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Technetium-99 NMR Spectroscopy: Chemical Shift Trends and Long Range Coupling Effects

LYNNE A. O'CONNELL, RONALD M. PEARLSTEIN, ALAN DAVISON*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139 (U.S.A.)

JOHN R. THORNBACK, JAMES F. KRONAUGE and ALUN G. JONES

Department of Radiology, Harvard Medical School and Brigham and Women's Hospital, Boston, MA 02115 (U.S.A.)

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Abstract

Values for the chemical shifts and linewidths of a variety of technetium compounds in oxidation states V, III and I were measured. Correlations between the shift and oxidation state, ligand field strength and shielding effects for these, and other previously measured compounds, are discussed. An extensive series of substituted hexakis(isonitrile)technetium(I) compounds was studied which exhibits a chemical shift range of over 75 ppm. Studies of coupling between ^{99}Tc and other nuclei, including four-bond, long range ^{99}Tc–^{1}H coupling, are described.

Introduction

Interest in the synthesis of technetium compounds has been sparked and sustained by their use in diagnostic nuclear medicine. As a result, knowledge of the coordination chemistry of this element has expanded which has inspired further exploration into its inorganic chemistry. While conventional spectroscopic methods have been employed in studying technetium complexes, recently we have investigated the use of a lesser known tool, that of ^{99}Tc NMR spectroscopy. Due to the high sensitivity of the ^{99}Tc nucleus (it is the fifth most sensitive nucleus) [1], data acquisition is relatively simple and fast. The phenomenon of ^{99}Tc nuclear magnetic resonance was first extensively explored by Lock and co-workers who reported the resonances and linewidths of several Tc(VII) compounds as well as a Tc(V), a Tc(III) and a Tc(I) compound [2]. More recently, Wahren and co-workers measured a series of Tc(I) compounds [3]. The following account compiles ^{99}Tc NMR data on these and a number of other compounds which we have studied and discusses some of the trends that have become apparent to us during our investigations. The results of studies of compounds which exhibit coupling between the ^{99}Tc nucleus and other nuclei are also discussed.

Experimental

Caution: ^{99}Tc is a β^- emitter ($t_{1/2} = 2.1 \times 10^5$ y). All manipulations of solutions and solids were performed in a laboratory approved for the handling of radioisotopes using precautions outlined elsewhere [4].

The complexes $[TcO_2(py)_4]Cl$ [5], $[TcO_2(en)_2]Cl$ [6], $[TcO_2(im)_4]Cl$ (im = imidazole) [7], $Na[TcO(eg)_2]$ (eg = ethylene glycol) [8], $Bu_4N[TcOCl_4]$ [9], $Tc(CO)(PMe_2Ph)_3Cl_3$ [10], $[Tc(CNCMe_3)_6X](PF_6)_2$, $[Tc(CNCMe_3)_5(CN)X]PF_6$ (X = Cl, Br) [11], $[Tc(CNR)_6](PF_6)$ [12], were prepared by literature methods. The isocyanide ligands were either commercially available or synthesized by reported methods [13]. A sample of $[Tc(CNCH_2CMe_2OMe)_6](PF_6)$ and the ammonium pertechnetate used for this study were the gift of DuPont Biomedical Products.

All ^{99}Tc NMR spectra were recorded using either a Varian XL-300, XL-400 or VXR-500 spectrometer. The primary reference ($[NH_4][^{99}TcO_4]$ in D_2O = 0 ppm) resonates at 67.516, 90.025 and 112.508 MHz, respectively, in these spectrometers. The pulse width necessary to obtain a 90° tip angle was determined for each instrument for an aqueous solution of $NH_4[TcO_4]$. No relaxation delay in addition to the acquisition time was employed unless TcO_4^- (T_1 = 0.1 s) [2, 14] was present. For differences greater than the maximum spectral width (10^5 Hz) obtainable, chemical shifts could be calculated based on the spectrometer frequency, transmitter offset, transmitter base offset, and relative shift within the spectral window. We estimate that the error associated with these values is ±2 ppm. The $^{1}H\{^{99}Tc\}$ spectrum was obtained with use of the synthesizer on the Varian VXR-500 instrument to provide single-frequency excitation of the technetium nucleus.

