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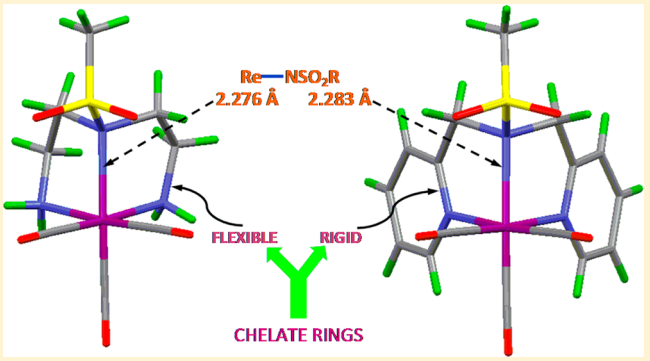
Complexes Possessing Rare "Tertiary" Sulfonamide Nitrogen-to-Metal Bonds of Normal Length: *fac*-[Re(CO)$_3$(*N*(SO$_2$R)dien)]PF$_6$ Complexes with Hydrophilic Sulfonamide Ligands

Pramuditha L. Abhayawardhana, Patricia A. Marzilli, Frank R. Fronczek, and Luigi G. Marzilli*

Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803, United States

Supporting Information

ABSTRACT: Tertiary sulfonamide nitrogen-to-metal bonds of normal length are very rare. We recently discovered such a bond in one class of *fac*-[Re(CO)$_3$(N(SO$_2$R)(CH$_2$Z)$_2$)]^n complexes (Z = 2-pyridyl) with *N*(SO$_2$R)dpa ligands derived from di-(2-picolyl)amine (*N*(H)dpa). *fac*-[M(CO)$_3$(N-(SO$_2$R)(CH$_2$Z)$_2$)]^n agents (M = $^{186/188}$Re, ^{99m}Tc) could find use as radiopharmaceutical bioconjugates when R is a targeting moiety. However, the planar, electron-withdrawing 2-pyridyl groups of *N*(SO$_2$R)dpa destabilize the ligand to base and create relatively rigid chelate rings, raising the possibility that the rare M−N(sulfonamide) bond is an artifact of a restricted geometry. Also, the hydrophobic 2-pyridyl groups could cause undesirable accumulation in the liver, limiting future use in radiopharmaceuticals. Our goal is to identify a robust, hydrophilic, and flexible N(CH$_2$Z)$_2$ chelate framework. New C_2-symmetric ligands, N(SO$_2$R)(CH$_2$Z)$_2$ with (Z = CH$_2$NH$_2$; R = Me, dmb, or tol), were prepared by treating *N*(H)dien(Boc)$_2$, a protected diethylenetriamine (*N*(H)dien) derivative, with methanesulfonyl chloride (MeSO$_2$Cl), 3,5-dimethylbenzenesulfonyl chloride (dmbSO$_2$Cl), and 4-methylbenzenesulfonyl chloride (tolSO$_2$Cl). Treatment of *fac*-[Re(CO)$_3$(H$_2$O)$_3$]$^+$ with these ligands, designated as *N*(SO$_2$R)dien, afforded new *fac*-[Re(CO)$_3$(*N*(SO$_2$R)dien)]PF$_6$ complexes. Comparing the *fac*-[Re-(CO)$_3$(*N*(SO$_2$Me)dien)]PF$_6$ and *fac*-[Re(CO)$_3$(*N*(SO$_2$Me)dpa)]PF$_6$ complexes, we find that the Re$^{\mathrm{I}}$−N(sulfonamide) bonds are normal in length and statistically identical and that the methyl ^{13}C NMR signal has an unusually upfield shift compared to that in the free ligand. We attribute this unusual upfield shift to the fact that the sulfonamide N undergoes an sp^2-to-sp^3 rehybridization upon coordination to Re$^{\mathrm{I}}$ in both complexes. Thus, the sulfonamide N of *N*(SO$_2$R)dien ligands is a good donor, even though the chelate rings are conformationally flexible. Addition of the strongly basic and potentially monodentate ligand, 4-dimethylaminopyridine, did not affect the *fac*-[Re(CO)$_3$(*N*(SO$_2$tol)dien)]PF$_6$ complex, even after several weeks. This complex is also stable to heat in aqueous solution. These results indicate that *N*(SO$_2$R)dien ligands form *fac*-[Re(CO)$_3$(*N*(SO$_2$R)dien)]PF$_6$ complexes sufficiently robust to be utilized for radiopharmaceutical development.



INTRODUCTION

Many *fac*-[^{99m}Tc(CO)$_3$L]^n imaging agents with facially coordinated tridentate ligands (L) have been studied[1−8] because of the convenient generation of the *fac*-[^{99m}Tc-(CO)$_3$(H$_2$O)$_3$]$^+$ precursor.[9,10] Some of these imaging agents have exhibited satisfactory results in human volunteers and in early patient studies.[4,7,8] Such *fac*-[^{99m}Tc(CO)$_3$L]^n agents are more robust and have better pharmacokinetic properties than agents with bidentate ligands.[11] The γ-emitting ^{99m}Tc radionuclide has ideal nuclear properties[12,13] for diagnostic applications in nuclear medicine.[1,14−17]

The development of ^{99m}Tc radiopharmaceutical agents benefits from an understanding of the chemistry of their Re analogues. The discovery of a straightforward preparation of the *fac*-[Re(CO)$_3$(H$_2$O)$_3$]$^+$ precursor[18] has led to significantly improved aqueous synthetic methods for *fac*-[M(CO)$_3$L]^n agents (M = various isotopes of Tc and Re).[3,16,17,19−21] *fac*-[Re(CO)$_3$L]^n complexes serve as excellent structural models for *fac*-[^{99m}Tc(CO)$_3$L]^n imaging agents.[4,22−27] Moreover, *fac*-[$^{186/188}$Re(CO)$_3$L]^n agents themselves are emerging as promising radiopharmaceuticals, owing to their potential usefulness in radiotherapy.[1,12,20,28]

