

Mixed-ligand Complexes of Technetium.

IV. Cationic, Hexa-coordinated Tc(I) Complexes with Two Different Isocyanide Ligands in the Coordination Sphere, $[\text{Tc}(\text{R}^1\text{NC})_k(\text{R}^2\text{NC})_{6-k}]^+$ ($k = 0-6$)*

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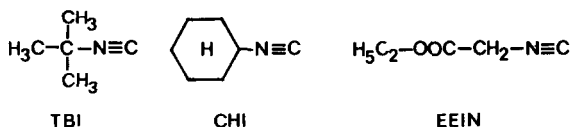
Stimulated by the fact that $^{99\text{m}}\text{Tc}$ (γ -emitter, half-life $t_{1/2} = 6$ h) is one of the most important isotopes in diagnostic nuclear medicine [2, 3], interest in the chemistry of the first man-made element has increased in recent years [4–6]. Most of these chemical studies have been undertaken with the long-lived isotope ^{99}Tc (weak β^- -emitter, $t_{1/2} = 2.15 \times 10^5$ y) which is available in macroscopic amounts from fission products and can be handled with conventional chemical techniques. If working with milligram samples, the weak β^- -emission of ^{99}Tc is retained on the glass walls. Secondary X-rays (bremsstrahlung) only become important if manipulating ^{99}Tc in quantities >20 mg.

During the last few years a number of hexakis-(alkylisocyanide) complexes of technetium(I) have been synthesized and characterized [7–9]. Some of these compounds (especially the t-butylisocyanide complex) possess potential as myocardial imaging agents if prepared with $^{99\text{m}}\text{Tc}$ [10, 11]. More recently, better results in terms of biological behaviour have been obtained using isocyanides (RNC), the carbon skeletons of which contain an ether or ester group [12, 13]. Up to now, no attempts have been undertaken to prepare isocyanide technetium(I) complexes with differently substituted ligands. With such coordination compounds a stepwise variation of the lipophilic and polar properties of a potential radiopharmakon should be possible.

In this paper, we report the synthesis and ^{99}Tc NMR characterization of prototype mixed-ligand complexes of the general formula $[\text{Tc}(\text{R}^1\text{NC})_k(\text{R}^2\text{NC})_{6-k}]^+$, where R^1 and R^2 may be t-butyl, cyclohexyl or (ethoxycarbonyl)methyl (see Scheme).

Experimental

The ligands were synthesized following a literature procedure [14]. Homoleptic hexakis(alkylisocyanide)technetium(I) complexes were prepared by ligand-exchange reactions starting from $[\text{Tc}(\text{tu})_6]\text{Cl}_3$, as described by Abrams *et al.* [8]. The products were isolated as hexafluorophosphate (TBI, CHI) and tetraphenylborate (EEIN) salts, respectively, and characterized by their infrared spectra and melting points [7, 9].



$[\text{Tc}(\text{R}^1\text{NC})_k(\text{R}^2\text{NC})_{6-k}]^+$ complex mixtures have been obtained by refluxing 36 mg $[\text{Tc}(\text{tu})_6]\text{Cl}_3 \cdot 4\text{H}_2\text{O}$ (50 μmol) in 50 ml methanol with a 100-fold excess of mixtures of two isocyanides (molar ratios 3:1, 1:1, 1:3). After 2 h the volume was reduced to 5 ml and addition of a saturated aqueous NaBPh_4 solution resulted in precipitation of a brownish solid which was separated by centrifugation. This precipitate contained all of the initial radioactivity. It was dissolved in CH_2Cl_2 , filtered and reprecipitated by addition of ether. The product is soluble in polar organic solvents and was used for the ^{99}Tc NMR experiments without further purification.

Infrared spectra were recorded on KBr pellets on a UR 20 spectrometer (Carl-Zeiss-Jena). ^{99}Tc NMR spectra were obtained at room temperature on a Bruker AM-250 spectrometer with a magnetic field strength of 5.87 T. A broad band probe head was used. The resonance frequency of ^{99}Tc was found at 56.30 MHz. As external standard a solution of NaTcO_4 in D_2O was used.

