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Technetium and Rhenium Pentacarbonyl Complexes with C_2 and C_{11} ω-Isocyanocarboxylic Acid Esters

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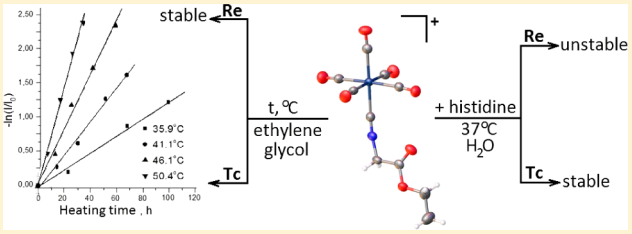
Supporting Information

ABSTRACT: Technetium(I) and rhenium(I) pentacarbonyl complexes with ethyl 2-isocyanoacetate and methyl 11-isocyanoundecanoate, $[M(CO)_5(CNCH_2COOEt)]ClO_4$ (M = Tc (**1**) and Re (**2**)) and $[M(CO)_5(CN(CH_2)_{10}COOMe)]ClO_4$ (M = Tc (**3**) and Re (**4**)), were prepared and characterized by IR, ^{1}H NMR, and $^{13}C\{^1H\}$ NMR spectroscopy. The crystal structures of **1** and **2** were determined using single-crystal X-ray diffraction. The kinetics of thermal decarbonylation of technetium complexes **1** and **3** in ethylene glycol was studied by IR spectroscopy. The rate constants and activation parameters of this reaction were determined and compared with those for $[Tc(CO)_6]^+$. It was found that rhenium complexes **2** and **4** were stable with respect to thermal decarbonylation. Histidine challenge reaction of complexes **1** and **2** in phosphate buffer was examined by IR spectroscopy. In the presence of histidine, the rhenium pentacarbonyl isocyanide complex partially decomposes to form an unidentified yellow precipitate. Technetium analogue **1** is more stable under these conditions.



INTRODUCTION

Despite the fact that $[M(CO)_3(H_2O)_3]^+$ cations (M = Tc or Re) are readily synthesized and are very convenient precursors for tethering technetium-99m or rhenium-186,188 to various biomolecules, the search for new technetium and rhenium coordination cores suitable for this purpose still remains a topical problem.[1] This is probably due to the fact that introduction of a $M(CO)_3$ core into a biomolecule requires bulky tridentate chelators or a combination of mono- and bidentate coordination units, which can negatively affect the native properties of the biomolecule. One of the possible ways to minimize the negative effect of the metal coordination core is using higher technetium or rhenium carbonyls in combination with simpler coordination units. This approach is inspired by the fact that the technetium hexacarbonyl cation, surprisingly, turned out to be rather stable in solutions.[2] Replacement of one carbonyl group in the hexacarbonyl cation with its isoelectronic σ-donor and π-acceptor analogue, the isocyanide group, performed in our previous study, yielded a stable technetium pentacarbonyl isocyanide complex.[3] The approach developed was also demonstrated to be applicable to ^{99m}Tc.[3]

Our previous experiments were performed with a simple ligand, *tert*-butyl isocyanide, but they open prospects for conjugation of biomolecules to the Tc or Re pentacarbonyl core via an isocyanide group introduced into the biomolecule.[3] Fatty acids are promising objects for examining this possibility. First, fatty acids are accumulated in the myocardium tissue and metabolized there via β-oxidation. The use of fatty acids labeled with ^{99m}Tc may allow imaging of various myocardial diseases. Second, fatty acids can be used as spacers in conjugation of therapeutic radionuclides (e.g., ^{186,188}Re) with large biomolecules (e.g., peptides). Therefore, the next step of our study involved synthesis of technetium and rhenium pentacarbonyl complexes with model ω-isocyanoalkanoic acid esters and evaluation of the stability of the resulting conjugates in solutions. The results we obtained are reported in this paper.

EXPERIMENTAL SECTION

Materials and Methods. All chemicals were of reagent grade and were purchased from Fluka (St. Petersburg, Russia). Methylene chloride and acetonitrile were distilled from P_2O_5. Ethylene glycol (EG) was used as received. Silver perchlorate was prepared by precipitation of silver carbonate from silver nitrate aqueous solution with sodium carbonate, followed by dissolution of the precipitate in concentrated perchloric acid. Prior to use, silver perchlorate was dehydrated by heating in a vacuum at 50–60 °C. $[TcI(CO)_5]$ was prepared by high-pressure carbonylation of potassium pertechnetate in a mixture of formic and hydroiodic acids.[3] $[ReCl(CO)_5]$ was prepared similarly starting from K_2ReCl_6.

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The IR spectra were recorded with a Shimadzu FT-IR 8700 spectrometer in the range of 1600−2500 cm^{-1} using CaF_2 cells. The samples were prepared as solutions in methylene chloride, acetonitrile, or ethylene glycol.

The ^{99}Tc NMR spectra were recorded in a methylene chloride solution on a Varian Gemini 2000 spectrometer (67.5 MHz). The ^{99}Tc shifts are given relative to aqueous $KTcO_4$ as external reference. ^{1}H and ^{13}C NMR measurements were performed at the Center for Magnetic Resonance, St. Petersburg State University. The ^{1}H and $^{13}C\{^1H\}$ NMR spectra were recorded on a Bruker Avance III 400 spectrometer (400.13 MHz for ^{1}H, 100.61 MHz for ^{13}C) at room temperature using CD_3OD as solvent. The spectra were measured using the solvent peak as internal reference, and the chemical shifts were converted to the conventional TMS scale ($\delta(C\underline{H}D_2OD)$ = 3.31 ppm; $\delta(\underline{C}D_3OD)$ = 49.15 ppm). The pulse delay for 30° pulses was 1 s for ^{1}H and 30 s for $^{13}C\{^1H\}$ inverse-gated NMR spectra. The number of scans varied between 16 for ^{1}H and 7400 for $^{13}C\{^1H\}$ NMR spectra.

Elemental analysis was performed on a PerkinElmer 2400 Series II CHNS/O analyzer. The content of Tc and Re in the samples was determined by ICP-OES on a Varian 725-OES device.

Care should be taken in handling compounds of radioactive technetium. Perchlorate salts are potentially explosive and should also be handled with care.

The IR frequencies and intensities were calculated by DFT methods using Gaussian 09 software.[4] The hybrid exchange-correlation functional PBE0 was chosen with a mixed basis set: the SDD basis with relativistic effective core potentials for the Tc and Re atoms, and the DGDZVP basis for other atoms. The PCM model for CH_2Cl_2 solvent was used. All calculations were performed with the aid of computational resources provided by the Resource Center "Computer Center of SPbU". The results of our calculations are summarized in Table S5 (Supporting Information).

Synthesis. Methyl 11-isocyanoundecanoate ($CN(CH_2)_{10}COOMe$) was prepared in three steps by the known procedure with some modifications.[5]

11-Methoxy-11-oxoundecanammonium Chloride. 11-Aminoundecanoic acid (2.01 g, 0.01 mol) was mixed with methanol (11.89 g, 0.37 mol) in a 50 mL round-bottom flask equipped with a reflux condenser. Then, $SOCl_2$ (0.8 mL, 1.32 g, 0.011 mol) taken in 10% excess was added dropwise. The mixture was stirred for 1 h at room temperature. The volatiles were removed on a rotary evaporator. The resulting white residue of 11-methoxy-11-oxoundecanammonium chloride was washed with methanol and dried in a rough vacuum.