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*Author to whom correspondence should be addressed.

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The presence of spectral folding or other artifacts was ruled out by changing the transmitter offset by a known frequency and verifying that the resonance moved within the spectral window by the appropriate amount and in the expected direction.

The variable temperature ^1H spectra were obtained on the Varian XL-300 instrument and were referenced to the resonance of the residual protons in the deuterated solvent. The ^{31}P spectrum was obtained on the Varian VXR-500 instrument and was referenced to PPh_3 present as a secondary, internal standard.

Results and Discussion

Table 1 lists the chemical shifts of the compounds which we have measured as well as those which are representative of the five oxidation states: 0, I, III, V and VII. One of the first things to be noted from this list is the extremely wide range over which these shifts extend, the highest being 5500 ppm and the lowest −3672 ppm with the shift of TcO_4^- being the reference at zero. Secondly, it is possible to group compounds of the same oxidation state in smaller ranges of chemical shift values as seen in Fig. 1. This trend, where the ^{99}Tc NMR resonance correlates to the oxidation state of the metal, is consistent among all the compounds we have studied with the exception of the Tc(VII) compounds, which presumably deviate due to the lack of electrons in their valence d orbitals. The chemical shifts decrease monotonically on reducing the formal oxidation state from Tc(V) to Tc(I), hence the shielding must correspondingly increase. According to molecular orbital theory, the paramagnetic contribution to shielding is directly proportional to $\langle r^{-3}\rangle$ and inversely proportional to ΔE, where r is the radius of the valence orbitals and ΔE is an averaged excitation energy [16]. Thus, the correlation between oxidation state and chemical shift is likely due to the increasing diffuseness of orbitals, with concomitant reduction in $\langle r^{-3}\rangle$, as the formal oxidation state is lowered. In addition, the resonance is sensitive to electronic effects of the ligands, such as ligand field strength, as demonstrated by the significant decrease in chemical shift on substituting the strong-field ligand cyanide $\{[TcO_2(CN)_4]^{3-}$, δ 806$\}$ for the moderate-field nitrogen base $\{[TcO_2(py)_4]^+$, δ 2881$\}$. Another oxotechnetium(V) complex, $[TcOCl_4]^-$, has an even higher chemical shift of ≈5000 ppm which is consistent with the weak ligand field strength of the chloride ligand.

The chemical shifts of the hexakis(isonitrile)Tc(I) mono-cations, $Tc(CNR)_6^+$, have been compiled separately in Table 2. These compounds exhibit relatively small, though significant, chemical shift differences which must be due to local diamagnetic and neighboring group anisotropic shielding effects. For instance, the arylisonitrile derivatives are appreciably deshielded relative to all of the alkylisonitrile examples, possibly due to ring currents induced in the aryl rings.

TABLE 1. Summary of Selected ^{99}Tc NMR Data[a]