New types of tridentate ligands and ligand conjugation methods will expand the likelihood of developing useful new agents with the *fac*-[M$^{\mathrm{I}}$(CO)$_3$]$^+$ core (M = ^{99m}Tc, $^{186/188}$Re).[10,29,30] Meeting such goals requires the identification of suitable linker systems with high stability, small size, and core ligands having a tridentate donor framework that does not increase the number of isomers.[31−34] Symmetrical linear tridentate ligands with linkage at the center donor are thus suitable candidates because the generation of racemic or diastereoisomeric mixtures of radiopharmaceuticals can be

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avoided.[35] Recent studies have reported promising biomedical properties for *fac*-$[Re(CO)_3L]^n$ complexes bearing a tridentate L with three N donors having a substituent replacing the proton at the central sp^3 N.[16,29,36,37] However, the conjugation of biologically important groups in these complexes was limited to groups attached via an N−C bond to the central N of ligands with the $N(CH_2Z)_2$ tridentate ligand framework. Z is commonly an N donor (e.g., 2-pyridyl)[16,36] or a carboxyl group.[3] The use of a biologically compatible linking group that did not create an N−C bond would greatly increase the chances of discovering useful agents.

Molecules containing a sulfonamide represent a very important class of biologically active molecules with a wide variety of applications.[39−45] Therefore, we previously set out to explore conjugation that utilizes an N−S bond with the central N being the sulfonamide N.[35] The reaction of various sulfonyl chlorides (RSO_2Cl) with di-(2-picolyl)amine (*N*(H)dpa) afforded *N*(SO_2R)dpa ligands.[35] [Note that we use the normal convention: an *N* (italic N) designates a substituent location on nitrogen in the name of a compound. In this article, *N* designates a substituent located on the central or anchoring nitrogen atom of a tridentate ligand.] These *N*(SO_2R)dpa ligands readily added to *fac*-$[Re(CO)_3(H_2O)_3]^+$ to form *fac*-$[Re(CO)_3(N(SO_2R)dpa)]PF_6$ (or BF_4) complexes. We learned that these were the only examples of structurally characterized complexes bearing an N-bound, open-chain tertiary sulfonamide linkage with a normal M−N bond length. These *fac*-$[Re(CO)_3(N(SO_2R)dpa)]PF_6$ complexes were the first examples of such structurally characterized complexes with a neutral tertiary sulfonamide donor bound not only to the *fac*-$[Re^I(CO)_3]^+$ core but to any metal center.[35] Although the results in that report appeared to serve as proof of principle, the tridentate framework, $N(CH_2Z)_2$ with Z = 2-pyridyl, is relatively rigid, and the resulting geometric constraints could possibly account for the observation of the M−N(sulfonamide) bond of normal length, as found in cases when complicated ligand ring structures fix the bond lengths.[35] Thus, the study of *fac*-$[Re(CO)_3(N(SO_2R)(CH_2Z)_2)]^n$ complexes with more flexible chelate rings is of fundamental importance to coordination chemistry.

The new *fac*-$[Re(CO)_3(N(SO_2R)dpa)]X$ complexes revealed the feasibility of having a tridentate ligand anchored by a central tertiary sulfonamide N. However, the two 2-pyridyl rings in a potential *fac*-$[M(CO)_3(N(SO_2R)dpa)]^n$ imaging agent are hydrophobic, an undesirable property in an imaging agent because it is expected to promote liver uptake.[12] Also, the 2-pyridyl groups are electron withdrawing, facilitating decomposition of coordinated *N*(SO_2R)dpa ligands by strong base.[35]

With the goals of exploring fundamental coordination chemistry of sulfonamides and of identifying ligands for use in imaging agents, we have now explored a more hydrophilic and more flexible ligand system that is suitable for our new conjugation method. Here, we employ a prototypical triamine ligand framework based on diethylenetriamine (*N*(H)dien).[46] In the new *N*(SO_2R)dien ligands, the aromatic 2-pyridyl groups of the dpa moiety are replaced with hydrophilic $-CH_2NH_2$ groups. The new ligands are stable to base and have the advantage of being small in size, a feature considered to be desirable for bioconjugates.[32,34] All of the new complexes discussed below have the facial geometry, and thus from this point onward, we omit the *fac*- designation when discussing specific compounds.

EXPERIMENTAL SECTION

Starting Materials. Methanesulfonyl chloride ($MeSO_2Cl$), 3,5-dimethylbenzenesulfonyl chloride ($dmbSO_2Cl$), 4-methylbenzenesulfonyl chloride ($tolSO_2Cl$), *N,N,N*-triethylamine, trifluoroacetic acid (TFA), *N*(H)dien, 2-(*tert*-butoxycarbonyloxyimino)-2-(phenylacetonitrile), 4-dimethylaminopyridine, and $Re_2(CO)_{10}$ were used as received from Aldrich. Aqueous $[Re(CO)_3(H_2O)_3]OTf$ (OTf = trifluoromethanesulfonate) was prepared by a known method.[18]

NMR Measurements. ^1H NMR and ^{13}C NMR spectra were recorded on a 400 MHz Bruker spectrometer. Peak positions are relative to TMS or to solvent residual peak, with TMS as reference. All NMR data were processed with TopSpin and MestReNova software. NMR data not presented in the Experimental Section can be found in the Results Section or in Supporting Information.

Mass Spectrometric Measurements. High-resolution mass spectra were recorded on a Bruker Ultraflex MALDI TOF mass spectrometer and an Agilent 6210 ESI TOF LCMS mass spectrometer.

X-ray Data Collection and Structure Determination. Intensity data were collected at low temperature on a Bruker Kappa Apex-II DUO CCD diffractometer fitted with an Oxford Cryostream cooler with graphite-monochromated Mo Kα (λ = 0.71073 Å) radiation. Data reduction included absorption corrections by the multiscan method, with SADABS.[47] The structures were determined by direct methods and difference Fourier techniques and were refined by full-matrix least-squares using SHELXL-97.[48] All non-hydrogen atoms were refined anisotropically. All H atoms were visible in difference maps but were placed in idealized positions, except for N−H hydrogen atoms, for which coordinates were refined. A torsional parameter was refined for each methyl group. Compound **6** has two independent formula units in the asymmetric unit.