Results and Discussion

With ^{99}Tc NMR spectroscopy (^{99}Tc , nuclear spin $I = 9/2$; receptivity relative to natural abundance ^{13}C , 2134 [15]) an excellent analytical method is given for investigations on highly symmetric diamagnetic technetium complexes for which small linewidths can be obtained (in the range <100 Hz) [16–22]. For the homoleptic hexakis(alkylisocyanide)technetium(I) complexes, $[\text{Tc}(\text{RNC})_6]^+$, only single, narrow ^{99}Tc NMR signals can be observed corresponding to the O_h symmetry of the $\text{Tc}-(\text{C})_6$ coordination sphere and the d^6 configuration of $\text{Tc}(\text{I})$ (See Fig. 1). Their chemical shifts range between -1800 and -1840 ppm versus TcO_4^- . This strong upfield shift seems to be typical for $\text{Tc}(\text{I})$

*For Part III, see ref. 1.

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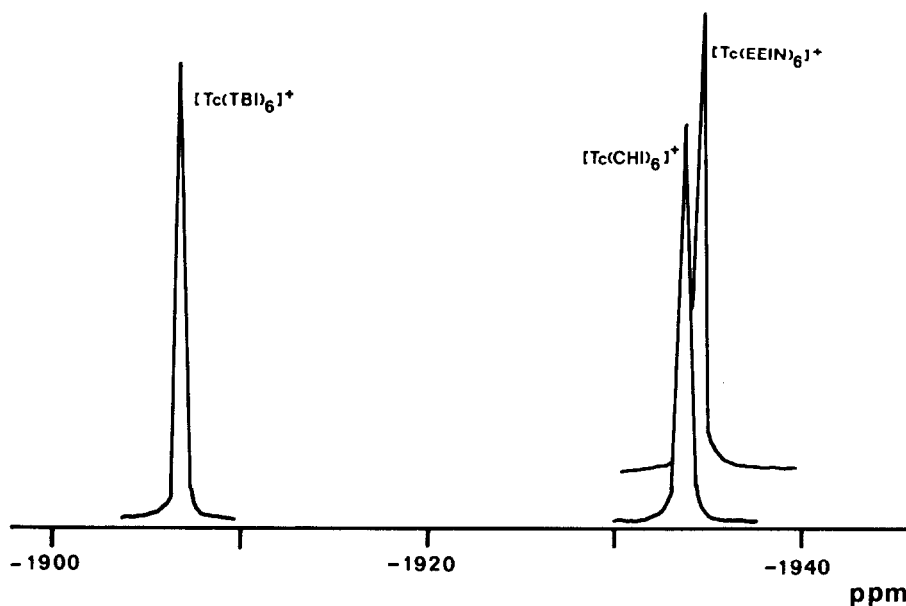


Fig. 1. ^{99}Tc NMR spectra of homoleptic $[\text{Tc}(\text{RNC})_6]^+$ complexes (measured in CDCl_2 at $T = 295\text{ K}$).

