more complex. the difference in N basicity (N1 vs. N7) for adenine can be estimated to be ca. 6 pK_a units.[22] This difference is similar, ca. 7 pK_a units, for guanine. However, there is an oxo group ortho to N1 in guanine derivatives. We made an attempt to evaluate the effect of an oxygen at the 2-position by examining the effects of 2-OH-py under basic conditions (1 equiv of triethylamine added). The O^- group is shielding about as strongly as the NH_2 group in the two series where a compound could be tentatively identified (Table II). However, an extrapolation of this result to purines and pyrimidines may be unwarranted for two reasons: First, the CO bond is essentially a double bond in the latter compounds but has only partial double-bond character in 2-O-py$^-$.[23] Second, 2-O-py$^-$ is charged and we have no means for allowing for charge in this

(22) Martin, R. B. *Acc. Chem. Res.* **1985**, *18*, 32.
(23) See: Hollis, L. S.; Lippard, S. J. *Inorg. Chem.* **1983**, *22*, 2708. This article contains an excellent discussion of the nature of the CO bond in platinum complexes of 2-OH-py.

study. Furthermore, the evidence that we have identified the correct geometry for this species is circumstantial at best since we cannot allow for the charge and did not observe the sequential formation of *trans*- and then *cis*-$[Pt(Xpy)(Me_2SO)Cl_2]$.

Further studies are needed to evaluate the effects of ortho oxo groups and charge on ^{195}Pt NMR shifts. Also, since the effects of the nonvaried ligands on Pt may modulate the effects of the heterocyclic N-donor ligands on the ^{195}Pt NMR shifts, several additional series need to be investigated to confirm the generality of the nonbonded effects on shifts reported here.

Acknowledgment. We thank the NIH for support through Grant GM 29222 and Matthey Bishop, Inc., for a loan of $K_2[PtCl_4]$. We also thank the NSF for partial support of the purchase of the 360-MHz spectrometer and the EURC for partial support.

Contribution from the Department of Chemistry,
Brown University, Providence, Rhode Island 02912

Application of ^{59}Co NMR to Cobalt(III) Porphyrins. Linear Relationship between ^{59}Co and ^{57}Fe Chemical Shifts

Karen I. Hagen, Catherine M. Schwab, John O. Edwards,* and Dwight A. Sweigart[1]

Received October 28, 1985

The ^{59}Co NMR spectra have been recorded for various cobalt(III) complexes: $Co(NH_3)_5L^{3+}$ and $Co(por)L_2^+$, where L = imidazole (HIm), *N*-methylimidazole (MeIm), pyridine, and ammonia and por = dianion of tetraphenylporphyrin (TPP) and octaethylporphyrin (OEP). Chemical shift and line width data suggest that ammonia, imidazole, and porphyrin ligands are very close in the spectrochemical series. It seems that ^{59}Co NMR is more sensitive than optical spectroscopy for placing ligands in the spectrochemical series and should prove useful for predicting d-d excitation energies for complexes in which allowed bands obscure these transitions. Hydrogen bonding by axial imidazole in $Co(por)(HIm)_2^+$ to solvent or external base influences the chemical shift and line width. A linear correlation between ^{59}Co and ^{57}Fe chemical shifts is postulated that depends on a simplified Ramsey equation in which the chemical shift is determined principally by the lowest energy d-d excitation; this correlation may be useful for predicting ^{57}Fe chemical shifts in iron(II) porphyrins and other iron complexes. Two shiftability ratios (0.57 for Fe/Co and 1.16 for Mo/V) have been estimated.

NMR on the iron nucleus is a difficult and tedious task because the only naturally occurring isotope with a nonzero spin, ^{57}Fe ($I = {}^1/_2$, 2.19% abundance), has a very low receptivity and long relaxation time. Accordingly, there are few data on ^{57}Fe chemical shifts in the literature. Cobalt, on the other hand, exists as 100% ^{59}Co ($I = {}^7/_2$; $Q = 0.40$ b) and has a receptivity 4×10^5 times larger than for iron. Therefore, ^{59}Co NMR is easily performed and a considerable volume of data exists.[2-4] In this paper we show that the ^{57}Fe chemical shift in a given complex can be predicted from the ^{59}Co chemical shift in the corresponding isoelectronic cobalt complex. This discovery should prove to be of significance in a number of areas of iron chemistry, including iron porphyrins and proteins.