Synthesis of *N,N″*-Bis(*tert*-butoxycarbonyl)diethylenetriamine (*N*(H)dien(Boc)$_2$). The *N*(H)dien$(Boc)_2$ ligand was prepared in 96% yield by a known method.[49] ^1H NMR signals (ppm) in $CDCl_3$: 4.89 (br s, 1H, NH), 3.20 (m, 4H, $2CH_2$), 2.72 (t, 4H, $2CH_2$), 1.44 (s, 18H, $6CH_3$). These ^1H NMR chemical shifts matched the previously reported values.[49]

General Synthesis of *N*(SO_2R)dien. The following general procedure was employed to obtain the $[N(SO_2Me)dienH_2]$-$(CF_3CO_2)_2$ (**1**) and *N*(SO_2R)dien (R = dmb (**2**), R = tol (**3**)) ligands: a solution of the sulfonyl chloride (2 mmol) in 30 mL of dioxane was added dropwise over 2 h to a solution of *N*(H)dien$(Boc)_2$ (0.61 g, 2 mmol) and triethylamine (0.28 mL, 2 mmol) in dioxane (100 mL) at room temperature. The reaction mixture was stirred at room temperature for 20 h and filtered to remove any precipitate. The solvent was completely removed by rotary evaporation, water (50 mL) was added to the resulting oil, and the product was extracted into CH_2Cl_2 (2 × 25 mL). The CH_2Cl_2 extracts were combined and washed again with water (2 × 25 mL) at pH ∼6. The organic layer was dried with anhydrous Na_2SO_4, and the CH_2Cl_2 was removed by rotary evaporation to yield an off-white solid. The Boc-protected diensulfonamide, *N*(SO_2R)dien$(Boc)_2$, was purified if necessary by column chromatography (silica gel column and a mixture of ethyl acetate/hexane). After characterization by ^1H NMR spectroscopy, this *N*(SO_2R)dien$(Boc)_2$ product was then deprotected by dropwise addition of trifluoroacetic acid (0.16−0.24 mL, 2−3 mmol) to a CH_2Cl_2 solution (at ∼0 °C) of the compound (5 mL, 1 mmol). The reaction mixture was allowed to warm to room temperature, stirred for 16 h at room temperature, and then filtered; the filtrate was taken to dryness by rotary evaporation. Water at pH ∼8−9 (50 mL) was added to the residue, and the product was extracted into $CHCl_3$ (2 × 25 mL). The combined $CHCl_3$ extracts were dried over anhydrous Na_2SO_4, and the solvent was removed by rotary evaporation, leaving a white/off-white powder or, when R = Me, a yellow oil.

General Synthesis of $[Re(CO)_3(N(SO_2R)dien)]PF_6$. A solution of the *N*($SO_2R$)dien ligand (0.1 mmol) in methanol (2 mL) was added to an aqueous solution of $[Re(CO)_3(H_2O)_3]OTf$ (5 mL, 0.1 mmol). Methanol (1−2 mL) was added to dissolve any precipitate that formed. The pH of the reaction mixture was adjusted to ∼6−7 with

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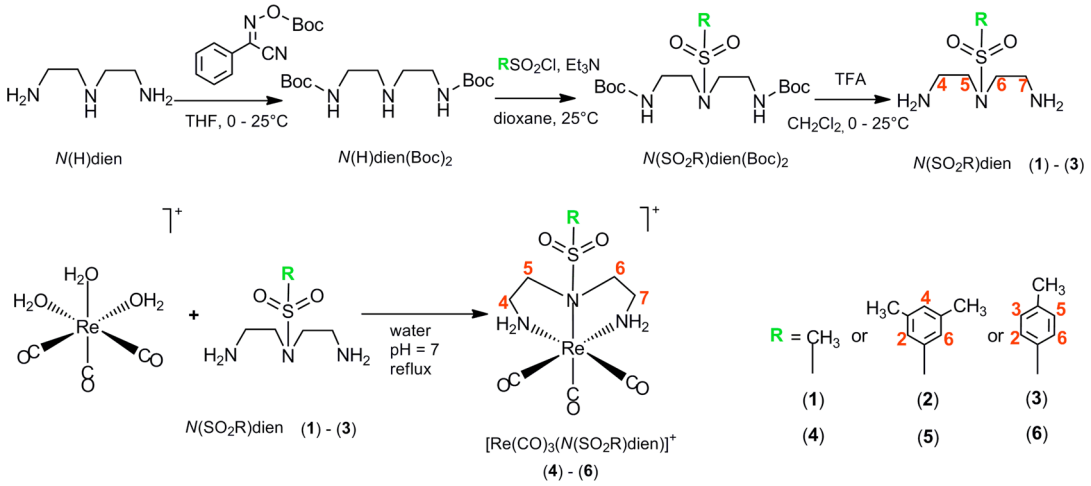

Figure 1. General reaction scheme for the synthesis of $N(SO_2R)$dien ligands (top) and $[Re(CO)_3(N(SO_2R)dien)]^+$ complexes (bottom).

0.5 M NaOH if necessary, and the clear reaction mixture was heated at reflux for 24 h. An excess (0.16 g, 1 mmol) of $NaPF_6$ was added to the clear solution, and the precipitate that formed within ~30 min was collected on a filter, washed with water, and air-dried.