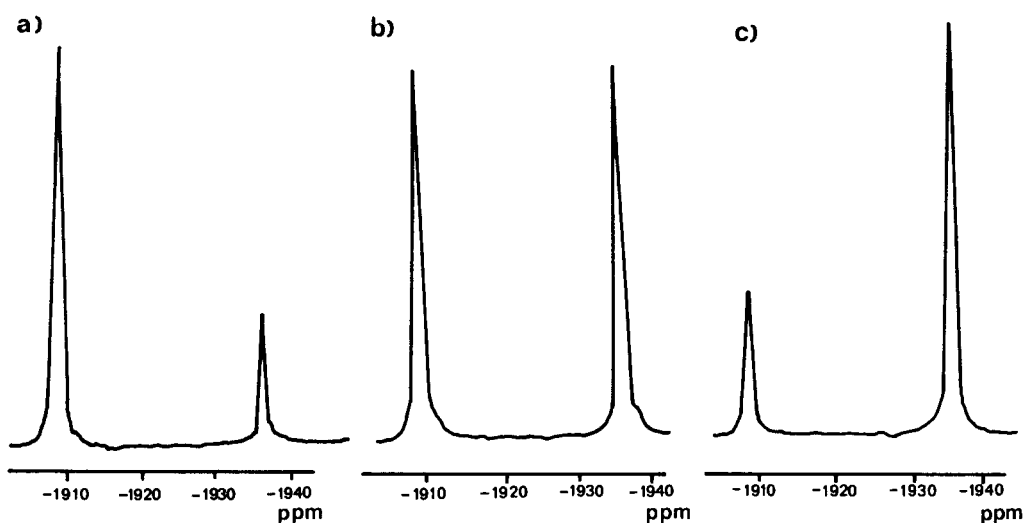


Fig. 2. ^{99}Tc NMR monitoring of attempted ligand exchange reactions between $[\text{Tc}(\text{TBI})_6]^+$ and $[\text{Tc}(\text{CHI})_6]^+$ (initial $[\text{Tc}(\text{TBI})_6]^+ / [\text{Tc}(\text{CHI})_6]^+$ ratios: (a) 3:1; (b) 1:1; (c) 1:3).

complexes with π -acceptor ligands [16, 19, 20, 22]. Couplings due to ^{13}C nuclei (^{13}C , $I = 1/2$) of the ligands cannot be expected because of the low natural abundance (1.1%) of this isotope. For coordinated Tc–phosphine and Tc–phosphite complexes, however, ^{99}Tc – ^{31}P couplings in the magnitude of 500–900 Hz could be observed [18, 21, 22].

The chemical shift differences between $[\text{Tc}(\text{TBI})_6]^+$ and $[\text{Tc}(\text{CHI})_6]^+$ or $[\text{Tc}(\text{EEIN})_6]^+$ (about 30 ppm) allow a reasonable method for the detection of mixed-ligand complexes of the type $[\text{Tc}(\text{R}^1\text{NC})_k(\text{R}^2\text{NC})_{6-k}]^+$ if their preparation is pos-

sible. We undertook three experiments for the preparation of such compounds.

First, we refluxed equimolar amounts of $[\text{Tc}(\text{TBI})_6]\text{PF}_6$ and $[\text{Tc}(\text{CHI})_6]\text{PF}_6$ or $[\text{Tc}(\text{EEIN})_6]\text{BPh}_4$ for 5 h in acetone. The ^{99}Tc NMR spectra are illustrated in Fig. 2. Only the starting materials could be detected. The fact that the starting compounds are preserved in their initial ratios and that the relative signal intensity does not decrease, confirms that ligand exchange reactions or redox processes occur.

Secondly, a 50 μmol sample of $[\text{Tc}(\text{TBI})_6]\text{PF}_6$ was refluxed with a 600-fold excess of cyclohexyl-

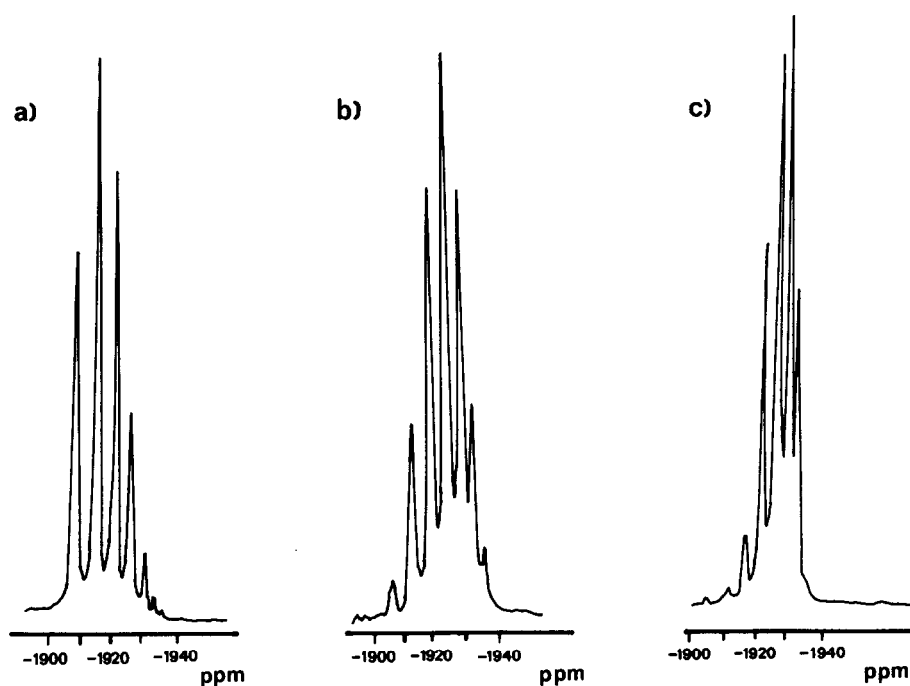


Fig. 3. ^{99}Tc NMR spectra of $[\text{Tc}(\text{TBI})_k(\text{CHI})_{6-k}]^+$ complexes (initial TBI/CHI ratios: (a) 3:1; (b) 1:1; (c) 1:3).