Compounds	Chemical shift (ppm)	Linewidth (Hz)	Reference
TcO_4^-	0 (D_2O)	2.7	2, 14
TcO_2F_3	396.3 (HF)	375	2
TcH_9^{2-}	−3672 (40% KOH/H_2O)	22	2
$TcO_2(CN)_4^{3-}$	806 (D_2O)	642	2
$TcO_2(en)_2^+$	2410 (D_2O)	3500	b
$TcO_2(im)_4^+$	2904 (CD_3OD)	10000	b
$TcO_2(py)_4^+$	2881 (CH_3OD)	12000	b
$TcOCl_4^-$	5501 (CH_3OD)	20000	b
	4695 (CD_2Cl_2)	10000	b
$TcO(eg)_2^-$	1904 (CH_3OD)	19000	b
$Tc(CO)(P(CH_3)_2Ph)_3Cl_3$	−78 ($CDCl_3$)	570	b
$Tc(CNC(CH_3)_3)_6Br^{2+}$	−879 (CD_3CN)	10000	b
$Tc(CNC(CH_3)_3)_5(CN)Br^+$	−899 (CD_3CN)	8000	b
$Tc(CNC(CH_3)_3)_6Cl^{2+}$	−934 (CD_3CN)	5000	b
$Tc(CNC(CH_3)_3)_5(CN)Cl^+$	−324 (CD_3CN)	5000	b
$Tc(CN)_7^{4-}$	−1329	5000	2
$TcBr(CO)_3(PPh_3)_2$	−1460 (CD_2Cl_2)	3300	3
$Tc(CNC(CH_3)_3)_6^+$	−1914 ($CDCl_3$)	70	2
$Tc(dmpe)_3^+$	−1854 ($CDCl_3$)	<40	15
$Tc(P(OCH_3)_3)_6^+$	−1658 ($CDCl_3$)	<40	15
$Tc(CO)_3(CH_3CN)(dppe)^+$	−3517 (CD_2Cl_2)	2000	3

[a] Values are reported with respect to TcO_4^- as the reference at 0 ppm. The solvent used to obtain the spectrum is indicated in parentheses. [b] This work.

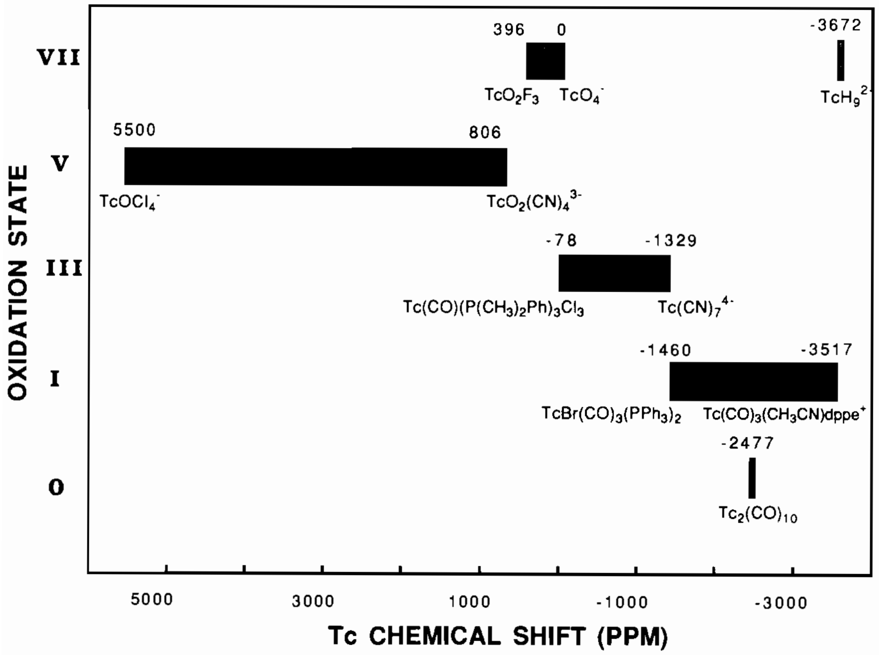

Fig. 1. Graphical representation of the correlation between the ^{99}Tc NMR chemical shift and the oxidation state of technetium in the compound.