Synthesis of $[N(SO_2Me)dienH_2](CF_3CO_2)_2$ ($[\mathbf{1}H_2](CF_3CO_2)_2$). The use of $MeSO_2Cl$ (0.16 mL, 2 mmol) in the general method described above yielded crude $N(SO_2Me)dien(Boc)_2$ as a brown oil (0.65 g, 85% yield). ^{1}H NMR signals (ppm) in DMSO-d_6: 6.92 (br s, 2H, 2NH), 3.14 (m, 4H, $2CH_2$), 3.06 (m, 4H, $2CH_2$), 2.89 (s, 3H, CH_3), 1.37 (s, 18H, $6CH_3$).

The deprotection process described in the general method above afforded $N(SO_2Me)$dien (**1**) as a pale-yellow, oily substance (yield: 0.004 g, 18%). ^{1}H NMR signals (ppm) in $CDCl_3$: 3.25 (t, J = 6.3 Hz, 4H, 2C(5/6)H_2), 2.93 (s, 3H, CH_3), 2.90 (t, J = 6.4 Hz, 4H, 2C(4/7)H_2); in acetonitrile-d_3: 3.14 (t, J = 6.5 Hz, 4H, 2C(5/6)H_2), 2.86 (s, 3H, CH_3), 2.76 (t, J = 6.5 Hz, 4H, 2C(4/7)H_2); in DMSO-d_6: 3.08 (broad t, 4H, 2C(5/6)H_2), 2.91 (s, 3H, CH_3), 2.67 (broad t, 4H, 2C(4/7)H_2). ^{13}C NMR signals (ppm) in $CDCl_3$: 51.59 (C5/6), 40.70 (C4/7), 37.60 (CH_3).

Compared to ligands with other R groups, isolation for R = Me produced a low yield, owing to the more hydrophilic nature of $N(SO_2Me)$dien. To increase the amount of material available for synthesis of the complex, the general deprotection process was modified by adding a slight excess of trifluoroacetic acid to obtain the protonated ligand $[N(SO_2Me)dienH_2](CF_3CO_2)_2$ ($[\mathbf{1}H_2](CF_3CO_2)_2$). A mixture of $N(SO_2Me)dien(Boc)_2$ (0.38 g, 1 mmol) and trifluoroacetic acid (0.24 mL, 3 mmol) was stirred at room temperature for 16 h, and the resulting mixture was filtered; the white precipitate that was collected on a filter paper was washed several times with CH_2Cl_2 and air-dried. The precipitate was then dissolved in methanol (3 mL), and the solution was filtered. CH_2Cl_2 (~10 mL) was added to the filtrate until cloudiness was observed. After 24 h, the undisturbed solution yielded thin, colorless, needle-like crystals of the trifluoroacetate salt of the protonated ligand $[N(SO_2Me)dienH_2](CF_3CO_2)_2$ ($[\mathbf{1}H_2](CF_3CO_2)_2$) (0.29 g, 72% yield). ^{1}H NMR signals (ppm) in DMSO-d_6: 7.81 (br s, 6H, 2^+NH_3), 3.37 (t, J = 6.2 Hz, 4H, $2CH_2$), 3.04 (s, 3H, CH_3), 3.00 (t, J = 6.3 Hz, 4H, $2CH_2$). ESI-MS m/z: $[M + H]^+$ calcd for $C_5H_{15}O_2N_3S$, 182.0958; found, 182.0957.

Synthesis of $N(SO_2dmb)$dien (2). The use of $dmbSO_2Cl$ (0.40 g, 2 mmol) according to the general synthetic procedure above yielded a pale yellow oil, which was purified by dissolving the oil in a minimum (~1 mL) of ethyl acetate and loading the solution onto a silica gel column. A 1:5 mixture of ethyl acetate:hexane was used to elute the remaining $dmbSO_2Cl$ starting material (UV–vis). The product (UV–vis) was then eluted with a 2:3 (v/v) mixture of ethyl acetate/hexane. Thin-layer chromatography was used to determine the progress of separation. Removal of solvent by rotary evaporation yielded $N(SO_2dmb)dien(Boc)_2$ as a pale yellow powder (0.87 g, 92% yield). ^{1}H NMR signals (ppm) in $CDCl_3$: 7.65 (s, 2H, H2/6), 7.21 (s, H, H4), 5.19 (br s, 2H, NH), 3.32 (m, 4H, $2CH_2$), 3.18 (m, 4H, $2CH_2$), 2.38 (s, 6H, $2CH_3$), 1.45 (s, 18H, $6CH_3$).

Deprotection of $N(SO_2dmb)dien(Boc)_2$ (0.47 g, 1 mmol) with trifluoroacetic acid (0.16 mL, 2 mmol), by the procedure described above, afforded $N(SO_2dmb)$dien (**2**) as a white powder (0.26 g, 98% yield). ^{1}H NMR signals (ppm) in $CDCl_3$: 7.42 (s, 2H, H2/6), 7.20 (s, H, H4), 3.15 (t, J = 6.4 Hz 4H, 2C(5/6)H_2), 2.91 (t, J = 6.4 Hz, 4H, 2C(4/7)H_2), 2.38 (s, 6H, $2CH_3$). ESI-MS m/z: $[M + H]^+$ calcd for $C_{12}H_{21}O_2N_3S$, 272.1427; found, 272.1431.

Synthesis of $N(SO_2tol)$dien (3). The general procedure using $tolSO_2Cl$ (0.44 g, 2 mmol) yielded $N(SO_2tol)dien(Boc)_2$ as a pale yellow oil (0.78 g, 86% yield). ^{1}H NMR signals (ppm) in $CDCl_3$: 7.67 (d, J = 8.3 Hz, 2H, H2/6), 7.31 (d, J = 8.1 Hz, 2H, H3/5), 5.18 (br s, 2H, NH), 3.32 (m, 4H, $2CH_2$), 3.17 (m, 4H, $2CH_2$), 2.43 (s, 3H, CH_3), 1.45 (s, 18H, $6CH_3$).