TABLE 1. ^{99}Tc chemical shifts of hexakis(isocyanide)technetium(I) complexes (in ppm relative to TcO_4^-)

k	$[\text{Tc}(\text{CHI})_k(\text{TBI})_{6-k}]^+$	$[\text{Tc}(\text{EEIN})_k(\text{TBI})_{6-k}]^+$
0	1906.6	190.6
1	1913.7	1911.9
2	1919.7 ^b	1914.7, 1916.9 ^a
3	1924.1 ^b	1920.7, 1921.9 ^a
4	1927.9 ^b	1926.0 ^b
5	1930.9	1930.5
6	1933.3	1934.5

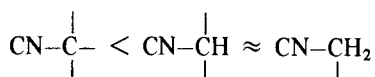
^a Splittings arising from *cis/trans* and *fac/mer* isomers (see also ref. 20). ^b Isomers not resolved.

isocyanide in acetone. No evidence for ligand exchange could be found. Even after a 50-h refluxing period only the starting material could be detected. This confirms that hexakis(alkylisocyanide)technetium(I) complexes are inert against ligand exchange and redox reactions, as stated by Linder and co-workers [23].

Nevertheless, the title mixed-ligand complexes can be produced by reacting $[\text{Tc}(\text{tu})_6]^{3+}$ with isocyanide mixtures. The ^{99}Tc NMR spectra (Fig. 3) show the signals of the seven $[\text{Tc}(\text{R}^1\text{NC})_k(\text{R}^2\text{NC})_{6-k}]^+$ complexes. Their upfield chemical shifts, which are summarized in Table 1, reflect the increasing shielding of the growing π -acceptor capacity in the series

TABLE 2. Comparison of calculated probabilities and experimental mole fractions for $[\text{Tc}(\text{TBI})_k(\text{CHI})_{6-k}]^+$ complexes taken from the ^{99}Tc NMR spectra

	TBI/CHI ratio							
	3:1		1:3		1:1		1.7:1	
	Calc.	Exp.	Calc.	Exp.	Calc.	Exp.	Calc.	Exp.
$[\text{Tc}(\text{TBI})_6]^+$	0.178	0.25	0.0002	0.003	0.016	0.02	0.062	0.06
$[\text{Tc}(\text{TBI})_5(\text{CHI})_1]^+$	0.356	0.32	0.004	0.014	0.094	0.10	0.220	0.22
$[\text{Tc}(\text{TBI})_4(\text{CHI})_2]^+$	0.297	0.26	0.033	0.056	0.234	0.23	0.323	0.29
$[\text{Tc}(\text{TBI})_3(\text{CHI})_3]^+$	0.132	0.12	0.132	0.16	0.313	0.29	0.254	0.25
$[\text{Tc}(\text{TBI})_2(\text{CHI})_4]^+$	0.033	0.03	0.097	0.30	0.234	0.22	0.112	0.12
$[\text{Tc}(\text{TBI})_1(\text{CHI})_5]^+$	0.004	0.008	0.356	0.31	0.094	0.097	0.026	0.04
$[\text{Tc}(\text{CHI})_6]^+$	0.0002	0.0001	0.178	0.17	0.016	0.035	0.003	0.01



because of the +I effect of the key carbon atom on the isocyanide group.

The assignment made for the complexes is strongly supported by the observed molar fractions of the individual complexes taken from the ^{99}Tc NMR spectra, which agree reasonably with a random coordination of the ligands during the synthesis. In this case the molar fraction should be equal to the probabilities of the formation of $\{(\text{R}^1\text{NC})_{6-k}(\text{R}^2\text{NC})_k\}$ ligand sets. These probabilities $P_n(k)$ can be calculated by using Newton's formula (eqn. (1)) with

$$P_n(k) = \binom{n}{k} p_1^k p_2^{n-k} \quad (1)$$

$n = 6$; p_1 and p_2 are the molar fractions of R^1NC and R^2NC in the reaction mixture. Table 2 shows a comparison of the calculated probabilities and the experimental mole fractions of the mixed-ligand complexes are different $\text{R}^1\text{NC}/\text{R}^2\text{NC}$ ratios. The results are very close. The differences which occur for small values are mainly due to the unreliability of the determination of small resonance line areas (noise, base-line distortions, etc.).