Yield ~ 100% (2.515 g). ^{1}H NMR, δ, ppm: 1.2−1.8 (16H, $-CH_2-C\underline{H}_2-CH_2-$), 2.31 (t, 2H, J = 7.4 Hz, $-C\underline{H}_2-C\underline{H}_2-COO-$), 2.93 (t, 2H, J = 7.7 Hz, $H_3N-C\underline{H}_2-C\underline{H}_2-$), 3.65 (s, 3H, $-O-CH_3$), 7.85 (br. s, NH). $^{13}C\{^1H\}$ NMR, δ, ppm: 25−31 (8C, $-CH_2-CH_2-CH_2-$), 34.9 (1C, $-CH_2-COO-$), 40.9 (1C, H_3N-CH_2-), 52.1 (1C, $-COOCH_3$), 176.1 (1C, $-COO-$). The ^{1}H and $^{13}C\{^1H\}$ NMR spectra are shown in Figure S1 (Supporting Information).

Methyl 11-(Formylamino)undecanoate. A mixture of 11-methoxy-11-oxoundecanammonium chloride (2.515 g, 0.01 mol), methanol (40 mL), ethyl formate (36.68 g, 0.47 mol), and Et_3N (1.01 g, 0.0099 mol) was refluxed for 36 h. Then, the reaction mixture was cooled to room temperature. White crystals were filtered off and dissolved in chloroform. The resulting solution was washed with three portions of water. The solvent was removed on a rotary evaporator. The product was isolated in the form of a white solid.

Yield 70% (1.773 g, 0.007 mol). ^{1}H NMR, δ, ppm: 1.2−1.7 (16H, $-CH_2-C\underline{H}_2-CH_2-$), 2.31 (t, 2H, J = 7.4 Hz, $-C\underline{H}_2-C\underline{H}_2-COO-$), 3.21 (t, 2H, J = 7.1 Hz, $-HN-C\underline{H}_2-C\underline{H}_2-$), 3.65 (s, 3H, $-O-CH_3$), 8.02 (s, 1H, $-CHO$). $^{13}C\{^1H\}$ NMR, δ, ppm: 25−31 (8C, $-CH_2-CH_2-CH_2-$), 34.9 (1C, $-CH_2-COO-$), 39.1 (1C, $-NH-CH_2-$), 52.1 (1C, $-COOCH_3$), 163.8 (1C, $-CHO$), 176.0 (1C, $-COOCH_3$). IR (CH_2Cl_2, cm^{-1}): 1732.0 ($\nu_{C=O,\ ester}$), 1687.6 ($\nu_{C=O,\ amide}$). The ^{1}H and $^{13}C\{^1H\}$ NMR spectra are shown in Figure S2 (Supporting Information).

Methyl 11-Isocyanoundecanoate. Methyl 11-(formylamino)-undecanoate (1.773 g, 0.007 mol) was dissolved in anhydrous pyridine (75 mL). The solution was cooled on an ice bath. *p*-Toluenesulfonyl chloride (1.68 g, 0.0088 mol, 25% excess) was added with stirring. Unlike the Walther's procedure, the reaction mixture was allowed to warm to room temperature and left overnight.[5] On the next day, the reaction mixture was poured onto ice (75 g). The mixture was allowed to warm to room temperature, and the dark brown oily product was extracted with three portions of diethyl ether. The extracts were combined and washed with a saturated aqueous solution of sodium chloride. The solvent was removed on a rotary evaporator, and the residue was dried under reduced pressure at 50−60 °C. The crude product was purified by flash chromatography on a silica gel column using a mixture of diethyl ether and *n*-hexane (2:5, v:v) as an eluent.

Yield 10%. ^{1}H NMR, δ, ppm: 1.2−1.8 (16H, $-CH_2-C\underline{H}_2-CH_2-$), 2.32 (t, 2H, J = 7.4 Hz, $-C\underline{H}_2-COO-$), 3.47 (tt, 2H, J = 6.6 Hz, $CN-C\underline{H}_2-C\underline{H}_2-$, J = 1.9 Hz, $C\underline{N}-C\underline{H}_2-CH_2-$), 3.56 (s, 3H, $-O-CH_3$). $^{13}C\{^1H\}$ NMR, δ, ppm: 25−31 (8C, $-CH_2-CH_2-CH_2-$), 34.9 (1C, $-CH_2-COO-$), 42.5 (t, 1C, J = 6.2 Hz, $C\underline{N}-CH_2-$), 52.1 (1C, $-COOCH_3$), 155.3 (t, 1C, J = 6.2 Hz, $\underline{C}N-CH_2-$), 176.1 (1C, $-COOCH_3$). IR (CH_2Cl_2, cm^{-1}): 2152.4 ($\nu_{C\equiv N}$), 1732.0 ($\nu_{C=O,\ ester}$). Elemental analysis, calcd., %: C 69.03, H 10.18, N 6.64; found, %: C 69.66, H 9.71, N 6.41. The ^{1}H and $^{13}C\{^1H\}$ NMR spectra are shown in Figure S3 (Supporting Information).

*[Tc(CO)$_5$(CNCH$_2$COOEt)]ClO$_4$ (**1**).* A portion of $[TcI(CO)_5]$ (0.108 g, 0.295 mmol) was mixed with excess dry $AgClO_4$ (0.122 g, 0.589 mmol) in dry methylene chloride (4 mL). The resulting mixture was stirred in the dark for 1 h. The yellowish precipitate of AgI was separated by filtration through a paper filter. A slight excess (1.24) of isocyanide ligand (0.04 mL, 0.366 mmol) was added to the filtrate, and the mixture was stirred for 1 h at room temperature. After that, the solution was allowed to crystallize overnight in a loosely closed vial. On the next day, white crystals of the target product were separated from the small volume of the supernatant by decantation and were washed with two portions of cold methylene chloride.

Yield 74%. ^{99}Tc NMR (CH_2Cl_2), δ, ppm: −2007.0 ($\Delta\nu_{1/2}$ 320 Hz). IR (CH_2Cl_2, cm^{-1}): 2258.5 w ($\nu_{C\equiv N}$), 2165.9 w ($\nu_{C\equiv N}$ and $\nu_{C\equiv O}$), 2119.6 vw ($\nu_{C\equiv O,\ eq}$), 2079.1 vs ($\nu_{C\equiv O}$), 1759.0 w ($\nu_{C=O,\ ester}$). Elemental analysis, calcd., %: C 26.58, H 1.55, N 3.32, Tc 21.9; found, %: C 26.76, H 1.44, N 3.20, Tc 21.1.

*[Re(CO)$_5$(CNCH$_2$COOEt)]ClO$_4$ (**2**).* This complex was prepared similarly to **1**, with $[ReCl(CO)_5]$ taken instead of $[TcI(CO)_5]$. Another difference is that a mixture of $[ReCl(CO)_5]$ with silver perchlorate in methylene chloride was stirred for 2 h prior to filtration. $[Re(CO)_5(CNCH_2COOEt)]ClO_4$ was isolated in the form of white crystals suitable for single-crystal X-ray diffraction.