Deprotection of $N(SO_2tol)dien(Boc)_2$ (0.45 g, 1 mmol) with trifluoroacetic acid (0.16 mL, 2 mmol) afforded $N(SO_2tol)$dien (**3**) as a white powder (0.23 g, 92% yield). ^{1}H NMR signals (ppm) in $CDCl_3$: 7.70 (d, J = 8.2 Hz, 2H, H2/6), 7.31 (d, J = 8.0 Hz, 2H, H3/5), 3.15 (t, J = 6.4 Hz, 4H, 2C(5/6)H_2), 2.91 (t, J = 6.4 Hz, 4H, 2C(4/7)H_2), 2.43 (s, 3H, CH_3); in acetonitrile-d_3: 7.69 (d, J = 8.4 Hz, 2H, H2/6), 7.39 (d, J = 7.9 Hz, 2H, H3/5), 3.07 (t, J = 6.4 Hz, 4H, 2C(5/6)H_2), 2.79 (t, J = 6.5 Hz, 4H, 2C(4/7)H_2), 2.41 (s, 3H, CH_3). ESI-MS m/z: $[M + H]^+$ calcd for $C_{11}H_{19}O_2N_3S$, 258.1271; found, 258.1277.

Synthesis of $[Re(CO)_3(N(SO_2Me)dien)]PF_6$ (4). The general method above, with the $[\mathbf{1}H_2](CF_3CO_2)_2$ ligand (0.04 g, 0.1 mmol) and $[Re(CO)_3(H_2O)_3]OTf$ (5 mL, 0.1 mmol), afforded $[Re(CO)_3(N(SO_2Me)dien)]PF_6$ (**4**) as a white crystalline precipitate (0.036 g, 60% yield) after the addition of $NaPF_6$ (~16 mg). (The pH of the acidic reaction mixture was adjusted to ~7 with 0.5 M NaOH before the solution was heated at reflux.) ^{1}H NMR signals (ppm) in DMSO-d_6: 5.65 (m, 2H, NH), 4.27 (m, 2H, NH), 3.57 (s, 3H, CH_3), 3.45 (m, 2H, CH_2), 3.22 (m, 2H, CH_2), 3.10 (m, 2H, CH_2), 2.97 (m, 4H, $2CH_2$). ^{1}H NMR signals (ppm) of the R group in acetone-d_6: 3.62 (s, 3H, CH_3); in acetonitrile-d_3: 3.33 (s, 3H, CH_3). Chelate ring ^{1}H NMR signals for **4**–**6** in these solvents are reported in the Results and Discussion. ^{13}C NMR signals (ppm) in DMSO-d_6: 55.91 (C5/6), 44.86 (C4/7), 32.50 (CH_3). ^{13}C NMR signals (ppm) in acetone-d_6: 55.11 (C5/6), 44.46 (C4/7), 30.97(CH_3). MALDI-TOF m/z: $[M^+]$ calcd for $C_8H_{15}O_5N_3SRe$, 452.029; found, 452.158.

Synthesis of $[Re(CO)_3(N(SO_2dmb)dien)]PF_6$ (5). The use of the general procedure with $N(SO_2dmb)$dien (**2**) (0.03 g, 0.1 mmol) afforded $[Re(CO)_3(N(SO_2dmb)dien)]PF_6$ (**5**) as a white precipitate (0.047 g, 69% yield) after the addition of $NaPF_6$ (~16 mg). ^{1}H NMR signals (ppm) in DMSO-d_6: 7.72 (s, 2H, H2/6), 7.57 (s, H, H4), 5.72 (m, 2H, NH), 4.28 (m, 2H, NH), 3.41 (m, 2H, CH_2), 3.14 (m, 2H, CH_2), 3.00 (m, 2H, CH_2), 2.65 (m, 2H, CH_2), 2.42 (s, 6H, $2CH_3$). ^{1}H NMR signals (ppm) of the R group in acetone-d_6: 7.77 (s, 2H, H2/6), 7.60 (s, H, H4), 2.46 (s, 6H, $2CH_3$); in acetonitrile-d_3: 7.65 (s, 2H,

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H2/6), 7.55 (s, H, H4), 2.44 (s, 6H, $2CH_3$). ^{13}C NMR signals (ppm) in acetone-d_6: 142.30 (dmb ring C1), 139.54 (dmb ring C4), 130.93 (dmb ring C2/6), 126.71(dmb ring C3/5), 57.83 (C5/6), 46.93 (C4/7), 22.09 ($2CH_3$). MALDI-TOF m/z: [M^+] calcd for $C_{15}H_{21}O_5N_3SRe$, 542.076; found, 542.155.

Synthesis of [Re(CO)$_3$(*N*(SO$_2$tol)dien)]PF$_6$ (6). The use of *N*(SO$_2$tol)dien (**3**) (0.02 g, 0.1 mmol) as described in the general synthesis afforded [Re(CO)$_3$(*N*(SO$_2$tol)dien)]PF$_6$ (**6**) as a white precipitate (0.056 g, 84% yield) after the addition of $NaPF_6$ (~16 mg). Slow evaporation of a solution of the compound in acetone produced colorless, X-ray quality, needle-shaped crystals. ^1H NMR signals (ppm) in DMSO-d_6: 7.99 (d, J = 8.5 Hz, 2H, H2/6), 7.61 (d, J = 8.1 Hz, 2H, H3/5), 5.70 (m, 2H, NH), 4.28 (m, 2H, NH), 3.40 (m, 2H, CH_2), 3.14 (m, 2H, CH_2), 3.01 (m, 2H, CH_2), 2.66 (m, 2H, CH_2), ~2.5, overlapped (s, 3H, CH_3). ^1H NMR signals (ppm) of the R group in acetone-d_6: 8.05 (d, 2H, H2/6), 7.65 (d, 2H, H3/5), 2.53 (s, 3H, CH_3); in acetonitrile-d_3: 7.91(d, 2H, H2/6), 7.58 (d, 2H, H3/5), 2.51 (s, 3H, CH_3). ^{13}C NMR signals (ppm) in DMSO-d_6: 147.80 (tol ring C4), 132.07 (tol ring C2/6), 131.00 (tol ring C3/5), 125.98 (tol ring C1), 56.20 (C5/6), 44.80 (C4/7), 21.69 (CH_3). ^{13}C NMR signals (ppm) in acetone-d_6: 148.88 (tol ring C4), 132.70 (tol ring C2/6), 131.58 (tol ring C3/5), 127.05 (tol ring C1), 56.94 (C5/6), 46.00 (C4/7), 21.74 (CH_3). MALDI-TOF m/z: [M^+] calcd for $C_{14}H_{19}O_5N_3SRe$, 528.060; found, 528.001.