Summarizing, the molar ratios of the title complexes can be estimated by a simple model. Thus, optimized starting ratios of the ligands can be obtained to yield a maximum of an individual mixed-ligand complex.

With the complexes described, a new approach may be available for the design of radiopharmaceutical preparations using the mixtures formed during the reaction or individual species after an appropriate chromatographic separation.

References

- 1 U. Abram, R. Beyer, R. Münze, J. Stach, L. Kaden, B. Lorenz and M. Findeisen, *Polyhedron*, in press.
- 2 E. Deutsch, K. Libson and S. Jurisson, *Prog. Inorg. Chem.*, **30** (1983) 70.
- 3 M. J. Clarke and L. Podbielski, *Coord. Chem. Rev.*, **78** (1987) 253.
- 4 K. Schwochau, *Radiochim. Acta*, **32** (1983) 139.
- 5 A. G. Jones and A. Davison, *Int. J. Appl. Radiat. Isot.*, **33** (1982) 867.
- 6 A. Davison and A. G. Jones, *Int. J. Appl. Radiat. Isot.*, **33** (1982) 875.
- 7 M. J. Abrams, A. Davison, A. G. Jones, C. E. Costello and H. Pang, *Inorg. Chem.*, **22** (1983) 2798.
- 8 M. J. Abrams, A. Davison, R. Faggiani, A. G. Jones and C. J. L. Lock, *Inorg. Chem.*, **23** (1984) 3284.
- 9 U. Abram and G. Knop, *Z. Chem.*, **28** (1988) 106.
- 10 A. G. Jones, M. J. Abrams, A. Davison, J. W. Brodack, A. K. Toothaker, S. J. Adelstein and A. J. Kassis, *Int. J. Nucl. Med. Biol.*, **11** (1984) 225.
- 11 B. L. Holman, A. G. Jones, J. Lister-James, A. Davison, M. J. Abrams, J. M. Kirshenbaum, S. S. Tumeh and R. J. English, *J. Nucl. Med.*, **25** (1984) 1350.
- 12 J. C. Maublant, P. Gachon and N. Moins, *J. Nucl. Med.*, **29** (1988) 48.
- 13 D. Piwnica-Worms, J. F. Kronauge, B. L. Holman, L. Lister-James, A. Davison and A. G. Jones, *J. Nucl. Med.*, **29** (1988) 55.
- 14 R. Appel, R. Kleinstück and K. D. Ziehn, *Angew. Chem.*, **83** (1971) 143.
- 15 R. K. Harris and B. E. Mann, *NMR and the Periodic Table*, Academic Press, London/New York/San Francisco, 1978, p. 222.
- 16 K. J. Franklin, C. J. L. Lock, B. G. Sayer and G. J. Schrobilgen, *J. Am. Chem. Soc.*, **104** (1982) 5303.
- 17 M. J. Buckingham, G. E. Hawkes and J. R. Thornback, *Inorg. Chim. Acta*, **56** (1981) L41.
- 18 J. L. Vanderheyden, A. R. Ketrings, K. Libson, M. J. Heeg, L. Roecker, P. Motz, R. Whittle, R. C. Elder and E. Deutsch, *Inorg. Chem.*, **23** (1984) 3184.
- 19 M. Findeisen, L. Kaden, B. Lorenz, S. Rummel and M. Wahren, *Inorg. Chim. Acta*, **128** (1987) L15.
- 20 M. Findeisen, L. Kaden, B. Lorenz and M. Wahren, *Inorg. Chim. Acta*, **142** (1988) 3.
- 21 D. W. Wester, D. H. Whittle, F. E. Miller, R. T. Dean, J. A. Schreifels and J. E. Hunt, *Inorg. Chim. Acta*, **131** (1987) 163.
- 22 M. Findeisen, B. Lorenz and U. Abram, *Z. Chem.*, **29** (1989) 29.
- 23 K. E. Linder, A. Davison, J. I. Devan, C. E. Costello and S. Maleknia, *Inorg. Chem.*, **25** (1986) 2085.