Yield 36%. ^{1}H NMR, δ, ppm: 1.33 (t, 3H, J = 7.1 Hz, $-O-C\underline{H}_2-C\underline{H}_3$), 4.33 (q, 2H, J = 7.2 Hz, $-O-C\underline{H}_2-C\underline{H}_3$), 4.98 (s, 2H, $-CN-CH_2-$). $^{13}C\{^1H\}$ NMR, δ, ppm: 14.4 (1C, $-O-CH_2-CH_3$), 48.0 (br, 1C, $CN-CH_2-COO-$), 64.4 (1C, $-O-CH_2-CH_3$), 125.4 (br., 1C, $-CN-CH_2-$), 165.3 (1C, $-COO-$), 176.8 (4C, CO(eq)), 177.8 (1C, CO(ax)). IR (CH_2Cl_2, cm^{-1}): 2260.4 w ($\nu_{C\equiv N}$), 2164.0 w ($\nu_{C\equiv N}$ and $\nu_{C\equiv O}$), 2110.0 vw ($\nu_{C\equiv O,\ eq}$), 2069.5 vs ($\nu_{C\equiv O}$), 1759.0 w ($\nu_{C=O,\ ester}$). Elemental analysis: calcd., %: C 22.28, H 1.3, N 2.6, Re 34.56; found, %: C 22.36, H 0.9, N 2.54, Re 35.30.

*[Tc(CO)$_5$(CN(CH$_2$)$_{10}$COOMe)]ClO$_4$ (**3**).* A portion of $[TcI(CO)_5]$ (0.101 g, 0.276 mmol) was mixed with excess dry $AgClO_4$ (0.145 g, 0.699 mmol) in dry methylene chloride (4 mL). The resulting mixture was stirred in the dark for 1 h. The yellowish precipitate of AgI was separated by filtration through a paper filter. A slight excess (1.4) of $CN(CH_2)_{10}COOMe$ (0.087 mg, 0.387 mmol) was added to the filtrate, and the mixture was stirred for 1 h at room temperature. After that, the solution was allowed to crystallize overnight in a loosely closed vial. On the next day, a slightly brownish white amorphous oily precipitate was isolated by decantation. The product was thoroughly ground under diethyl ether for 1 h, washed with two portions of diethyl ether, and then dried under reduced pressure to give a bulky white solid.

Yield 75%. IR (CH_2Cl_2, cm^{-1}): 2246.9 w ($\nu_{C\equiv N}$), 2164.0 m ($\nu_{C\equiv N}$ and $\nu_{C\equiv O}$), 2117.7 w ($\nu_{C\equiv O,\ eq}$), 2077.2 vs ($\nu_{C\equiv O}$), 1732.0 m

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Table 1. Crystallographic Data and Refinement Parameters for 1 and 2

compound	1	2
formula	$[Tc(CO)_5C_5H_7NO_2](ClO_4)$	$[Re(CO)_5C_5H_7NO_2](ClO_4)$
crystal system	monoclinic	monoclinic
a (Å)	7.3874(12)	7.4238(10)
b (Å)	11.6564(18)	11.6101(16)
c (Å)	18.762(3)	18.942(3)
α (deg)	90	90
β (deg)	90.907(3)	91.096(3)
γ (deg)	90	90
V (Å^3)	1615.4(4)	1632.3(4)
molecular wt	450.62	538.82
space group	$P2_1/n$	$P2_1/n$
μ (mm^{-1})	1.113	7.664
temp (K)	210(2)	210(2)
Z	4	4
D_{calc} (g/cm^3)	1.853	2.192
crystal size (mm^3)	0.30 × 0.20 × 0.18	0.35 × 0.25 × 0.22
radiation	Mo K_α	Mo K_α
total reflns	9220	14277
unique reflns	2849	4747
angle range 2θ (deg)	4.12−50.00	4.12−60.00
reflns with $\|F_o\| \geq 4\sigma_F$	2523	3754
R_{int}	0.0962	0.0673
R_σ	0.0688	0.0552
R_1 ($\|F_o\| \geq 4\sigma_F$)[a]	0.0577	0.0318
wR_2 ($\|F_o\| \geq 4\sigma_F$)[a]	0.1410	0.0727
R_1 (all data)[a]	0.0623	0.0435
wR_2 (all data)[a]	0.1474	0.0760
S	1.079	0.973
ρ_{min}, ρ_{max}, e/Å^3	−1.504, 2.412	−1.413, 0.980

[a] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$; $wR_2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{1/2}$; $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$, where $P = (F_o^2 + 2F_c^2)/3$; $s = \{\sum[w(F_o^2 - F_c^2)]/(n - p)\}^{1/2}$, where n is the number of reflections and p is the number of refinement parameters.

($\nu_{C=O,\ ester}$). Elemental analysis, calcd., %: C 38.41, H 4.13, N 2.49, Tc 17.41; found, %: C 38.63, H 4.33, N 2.60, Tc 17.64.

[Re(CO)$_5$(CN(CH$_2$)$_{10}$COOMe)]ClO$_4$ (4). This complex was prepared similarly, with $[ReCl(CO)_5]$ taken instead of $[TcI(CO)_5]$. Another difference is that a mixture of $[ReCl(CO)_5]$ with silver perchlorate in methylene chloride was stirred for 2 h prior to filtration. $[Re(CO)_5(CN(CH_2)_{10}COOMe)]ClO_4$ was isolated in the form of a white amorphous solid.

Yield 60%. ^{1}H NMR, δ, ppm: 1.2−2.0 (16H, −CH$_2$−CH$_2$−CH$_2$−), 2.31 (t, 2H, J = 7.4 Hz, −CH$_2$−CH$_2$−COO−), 3.65 (s, 3H, −O−CH$_3$), 4.02 (tt, 2H, J = 6.5 Hz, −CN−CH$_2$−CH$_2$−, $J \sim 2$ Hz, −CN−CH$_2$−CH$_2$−). ^{13}C{^{1}H} NMR, δ, ppm: 25−31 (8C, −CH$_2$−CH$_2$−CH$_2$−), 34.9 (1C, −CH$_2$−COO−), 46.6 (t, 1C, J = 6.2 Hz, −CN−CH$_2$−), 119.6 (t, 1C, J = 25.3 Hz, −CN−CH$_2$−), 176.1 (1C, −COO−), 176.9 (4C, CO(eq)), 178.0 (1C, CO(ax)). IR (CH_2Cl_2, cm^{-1}): 2250.8 w ($\nu_{C\equiv N}$), 2164.0 m ($\nu_{C\equiv N}$ and $\nu_{C\equiv O}$), 2117.7 w ($\nu_{C\equiv O,\ eq}$), 2067.5 vs ($\nu_{C\equiv O}$), 1732.0 w ($\nu_{C=O,\ ester}$). Elemental analysis, calcd., %: C 33.21, H 3.54, N 2.15, Re 27.99; found, %: C 32.94, H 3.29, N 2.14, Re 24.27.