TABLE 2. ^{99}Tc NMR Data for $Tc(CNR)_6^+$ Compounds[a]

R	Chemical shift (ppm)
CH_3[b]	−2.5
CH_2CH_3[c]	−2.4
$(CH_2)_2CH_3$[c]	−14.7
$CH(CH_3)_2$c	−1.5
$CH_2(CH(CH_3)_2)$[c]	−24.8
$C(CH_3)_3$[c]	0
$(CH_2)_4CH_3$[c]	−16.3
C_6H_{12}[c]	−24.8
$C(CH_3)_2CH_2C(CH_3)_2CH_3$[c]	−30.8
C_6H_5[c]	+24.7
$C_6H_3(CH_3)_2$[c]	+20.4
$CH_2C(O)OCH_3$[d]	−22.3
$CH_2C(O)OCH_2CH_3$[d]	−21.9
$CH_2C(O)O(CH_2)_2CH_3$[d]	−21.8
$CH_2C(O)OCH(CH_3)_2$[d]	−22.5
$CH_2C(O)O(CH_2)_3CH_3$[d]	−21.7
$CH_2C(O)OCH_2CH(CH_3)_2$[d]	−21.9
$CH_2C(O)OC(CH_3)_3$[d]	−21.9
$CH(CH_3)C(O)OCH_3$[d]	−22.4
$CH_2CH_2C(O)OCH_3$[d]	−15.8
$CH_2CH_2C(O)ONHCH_3$[d]	−18.8
$C(CH_3)_2C(O)OCH_3$[d]	−22.6
$C(CH_3)_2C(O)OH$[d]	−22.6
$CH(CH_2CH_3)C(O)OCH_3$[d]	−38.2
$CH(CH_2CH_3)C(O)ONHCH_3$[d]	−33.7
$CH(CH_3)CH_2C(O)OCH_3$[d]	−18.5
$CH(CH_3)CH_2C(O)ONHCH_3$[d]	−16.9
$CH_2CH(CH_3)C(O)OCH_3$[d]	−25.9
$CH(CH(CH_3)_2)C(O)OCH_3$[d]	−49.8
$CH(C(O)OCH_3)(CH_2C(O)OCH_3)$[d]	−34.2
$CH_2C(CH_3)_2OCH_3$[c]	−36.3

[a] Values are reported with respect to $[Tc(CNCMe_3)_6]PF_6$ as the reference at 0 ppm. Solvents used to obtain the spectra are [b] CD_3OD, [c] $CDCl_3$, [d] 50% $EtOH/D_2O$ with $CDCl_3$ as an external lock standard.

The linewidths of the ^{99}Tc NMR signals are also reported in Table 1. As can be seen from these values, the linewidths of the signals vary over a wide range. As would be anticipated for a quadrupolar nucleus, the more symmetric molecules produce very sharp lines, as in TcO_4^- (~3 Hz) or $Tc(CNCMe_3)_6^+$ (70 Hz), while a molecule of lower symmetry produces a very broad signal, as in $Tc(CNCMe_3)_6Br^{2+}$ (10 000 Hz).

Previously, we and others reported our findings with regard to coupling between the ^{99}Tc nucleus and the six equivalent ^{31}P nuclei in $Tc(dmpe)_3^+$ [15, 17]. We have seen similar coupling between technetium and three equivalent phosphorus nuclei in the seven coordinate, Tc(III) compound, $Tc(CO)(PMe_2Ph)_3Cl_3$, where the resulting signal is a quartet with a coupling constant of 700 Hz (see Fig. 2). The ^{31}P NMR spectrum of this compound displays a broad, flat signal centered at 31 ppm (relative to 85% H_3PO_4) and having a width of ≈5800 Hz (see Fig. 3). A ten line ^{31}P spectrum is expected if the technetium and

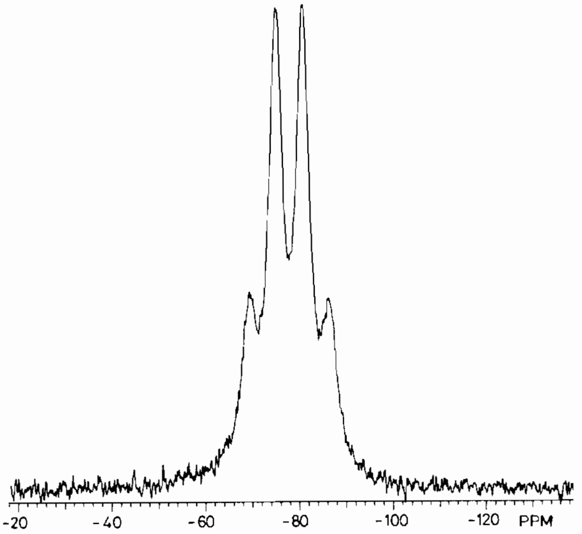

Fig. 2. The ^{99}Tc NMR spectrum (300 MHz) of Tc(CO)-($PMe_2Ph)_3Cl_3$ performed in $CDCl_3$ (referenced with respect to TcO_4^-).