Challenge Reactions of [Re(CO)$_3$(*N*(SO$_2$tol)dien)]PF$_6$ (6). Two 5 mM solutions of **6** in DMSO-d_6 (500 μL) were treated separately with 10 molar equiv (0.6 μL, 50 mM) or 2 molar equiv (0.12 μL, 10 mM) of diethylenetriamine and monitored over time by ^1H NMR spectroscopy. Another challenge experiment was carried out with a 5 mM solution of **6** in DMSO-d_6 by first adding 1 molar equiv of 4-dimethylaminopyridine (4-Me$_2$Npy) and then increasing the 4-Me$_2$Npy to 10 molar equiv.

RESULTS AND DISCUSSION

Synthesis of *N*(SO$_2$R)dien and [Re(CO)$_3$(*N*(SO$_2$R)dien)]PF$_6$. *N*(SO$_2$Me)dien (**1**), *N*(SO$_2$dmb)dien (**2**), and *N*(SO$_2$tol)dien (**3**) were synthesized by coupling *N*(H)dien with the respective sulfonyl chloride (Figure 1). In this case, unlike in the synthesis of *N*(SO$_2$R)dpa ligands,[35] additional steps are required to synthesize the *N*(SO$_2$R)dien ligands (**1**–**3**), owing to the possibility of attack by the terminal *N*(H)dien amino groups on the sulfur atom of the sulfonyl chloride. Thus, the *N*(H)dien terminal amine groups were protected with Boc groups. The products were obtained in good yield and purity, as indicated by ^1H NMR spectral data. Reaction of the deprotected ligands with an aqueous solution of [Re(CO)$_3$(H$_2$O)$_3$]OTf afforded [Re(CO)$_3$(*N*(SO$_2$Me)dien)]PF$_6$ (**4**), [Re(CO)$_3$(*N*(SO$_2$dmb)dien)]PF$_6$ (**5**), and [Re(CO)$_3$(*N*(SO$_2$tol)dien)]PF$_6$ (**6**) in 60–84% yields. All three complexes were characterized by ^1H and ^{13}C NMR spectroscopy and by mass spectrometry (Experimental Section).

X-ray quality crystals of **4** and **6** were grown by slowly cooling a 5 mM solution of the compound in warm water. Crystals of **5** (grown by slow evaporation of a 5 mM acetone solution) suffered from twinning, space-group ambiguity, and disorder problems in the molecule, which prevented refinement within acceptable values. However, the structural characterization of **5** (using the same procedures as for **4** and **6**) confirmed that all three N atoms of *N*(SO$_2$dmb)dien are coordinated to Re.

Structural Results. Crystal data and structural refinement details for [Re(CO)$_3$(*N*(SO$_2$Me)dien)]PF$_6$ (**4**) and [Re(CO)$_3$(*N*(SO$_2$tol)dien)]PF$_6$ (**6**) are summarized in Table 1, and the ORTEP plots appear in Figure 2 (see Figure 1 for the numbering scheme used to describe the solid-state data). Both **4** and **6** exhibit a pseudo octahedral structure, with the three carbonyl ligands occupying one face; the remaining three coordination sites are occupied by the three nitrogen atoms of the tridentate ligand.

Table 1. Crystal Data and Structure Refinement for [Re(CO)$_3$(*N*(SO$_2$Me)dien)]PF$_6$ (4) and [Re(CO)$_3$(*N*(SO$_2$tol)dien)]PF$_6$ (6)

	4	6
empirical formula	$C_8H_{15}N_3O_5ReS{\cdot}PF_6$	$C_{14}H_{19}N_3O_5ReS{\cdot}PF_6$
fw	596.46	672.55
crystal system	monoclinic	monoclinic
space group	$P2_1/c$	$P2_1/c$
unit cell dimensions		
a (Å)	12.822(3)	26.0233(14)
b (Å)	8.8089(19)	13.0607(7)
c (Å)	14.026(3)	12.2147(7)
β (deg)	94.373(10)	95.831(3)
V (Å^3)	1579.6(6)	4130.1(4)
T (K)	100	100
Z	4	8
ρ_{calc} (Mg/m^3)	2.508	2.163
abs coeff (mm^{-1})	8.02	6.15
$2\theta_{max}$ (°)	70	71.2
R indices[a]	0.018	0.029
wR2 = [$I > 2\sigma(I)$][b]	0.044	0.055
data collected, R_{int}	28379, 0.034	51479, 0.033
data/param	6953/239	18802/585

[a] $R = (\sum||F_o| - |F_c||)/\sum|F_o|$. [b] $wR2 = [\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]]^{1/2}$, in which $w = 1/[\sigma^2(F_o^2) + (dP)^2 + (eP)]$ and $P = (F_o^2 + 2F_c^2)/3$.