Kinetic Experiment. A portion of $[Tc(CO)_5(CN(CH_2)_{10}COOMe)]ClO_4$ or $[Tc(CO)_5(CNCH_2COOEt)]ClO_4$ (8−12 mg) was dissolved with stirring in ethylene glycol (8−9 mL). The mixture was kept at a required temperature maintained with an accuracy of ±0.1 °C in a Julabo thermostat. Solution samples were taken at definite time intervals, and the IR spectra (2200−1800 cm^{-1}) of the solution were recorded. The consumption of the pentacarbonyl complex with C_2 and C_{11} ω-isocyano carboxylic acid esters was monitored by the change in the optical density of the carbonyl band at 2071.4 and 2069.5 cm^{-1}, respectively.

Crystal Structure Determination. For single-crystal X-ray diffraction experiments, crystals of **1** and **2** were fixed on micro mounts, placed on a Bruker Smart Apex II diffractometer, and measured at a temperature of 210 K using monochromated Mo Kα radiation. The unit cell parameters of **1** (Table 1) were refined by the least-squares technique using 9220 reflections in the 2θ range of 4.12−50.00°. The structure was solved by the direct method and refined to $R_1 = 0.058$ ($wR_2 = 0.141$) for 2523 unique reflections with $|F_o| \geq 4\sigma_F$. The unit cell parameters of **2** (Table 1) were refined by the least-squares technique using 14 277 reflections in the 2θ range of 4.12−60.00°. The structure was solved by the direct method and refined to $R_1 = 0.032$ ($wR_2 = 0.073$) for 3754 unique reflections with $|F_o| \geq 4\sigma_F$. The structures of **1** and **2** were solved and refined using the SHELXL-97 program.[6] The program was incorporated in the OLEX2 program package.[7] The absorption correction was applied using the SADABS program.[8] The atomic coordinates and displacement parameters for all non-hydrogen atoms in the structures of **1** and **2** are presented in Tables S1 and S2 (Supporting Information), respectively. Selected interatomic distances and bond angles for **1** and **2** are listed in Tables S3 and S4 (Supporting Information), respectively.

RESULTS AND DISCUSSION

This study continues our efforts in using higher technetium and rhenium carbonyls to label biomolecules. Our work was aimed at conjugating the $M(CO)_5^+$ fragment (M = Tc and Re) with long-chain fatty acids via the isocyanide coordination unit. As starting metal compounds, we chose technetium and rhenium pentacarbonyl halides (namely, $[TcI(CO)_5]$ and $[ReCl(CO)_5]$). As ligands, we examined ethyl 2-isocyanoacetate (C_2, $CNCH_2COOEt$) and methyl 11-isocyanoundecanoate (C_{11}, $CN(CH_2)_{10}COOMe$). Ethyl 2-isocyanoacetate is a commercial compound. The fatty acid ester was prepared in

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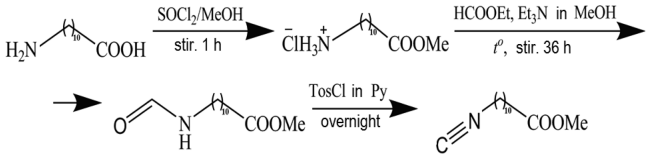
three steps (Scheme 1) by the known procedure with some modifications.[5]

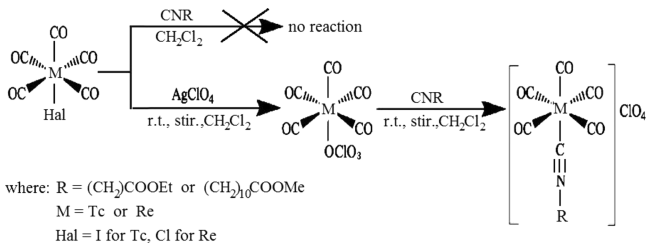
Scheme 1. Preparation of Methyl 11-Isocyanoundecanoate[a]



[a]Tos = *p*-toluenesulfonyl.

The short-chain ligand was studied to determine the crystal structure of pentacarbonyl isocyanides, because, in this case, the crystallization was expected to be easier than with $CN(CH_2)_{10}COOMe$. In addition, we used $CNCH_2COOEt$ to develop the conjugation procedure. Since two *cis*-carbonyl ligands in pentacarbonyltechnetium halides can be readily substituted by molecules of donor solvents, the reaction was performed in an inert solvent (methylene chloride). Unfortunately, the halide ligand in the metal pentacarbonyl halides is tightly bound to the central metal and cannot be directly substituted by isocyanides. No reaction between $[TcI(CO)_5]$ and $CNCH_2COOEt$ in methylene chloride was observed at room temperature in 3−4 h. At higher temperatures, $[TcI(CO)_5]$ is known to be unstable to decarbonylation.[9] To promote the substitution, the halide ligands were replaced by the labile perchlorate group. Treatment of $[TcI(CO)_5]$ and $[ReCl(CO)_5]$ with solid silver perchlorate in methylene chloride yields $[Tc(ClO_4)(CO)_5]$ and $[Re(ClO_4)(CO)_5]$, respectively. These compounds were isolated and characterized in our previous study.[10] We also found previously that the perchlorate ligand in $[Tc(ClO_4)(CO)_5]$ could be readily substituted by isocyanide ligands.[3] As we expected, the reaction of $[Tc(ClO_4)(CO)_5]$ and $[Re(ClO_4)(CO)_5]$ generated in the solution (without their isolation) with C_2 and C_{11} ω-isocyanocarboxylic acid esters gives new pentacarbonyl complexes. The overall preparation procedure is shown in Scheme 2.

Scheme 2. Preparation of $[M(CO)_5(CNR)]ClO_4$ (M = Tc or Re; R = CH_2COOEt or $(CH_2)_{10}COOMe$)



The IR spectra of the reaction mixtures in the range of stretching vibrations of carbonyl groups contain a strong band at 2065−2080 cm^{-1}, typical of a pseudohexacarbonyl $(NC)M(CO)_5$ moiety (cf. ν_{CO} of $[^{99}Tc(CO)_5TBI]ClO_4$ in $CHCl_3$: 2071.4 cm^{-1}, where TBI is *tert*-butyl isocyanide).[3] Slow evaporation of the reaction mixture gave white crystalline and brownish oily residues in the case of C_2 and C_{11} esters, respectively. Complexes with methyl 11-isocyanoundecanoate were additionally treated with diethyl ether to remove the unreacted ligand. The IR spectra of these products and of the initial isocyanides in methylene chloride are shown in Figures S5−S10 (Supporting Information). The spectra have similar structures and contain the bands of pentacarbonyl, isocyanide, and ester fragments, which is consistent with the expected composition of the reaction products. To assign the IR bands of the isocyanide complexes, we calculated the IR spectra of $[M(CO)_5(CNCH_2COOEt)]ClO_4$ (M = Tc, Re) in methylene chloride by the DFT method. In accordance with the calculation results (Table S5, Supporting Information), the weak band at ca. 2260 cm^{-1} was assigned to stretching vibrations of the coordinated isocyanide group. Upon coordination of ethyl 2-isocyanoacetate to technetium or rhenium, the frequency of the $\nu_{C\equiv N}$ band is shifted toward high frequencies by approximately 100 cm^{-1}. This significant shift suggests strong binding of the isocyanide ligands with the metal center. The band at ca. 2165 cm^{-1} in the spectra of the technetium and rhenium pentacarbonyl complexes with the C_2 ligand is due to mixed vibration of the CO and CN groups. The strong band at 2079.1 and 2069.5 cm^{-1} in the spectra of the technetium and rhenium complexes, respectively, is assigned to mixed vibration of the equatorial and axial carbonyl groups.