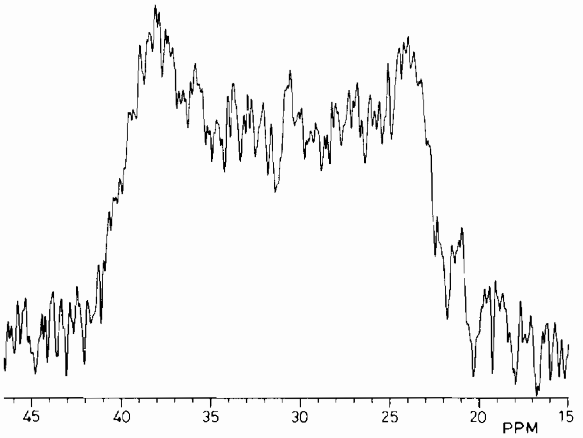

Fig. 3. The ^{31}P NMR spectrum (300 MHz) of Tc(CO)-($PMe_2Ph)_3Cl_3$ performed in $CDCl_3$. Value reported with respect to 85% H_3PO_4.

phosphorus are coupled due to the spin of 9/2 of ^{99}Tc, as has been seen in Tc(dmpe)$_3^+$; however, in the case of Tc(CO)($PMe_2Ph)_3Cl_3$, the splitting is not sufficiently resolved.

We have also seen a broad, flat signal in the ^{1}H NMR of [Tc(CNMe)$_6$]PF$_6$ which is centered at 3.32 ppm and has a width of 34 Hz; however, no coupling is evident in the ^{99}Tc NMR spectrum. Lock and co-workers reported ^{99}Tc–^{1}H coupling in TcH_9^{2-} which is evident in both spectra and has a coupling constant of 24 Hz [2]. To determine whether or not the proton signal for Tc(CNMe)$_6^+$ was due to four-bond ^{99}Tc–^{1}H coupling, variable temperature NMR experiments were performed (see Fig. 4). Theoretical treatments of coupling between quadrupolar nuclei and protons have been carried out elsewhere, and the following relationship is evoked:

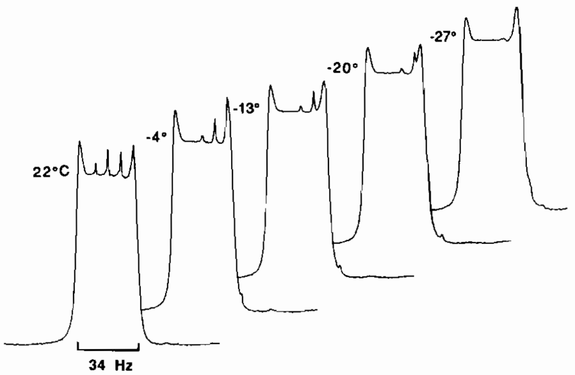

Fig. 4. Variable temperature proton NMR spectra (300 MHz) of Tc(CNMe)$_6^+$ in acetone-d$_6$.