The present study has two purposes. In one, we investigated the ^{59}Co NMR of cobalt(III) porphyrins with a variety of axial ligands in the hope of learning about hydrogen bonding to/from the axial ligands. Such hydrogen bonding is known[5-8] to influence stability constants, reactivities, and redox potentials of simple iron porphyrins. Similarly, hydrogen bonding from the distal histidine in Hb and Mb is known[9-11] to affect O_2 binding and stability to autoxidation. Hydrogen bonding from the metal-bound proximal histidine is thought[12] to provide a mechanism by which some heme proteins can modulate their metal-centered redox potentials.

The second purpose of this study is related to the NMR of cobalt and iron compounds. Cobalt porphyrins under proper circumstances can be good model systems to learn about iron porphyrin behavior; cobalt(III) is isoelectronic with iron(II) and has the same charge as iron(III). It was felt that a study of ^{59}Co NMR in ammine and porphyrin complexes, particularly ones with axial imidazole ligands, would provide information about metal-ligand interactions that could be transferred to the iron systems. To the best of our knowledge, no ^{59}Co NMR studies of porphyrins have been made. Herein we present data for a variety of cobalt ammine and porphyrin complexes and discuss the observed variations in ^{59}Co chemical shifts and line widths in a variety of solvent compositions. Possible hydrogen-bonding effects are discussed, as is the feasibility of using ^{59}Co data to predict ^{57}Fe chemical shifts.

Experimental Section

Materials. Starting compounds for syntheses such as Co(TPP) (Midcentury) and Co(OEP) (Aldrich) were used as obtained. Solvents and CF_3SO_3H were distilled before use. Imidazole (Aldrich) was vacuum sublimed and *N*-methylimidazole (Aldrich) was distilled prior to use.

Preparations. Pentaammine complexes were generally prepared according to the method of Dixon et al.[13] Preparations of cobalt(III) porphyrins with axial ligands normally followed published procedures.[8,14] Perchlorate complexes were converted to the tetraphenylborates by dissolving them along with an excess of $NaBPh_4$ in THF and stirring several hours. The THF was evaporated and the residue washed with water to remove $NaClO_4$ and remaining $NaBPh_4$. The residue was dissolved

(1) Recipient NIH Research Career Development Award, 1983-1988.
(2) Kidd, R. G.; Goodfellow, R. J. In "NMR and the Periodic Table"; Harris, R. K.; Mann, B. E., Eds.; Academic Press: New York, 1978; pp 225-244.
(3) Kidd, R. G. *Annu. Rep. NMR Spectrosc.* **1980**, *10A*, 1.
(4) Laszlo, P. In "NMR of Newly Accessible Nuclei"; Laszlo, P., Ed.; Academic Press: New York, 1983; Vol. 2, pp 253-274.
(5) Walker, F. A.; Lo, M. W.; Ree, M. T. *J. Am. Chem. Soc.* **1976**, *98*, 5552.
(6) (a) Meng, Q.; Tondreau, G. A.; Edwards, J. O.; Sweigart, D. A. *J. Chem. Soc., Dalton Trans.* **1985**, 2269. (b) Jones, J. G.; Tondreau, G. A.; Edwards, J. O.; Sweigart, D. A. *Inorg. Chem.* **1985**, *24*, 296. (c) Tondreau, G. A.; Sweigart, D. A. *Inorg. Chem.* **1984**, *23*, 1060. (d) Doeff, M. M.; Sweigart, D. A. *Inorg. Chem.* **1982**, *21*, 3699.
(7) Stanford, M. A.; Swartz, J. C.; Phillips, T. E.; Hoffman, B. M. *J. Am. Chem. Soc.* **1980**, *102*, 4492.
(8) Balch, A. L.; Watkins, J. J.; Doonan, D. J. *Inorg. Chem.* **1979**, *18*, 1228.
(9) (a) Phillips, S. E. V.; Scheonborn, B. P. *Nature (London)* **1981**, *292*, 81. (b) Shaanan, B. *Nature (London)* **1982**, *296*, 683.
(10) Mims, M. P.; Porras, A. G.; Olson, J. S.; Noble, R. W.; Peterson, J. A. *J. Biol. Chem.* **1983**, *258*, 14219.
(11) Jameson, G. B.; Drago, R. S. *J. Am. Chem. Soc.* **1985**, *107*, 3017.
(12) O'Brien, P.; Sweigart, D. A. *Inorg. Chem.* **1985**, *24*, 1405 and references therein.
(13) Dixon, N. E.; Jackson, W. G.; Lancaster, M. J.; Lawrance, G. A.; Sargeson, A. M. *Inorg. Chem.* **1981**, *20*, 470.
(14) Sugimoto, H.; Ueda, N.; Mori, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3425.

0020-1669/86/1325-0978$01.50/0