The ^1H NMR spectra of rhenium pentacarbonyl isocyanide complexes **2** and **4** in methanol-d_4 contain signals of the isocyanide ligands (Figures 1a and 2a). The signals of four equatorial carbonyl groups at δ 176.8 (4C, *CO*) and 176.9 ppm (4C, *CO*) and one axial carbonyl group at δ 177.8 (1C, *CO*) and 178.0 ppm (1C, *CO*) are observed in the $^{13}C\{^1H\}$ NMR spectra of **2** and **4** (Figures 1b and 2b), respectively. Coordination of the isocyanide fragment unambiguously follows from the downfield shift of the isocyanide carbon signal by approximately 35 ppm (by 35.7 and 34.8 ppm for **2** and **4**, respectively) in going from the free ligand (Figures S3 and S4, Supporting Information) to its rhenium complex.

Fortunately, complexes of technetium and rhenium pentacarbonyls with ethyl 2-isocyanoacetate were obtained in the form of X-ray quality crystals. They crystallize in the monoclinic system. The unit cell parameters are summarized in Table 1.

The crystal structures of $[M(CO)_5(CNCH_2COOCH_2CH_3)](ClO_4)$ (M = Tc, Re) (**1** and **2**, respectively) are similar and contain one symmetrically independent metal cation octahedrally coordinated by five carbon atoms of the carbonyl groups and one carbon atom of the isocyanide group (Figure 3). The C6−N1−C7 angles in the coordinated isocyanide are equal to 170.3(5)° and 170.7(5)° for **1** and **2**, respectively. The M−C≡O fragments are linear within 5.3° and 4.7° for **1** and **2**, respectively. The coordination polyhedron of the metal atom (Figure 3) is close to an ideal octahedron, with the bond angles between *cis*-CO and isocyanide groups equal to 90° (within ±4.4° in **1** and ±4.0° in **2**); the M−C(1−5) bond distances are almost equal and are in the range of 2.0−2.03 Å in **1** and 2.0−2.02 Å in **2**, whereas the M−C(6) bond is slightly longer (2.080(5) and 2.070(4) Å for **1** and **2**, respectively). The Cl atoms in the structures of **1** and **2** are tetrahedrally coordinated by four O atoms to form a perchlorate anion with the average Cl−O distance equal to 1.417 and 1.377 Å in **1** and **2**, respectively.

In the crystal structures, the $[M(CO)_5(CNCH_2COOCH_2CH_3)]^+$ (M = Tc, Re) cations form layers parallel to the (001) plane (Figure 4). Within the layers, the molecules are arranged so that the OC−M−$CNCH_2COOCH_2CH_3$ axes of the octahedra are parallel to the [012] direction, with the isocyanide fragments being alternately located up and down with respect to the layer plane. The perchlorate anions are

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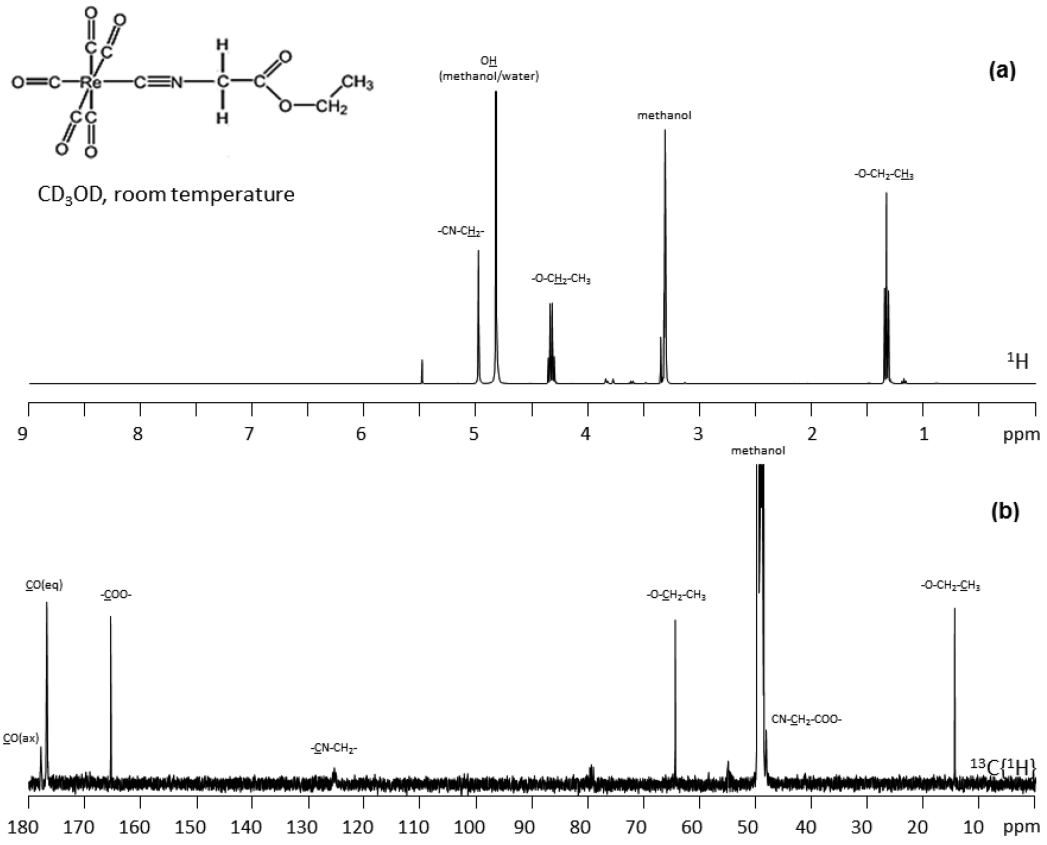

Figure 1. (a) ^{1}H and (b) $^{13}C\{^{1}H\}$ NMR spectra of $[Re(CO)_5(CNCH_2COOEt)]ClO_4$ in methanol-d_4.