Selected bond distances and angles of complexes **4** and **6** are presented in Table 2. The Re–C bond distance of the CO group trans to the sulfonamide group is not significantly different from those of the two cis Re–CO bonds, indicating the absence of any trans influence. All Re–N bond distances in **6** are generally similar to the Re–N(sp^3) distances observed in [Re(CO)$_3$L]$^+$ complexes with prototypical NNN donor ligands, which range from ~2.21 to 2.29 Å as the bulk of substituents on the N atoms increases.[46,50] However, the distances from Re to the central N2 (2.2763(14) Å in **4** and 2.2686(19) Å in **6**) are significantly longer than the Re–N1 distances (2.2377(14) Å for **4** and 2.221(2) Å for **6**) and Re–N3 distances (2.2072(15) Å for **4** and 2.216(2) Å for **6**) (Table 2). These Re–N2 distances in **4** and **6** are significantly longer than the Re–N2 distance in [Re(CO)$_3$(*N*(H)dien)]PF$_6$[46] (2.201(3) Å), but they are comparable to the Re–N2 distance of [Re(CO)$_3$(*N*(Me)dien)]PF$_6$.[46] The Re–N2 distance in the latter complex (2.250(4) Å) is not statistically different from the Re–N2 distance in [Re(CO)$_3$(*N*(SO$_2$tol)dien)]PF$_6$ (**6**, Table 2), suggesting that the bond lengthening in **6** is caused chiefly by steric effects, not electronic effects. Furthermore, the good overlap of the three donor N atoms observed when the three carbonyl carbon (C1, C2, and C3) and Re atoms in the structure of **6** are superimposed with the corresponding atoms in [Re(CO)$_3$(*N*(Me)dien)]PF$_6$[46] (Supporting Information, Figure S1) demonstrates the lack of any large effect of having a tertiary sulfonamide nitrogen instead of a typical sp^3 nitrogen serve as the central anchor of the tridentate ligand.

The lengthening of the Re–N2 bond in **4** and **6** versus [Re(CO)$_3$(*N*(H)dien)]PF$_6$ is similar to that observed in [Re(CO)$_3$(*N*(SO$_2$R)dpa)]PF$_6$ complexes (e.g., R = Me and tol) versus the parent [Re(CO)$_3$(*N*(H)dpa)]Br complex.[30,35]

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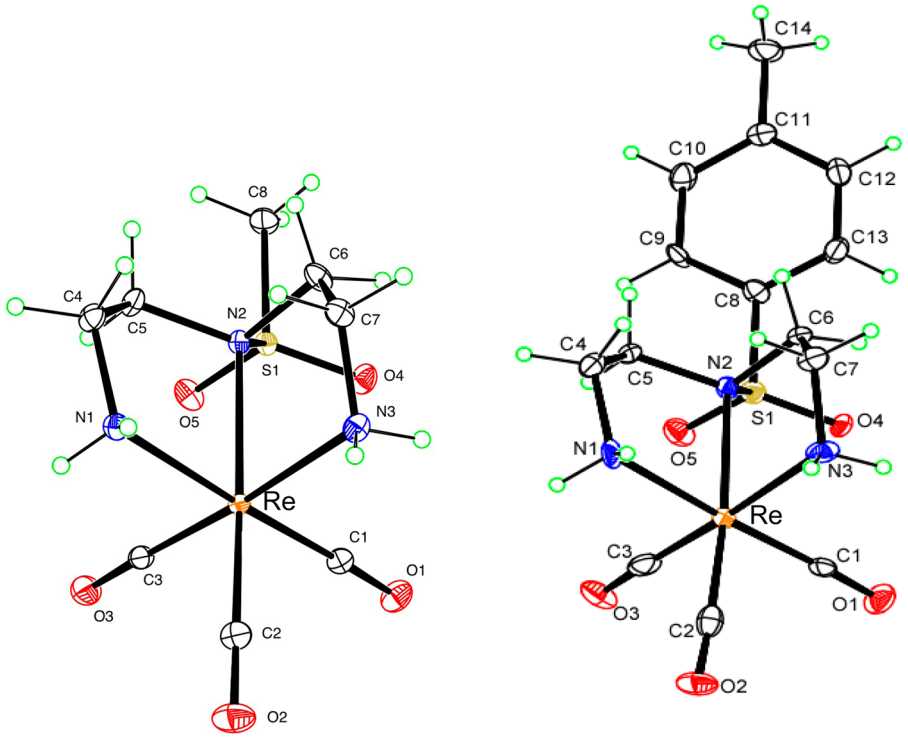

Figure 2. ORTEP plots of the cations in $[Re(CO)_3(N(SO_2Me)dien)]PF_6$ (**4**) (left) and $Re(CO)_3(N(SO_2tol)dien)]PF_6$ (**6**) (right). Thermal ellipsoids are drawn with 50% probability.

Table 2. Selected Bond Distances (Å) and Angles (deg) for $[Re(CO)_3(N(SO_2Me)dien)]PF_6$ (4) and $[Re(CO)_3(N(SO_2tol)dien)]PF_6$ (6)

	4	6		4	6
bond distance			bond angle		
Re−N1	2.2377(14)	2.221(2)	N1−Re−N2	77.07(5)	77.54(7)
Re−N2	2.2763(14)	2.2686(19)	N1−Re−N3	86.53(6)	85.83(8)
Re−N3	2.2072(15)	2.216(2)	N2−Re−N3	77.80(5)	77.86(7)
Re−C1	1.9128(16)	1.913(2)	C2−Re−N1	95.72(6)	92.70(9)
Re−C2	1.9109(18)	1.911(2)	C3−Re−N1	92.31(6)	94.99(9)
Re−C3	1.9136(19)	1.917(3)	C2−Re−N3	96.60(7)	98.29(9)
S1−O5	1.4273(13)	1.4280(18)	C1−Re−N3	93.12(6)	91.92(9)
S1−O4	1.4324(13)	1.4339(17)	Re−N2−S1	111.07(7)	111.35(9)
S1−N2	1.7434(13)	1.759(2)	Re−N2−C5	105.93(9)	106.14(13)
			Re−N2−C6	110.01(10)	109.86(13)
nonbonded distance			S1−N2−C5	109.13(10)	108.82(14)
N1−N3	3.046(2)	3.021(3)	S1−N2−C6	108.52(10)	108.18(13)
N1−N2	2.812(2)	2.812(3)	C5−N2−C6	112.19(13)	112.52(18)
N2−N3	2.816(2)	2.818(3)	C1−Re−N2	99.98(6)	100.55(8)
			C3−Re−N2	97.91(6)	96.81(8)
deviation of N2[a]	0.513(1)	0.514(2)	C1−Re−C2	87.25(7)	89.08(10)
			C3−Re−C2	87.62(7)	87.29(10)
			C1−Re−C3	87.83(7)	87.10(10)

[a]Distance to the sulfonamide N from the plane defined by the S and the two C atoms attached to N2 (average of two independent molecules for **6**).