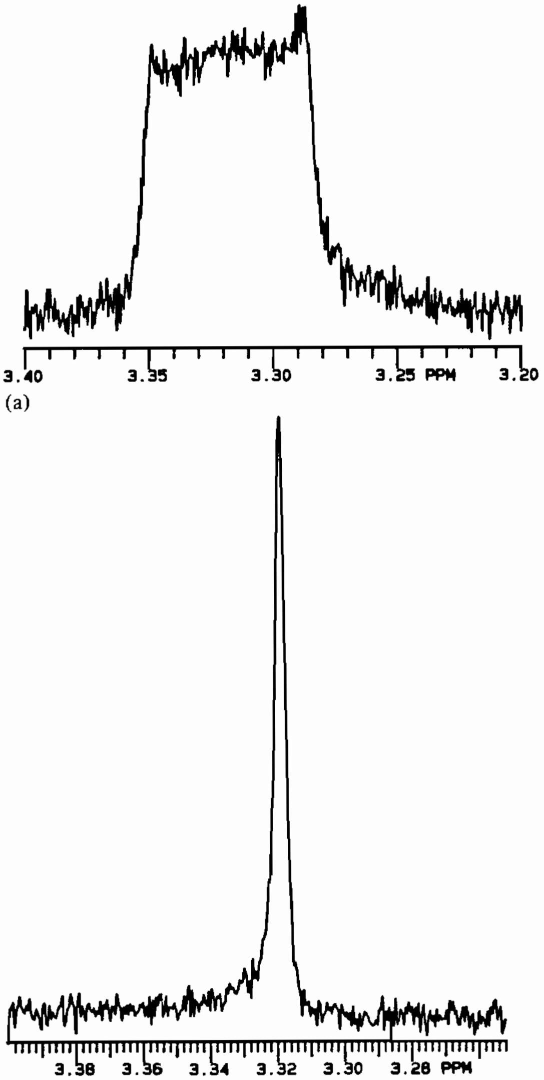

Fig. 5. (a) Proton NMR spectrum of Tc(CNMe)$_6^+$ showing ^{99}Tc–^{1}H coupling effects. (b) Proton NMR spectrum of Tc(CNMe)$_6^+$ where the signal has been decoupled from the ^{99}Tc nucleus. Both spectra were obtained in acetone-d$_6$.

$$\Delta\nu \approx \frac{1}{T_{1X}}$$

$$\frac{1}{T_{1X}} \propto \tau_c = \frac{4\pi a^3 \eta}{3kT}$$

where $\Delta\nu$ is the linewidth, $1/T_{1X}$ represents the relaxation rate, τ_c is the correlation time, η is viscosity, a is the radius of the molecule and T is temperature [18]. Thus, when the temperature is sufficiently decreased which, in the case of most solvents, also increases the viscosity, the relaxation rate will increase to the extent that the nuclei are effectively decoupled. While the resolution of the splitting in these spectra, presumably due to the ^{99}Tc—^{1}H coupling, begins to disappear with lowering of temperature, the ^{1}H signal does not completely collapse to a singlet. Lower temperature spectra were not obtained due to the movement of a water resonance which obscures the $Tc(CNMe)_6^+$ signal below −35 °C. An experiment was then carried out where a ^{99}Tc decoupled proton NMR spectrum was obtained (Fig. 5). In this case, the broad signal does collapse completely to a singlet showing unambiguously that long range ^{99}Tc—^{1}H coupling is present in this compound; however, the coupling constant is small enough (in the order of 4 Hz) that the splitting in the ^{99}Tc NMR spectrum, where the linewidth is 63 Hz, cannot be resolved.

Conclusions

Our investigations of ^{99}Tc NMR spectroscopy have resulted in a compilation of a number of characteristic resonances and linewidths for a wide variety of compounds. More important, however, are the trends which have been uncovered during this compilation which will aid in the identification and characterization of future technetium complexes. The relatively large chemical shift differences reported herein for the various hexakis(alkylisonitrile) cations make ^{99}Tc NMR spectroscopy a useful tool for the study of metabolic activity for this important class of radiopharmaceutical complexes [19]. In addition, the long range technetium—proton coupling seen in the methylisonitrile compound suggests the potential of ^{99}Tc NMR spectroscopy in illuminating the mode of technetium coordination to proteins and other biologically relevant molecules.

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