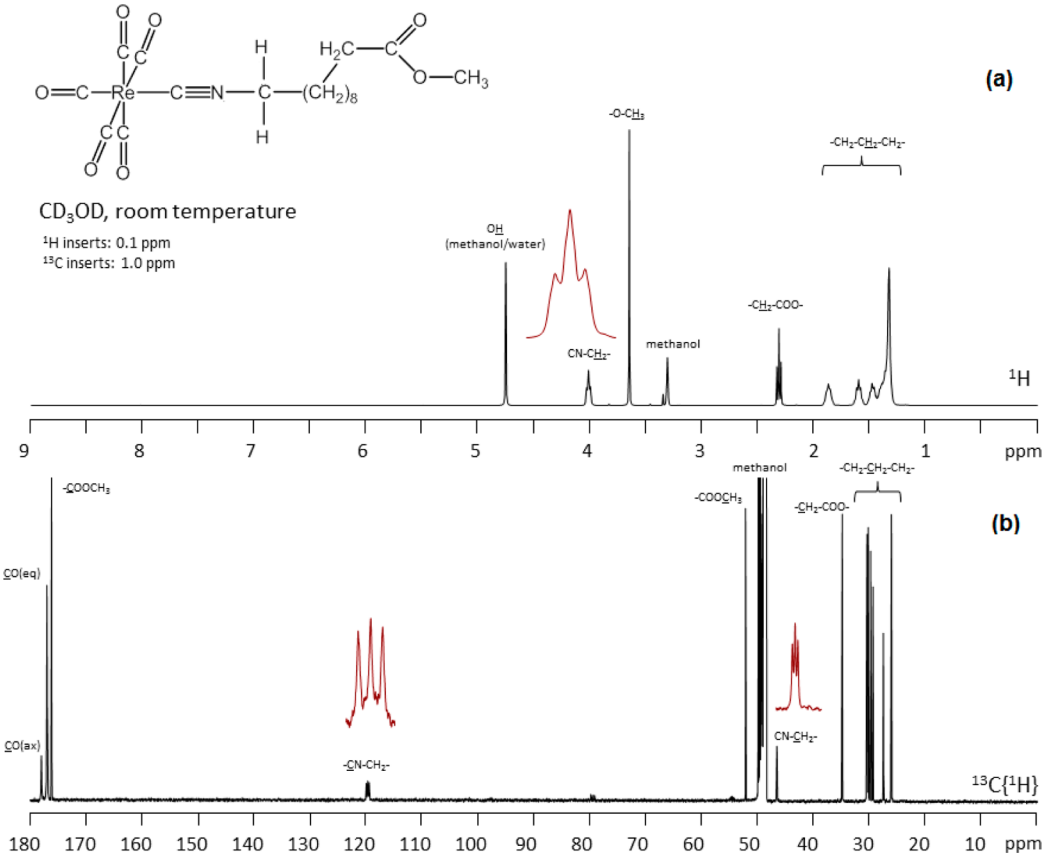

Figure 2. (a) ^{1}H and (b) $^{13}C\{^{1}H\}$ NMR spectra of $[Re(CO)_5(CN(CH_2)_{10}COOMe)]ClO_4$ in methanol-d_4.

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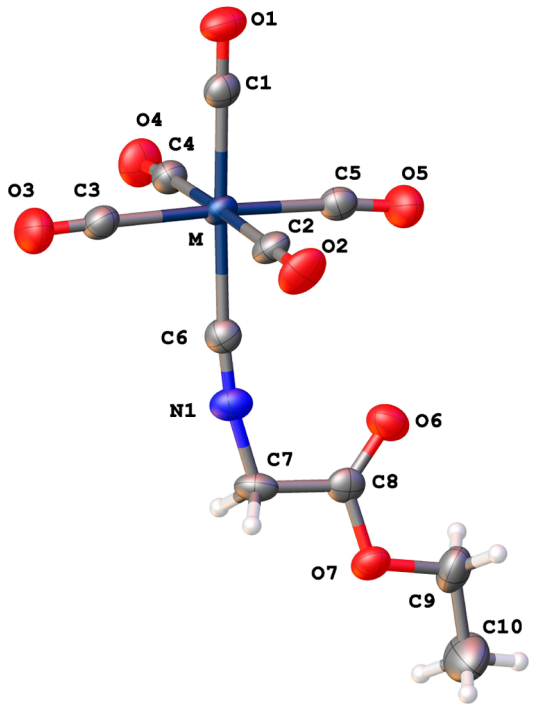

Figure 3. Molecular structure of $[M(CO)_5CNCH_2COOCH_2CH_3]^+$ complex cations (M = Tc, Re). Metal, carbon, oxygen, and nitrogen atoms are dark blue, gray, red, and light blue, respectively. Thermal ellipsoids are drawn at the 50% probability level.

arranged between the $[M(CO)_5(CNCH_2COOCH_2CH_3)]^+$ (M = Tc, Re) cations, thus compensating their positive charge.

Thus, the rhenium and technetium pentacarbonyl complexes with C_2 and C_{11} isocyano carboxylic acid esters have been prepared and fully characterized. To assess the possibility of their use in nuclear medicine, the stability of these complexes in solutions should be evaluated. We studied two pathways of their degradation: (1) thermal decarbonylation and (2) reactions with coordinating groups of blood proteins (with histidine used as a model). The degradation was monitored by IR spectroscopy, which turned out to be a very convenient method for this purpose.

We found that the intensity of the carbonyl band at 2079.1 cm^{-1} of technetium complex **1** in methylene chloride gradually decreased, suggesting its slow degradation in solution. On the contrary, the rhenium analogue was indefinitely stable in methylene chloride (at least for several days). To get quantitative data on thermal decarbonylation of the examined complex in solution, we used ethylene glycol (EG) as a solvent. This choice was motivated by the following reasons: (1) EG is a high-boiling (197.3 °C) solvent, which allowed us to perform the kinetic experiments in a wide temperature range without appreciable solvent evaporation; (2) EG is a weak O-donor solvent partially simulating an aqueous medium; and (3) it is transparent in the range of stretching vibrations of the carbonyl groups.

To study the kinetics of thermal decarbonylation of **1**, we recorded the IR spectra of its solution in EG heated at 35.9, 41.1, 46.1, and 50.4 °C for different times until a 70−90% conversion of the initial pentacarbonyl isocyanide complex was reached. In all cases, the intensity of the strongest carbonyl band at 2071.4 cm^{-1} gradually decreased and new bands at 2050.2 and 1928.7 cm^{-1} appeared with time. It should be noted that the frequency of the ester band of complex **1** at 1749.3

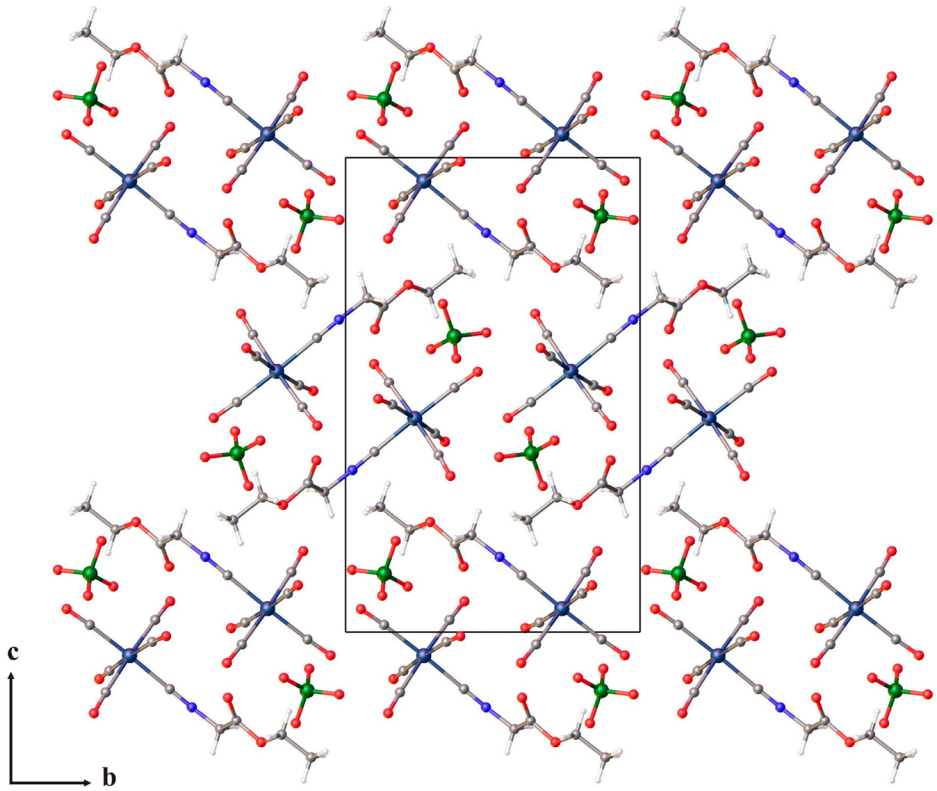

Figure 4. Crystal structure of $[M(CO)_5CNCH_2COOCH_2CH_3](ClO_4)$ (M = Tc, Re). Metal, chlorine, carbon, oxygen, and nitrogen atoms are dark blue, green, gray, red, and light blue, respectively.

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cm^{-1} did not change during the kinetic experiments, which indicates that the ethyl ester was not involved in transesterification with EG. The spectral transformations observed on heating at 41.1 °C are shown as examples in Figure 5.

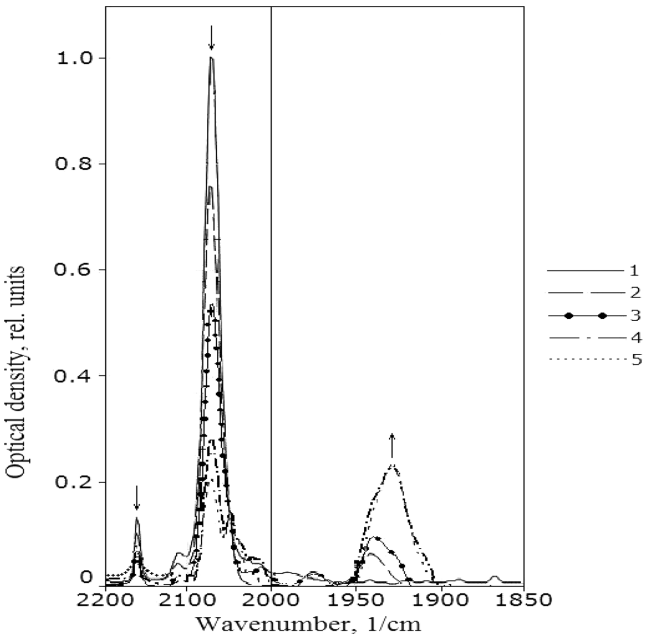

Figure 5. IR spectra of $[Tc(CO)_5(CNCH_2COOEt)](ClO_4)$ in EG heated at 41.1 °C for (1) 0, (2) 14.27, (3) 30.33, (4) 51.42, and (5) 67.45 h.

Unfortunately, we failed to identify the decarbonylation products. The absence of isosbestic points suggests formation of several reaction products. The bands at 2050.2 and 1928.7 cm^{-1} observed in the final decarbonylation steps are typical for tricarbonyl species.

The kinetic data on thermal decarbonylation of **1** were linearized in the $-\ln(I/I_0)$ vs t coordinates (I_0 and I are the optical densities of the band at 2071.4 cm^{-1}). The results are shown in Figure 6.

The rate constants of thermal decarbonylation, determined from the slopes of the kinetic curves, are presented in Table 2.

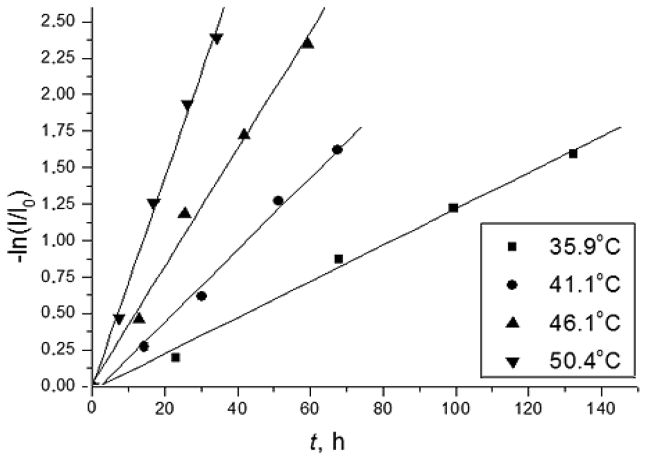

Figure 6. Kinetics of thermal decarbonylation of $[Tc(CO)_5(CNCH_2COOEt)]ClO_4$ in EG (semilog plot).

Table 2. Rate Constants of Thermal Decarbonylation of 1 in EG

T, K	k, s^{-1}
308.9	$(3.45 \pm 0.14) \times 10^{-6}$
314.1	$(7.2 \pm 0.6) \times 10^{-6}$
319.1	$(1.12 \pm 0.06) \times 10^{-5}$
323.4	$(1.99 \pm 0.07) \times 10^{-5}$

It should be noted that the rate constant of thermal decarbonylation of the technetium pentacarbonyl isocyanide complex is approximately 2 times higher than that of $[Tc(CO)_6]^+$ ($(3.40 \pm 0.11) \times 10^{-6}$ s^{-1} at 315.8 K).[5] Earlier, Aebischer et al. found that the ^{99}Tc NMR signal of $[Tc(CO)_6]^+$ disappeared within 2 days after CO pressure release.[11] At the same time, our experimental results showed that this complex was more stable.

To determine the activation energy of thermal decarbonylation of **1**, we constructed the Arrhenius plot ($\ln k$ vs $1/T$) (Figure 7). The activation energy calculated from the slope of the resulting straight line was 97 ± 6 kJ/mol.

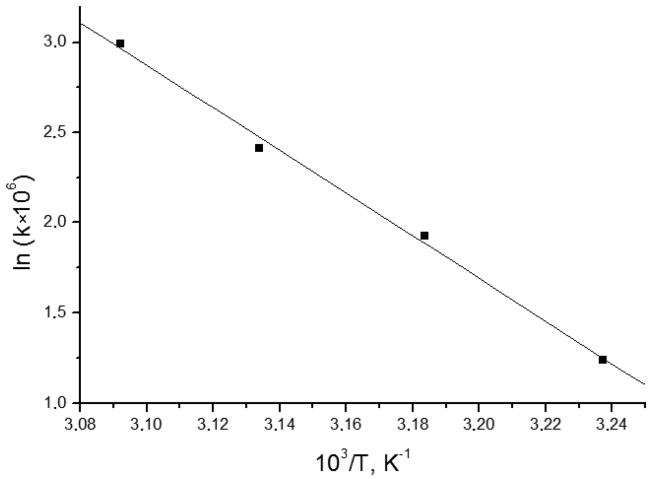

Figure 7. Arrhenius plot for the rate constant of thermal decarbonylation of $[Tc(CO)_5(CNCH_2COOEt)]ClO_4$ in EG.

This value is slightly lower than the activation energy of thermal decarbonylation of $[Tc(CO)_6]^+$ in acetonitrile (118 ± 4 kJ/mol).[2] The activation entropy of the reaction, determined by the Eyring analysis of the kinetic data, is ΔS = 129 ± 6 J/(mol K). The high positive value of the entropy suggests significant contribution of the dissociative pathway to the overall mechanism of the reaction.

To understand whether the kinetics of thermal decarbonylation changes in going from short- (C_2) to long-chain (C_{11}) ligand, we determined the rate constant of thermolysis of $[Tc(CO)_5(CN(CH_2)_{10}COOMe)]ClO_4$ in EG at 41.1 °C. The rate constant calculated from the slope of the kinetic curve (Figure 8) is $(4.49 \pm 0.18) \times 10^{-6}$ s^{-1}; i.e., it is still lower (by a factor of 1.6) than that for **1**. This means that only 1.5% of $[Tc(CO)_5(CN(CH_2)_{10}COOMe)]ClO_4$ can be expected to thermally decompose at 37 °C in 24 h. Thus, from the medical point of view, this complex is stable with respect to thermal decarbonylation.

As for analogous complexes of rhenium pentacarbonyl isocyanides **2** and **4**, no changes in the IR spectra of their solution in EG were observed even after heating at 50.4 °C for

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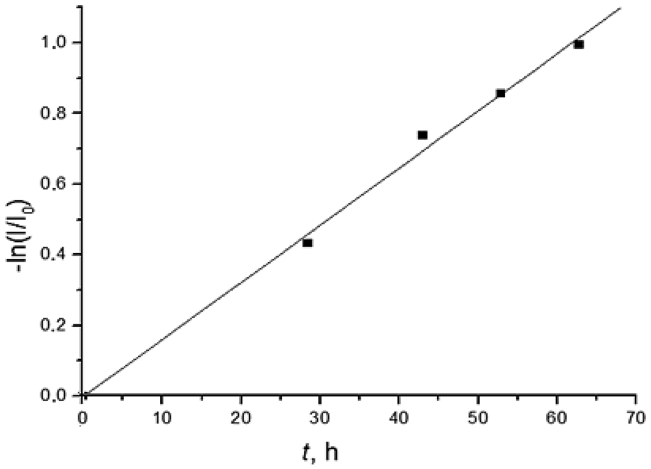

Figure 8. Kinetics of thermal decarbonylation of $[Tc(CO)_5(CN(CH_2)_{10}COOMe)]ClO_4$ in EG at 41.1 °C (semilog plot).

20 h. Thus, at the temperature of a human body, technetium and particularly rhenium pentacarbonyl isocyanide complexes **2** and **4** are sufficiently resistant to thermal decarbonylation in solution.

The other possible degradation pathway of the pentacarbonyl isocyanide complexes is their reaction with blood plasma proteins. To simulate interactions of our complexes with reactive groups of blood plasma, the histidine challenge reactions were performed. Since the complexes with C_{11} isocyano carboxylate are water-insoluble, we studied model complexes **1** and **2**. The reaction was monitored by IR spectroscopy. A solution of complexes **1** and **2** in a phosphate buffer was incubated at 37 °C for 1 h in the presence of histidine taken in a 10-fold excess. Surprisingly, a yellow precipitate was observed in the solution of the rhenium complex **2**. The technetium solution remained clear. The yellow precipitate is readily soluble in nonpolar solvents including hexane. Our attempts to crystallize this product from a solution or by vacuum sublimation failed. The IR spectra of the mother liquor of both rhenium and technetium systems contained mainly the bands of the initial pentacarbonyl isocyanide complexes, with the intensity of the bands of the rhenium complex being lower as compared to those of the initial solution (Figures 9 and 10). Thus, $[Re(CO)_5(CN(CH_2)COOEt)]ClO_4$ partially decomposes in a neutral

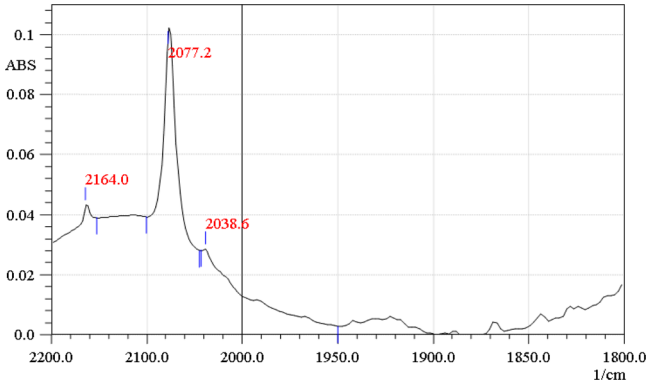

Figure 9. IR spectrum of $[Tc(CO)_5(CNCH_2COOEt)]ClO_4$ in phosphate buffer (pH 7.2) after heating for 1 h at 37 °C in the presence of histidine.

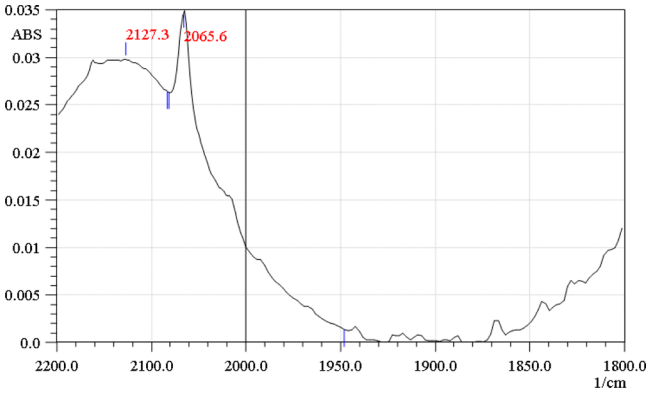

Figure 10. IR spectrum of $[Re(CO)_5(CNCH_2COOEt)]ClO_4$ solution in phosphate buffer (pH 7.2) after heating for 1 h at 37 °C in the presence of histidine.

aqueous solution containing histidine, whereas its technetium analogue is more stable under these conditions.

CONCLUSION

Rhenium(I) and technetium(I) pentacarbonyl complexes with C_2 and C_{11} ω-isocyanocarboxylic acid esters were prepared and fully characterized. Rhenium complexes $[Re(CO)_5(CNCH_2COOEt)]ClO_4$ and $Re(CO)_5(CN(CH_2)_{10}COOMe)]ClO_4$ are stable with respect to thermal decarbonylation in EG. Technetium complexes undergo slow decarbonylation in solution, but the reaction rate is sufficiently low for the complexes to be used in nuclear medicine. On the contrary, in aqueous solutions in the presence of histidine, rhenium pentacarbonyl isocyanide complex **2** significantly decomposes, whereas its Tc analogue is much more stable. We suggest that decomposition of $[Re(CO)_5(CN(CH_2)COOEt)]ClO_4$ in an aqueous solution is due to nucleophilic attack of hydroxide anion on the carbon atom of the carbonyl or isocyanide ligand. Thus, the isocyanide coordination core can be used to conjugate rhenium and technetium pentacarbonyl fragments with long-chain fatty acid esters. Unfortunately, the resulting Re bioconjugates are unstable in histidine-containing aqueous solutions.

ASSOCIATED CONTENT

Supporting Information

Figures giving ^1H and $^{13}C\{^1H\}$ NMR spectra and IR spectra and tables giving crystallographic data and refinement parameters (complexes **1** and **2**), atomic coordinates and displacement parameters for all atoms (complexes **1** and **2**), and selected interatomic distances and bond angles in the structure (complexes **1** and **2**). This material is available free of charge via the Internet at http://pubs.acs.org. Supplementary crystallographic data for this paper have been deposited at the Cambridge Crystallographic Data Centre (CCDC 956529 and 956530 for the crystal structures of **1** and **2**, respectively) and can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

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Notes

The authors declare no competing financial interest.

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