The similarity of the central Re−N bond distances of the analogous $[Re(CO)_3(N(SO_2R)dpa)]PF_6$ complexes (average = ~2.277 Å) and in **4** and **6** (average = ~2.272 Å) indicates that the donating ability of the sulfonamide N is similar for both ligands.[35] Furthermore, all three donor N atoms show good overlap when the C1, C2, C3, and Re atoms in $[Re(CO)_3(N(SO_2tol)dien)]PF_6$ and $[Re(CO)_3(N(SO_2tol)dpa)]PF_6$ are superimposed (Figure 3). The central Re−N bond distance of the $[Re(CO)_3(N(SO_2Me)dpa)]PF_6$ complex (2.2826(16) Å) is not significantly different from this distance in **4**. Thus, the normal length of the Re−N(sulfonamide) bonds in $[Re(CO)_3(N(SO_2R)dpa)]PF_6$ complexes is not a consequence of the rigidity of the five-membered dpa chelate rings.

The sulfonamide nitrogen of the $N(SO_2tol)$dpa ligand in a Pd^{II} complex is not bound to Pd^{II} and all bond angles around the sulfonamide nitrogen of the $N(SO_2tol)$dpa ligand in the bidentate binding mode are close to 120°, indicating sp^2 hybridization for this N atom.[52] In contrast, in **4** and **6**, all

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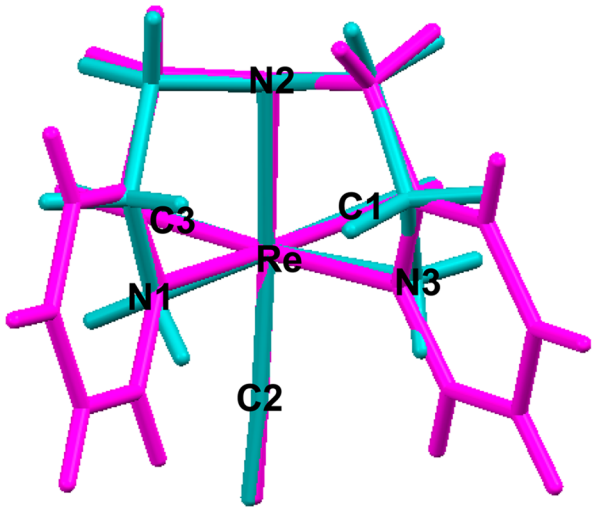

Figure 3. Overlay of Re, C1, C2, and C3 atoms of $[Re(CO)_3(N(SO_2tol)dien)]PF_6$ (**6**) (blue) and $[Re(CO)_3(N(SO_2tol)dpa)]PF_6$[35] (magenta) complexes. (The SO_2R groups have been omitted for clarity.)

bond angles around the sulfonamide N (N2) are ~109° (Table 2). This observation, which is consistent with data for $[Re(CO)_3(N(SO_2R)dpa)]PF_6$ complexes,[35] indicates that the sulfonamide nitrogen changes from sp^2 to sp^3 hybridization upon tridentate binding to Re^I.[35] This conclusion is confirmed by the fact that the C5–N2 (average = 1.511 Å) and C6–N2 (average = 1.512 Å) bond distances are longer than an average C–N(sp^2) distance (~1.28 Å).[53] Data for all of the bond angles and distances involving the sulfonamide N indicate that it is sp^3 hybridized.

In $[Re(CO)_3(N(SO_2R)dpa)]PF_6$ and other complexes that have metal-bound tertiary sulfonamide groups, the distance to the sulfonamide N from the plane defined by the S and the two C atoms attached to N typically ranges from 0.47–0.52 Å.[35] Such values are larger than those for the corresponding distance in complexes with an unbound sulfonamide N atom (0.06–0.26 Å).[35] In the new complexes, $[Re(CO)_3(N(SO_2Me)dien)]PF_6$ (**4**) and $[Re(CO)_3(N(SO_2tol)dien)]PF_6$ (**6**), this distance (Table 2) is in the range characteristic of a M–N bond.

Most of the known complexes with tertiary sulfonamide ligands exhibit relatively long M–N(sulfonamide) bond distances and short S–N distances, features attributed to the resonance contribution of the lone pair on the sulfonamide N and to the poor electron donation of the sulfonamide N to the metal.[54,55] Thus, both the comparatively short Re–N(sulfonamide) bond distance [2.2763(14) for **4** and 2.2686(19) Å for **6**] and the long S–N bond distance in these complexes [1.7434(13) for **4** and 1.759(2) Å) for **6**] indicate that the sulfonamide N is a relatively strong donor.

Only one other structurally characterized complex in which a diethylenetriamine derivative is bound to a metal (La^{III}) via a sulfonamide bond through the N has been reported;[56] the sulfonamide group in that complex, however, is part of a cyclic heptadentate ligand. Thus, the sulfonamide complexes reported here are the first structurally characterized metal complexes in which the metal is coordinated by the central tertiary sulfonamide N in a linear, highly flexible tridentate ligand.

We have previously discussed at length chelate ring pucker λ or δ chirality and the consequences on structure and NMR spectra of $[Re(CO)_3(polyamine)]X$ complexes.[38,46,50] The cation of $[Re(CO)_3(N(SO_2Me)dien)]PF_6$ (**4**) and one of the cations of $[Re(CO)_3(N(SO_2tol)dien)]PF_6$ (**6**) (the one shown in Figure 2) have five-membered chelate rings of different chirality (λ or δ). However, the other independent cation in the asymmetric unit of **6** (not shown) has chelate rings of the same chirality. The relative frequency of observing the same or different chiralities in the two chelate rings with a central

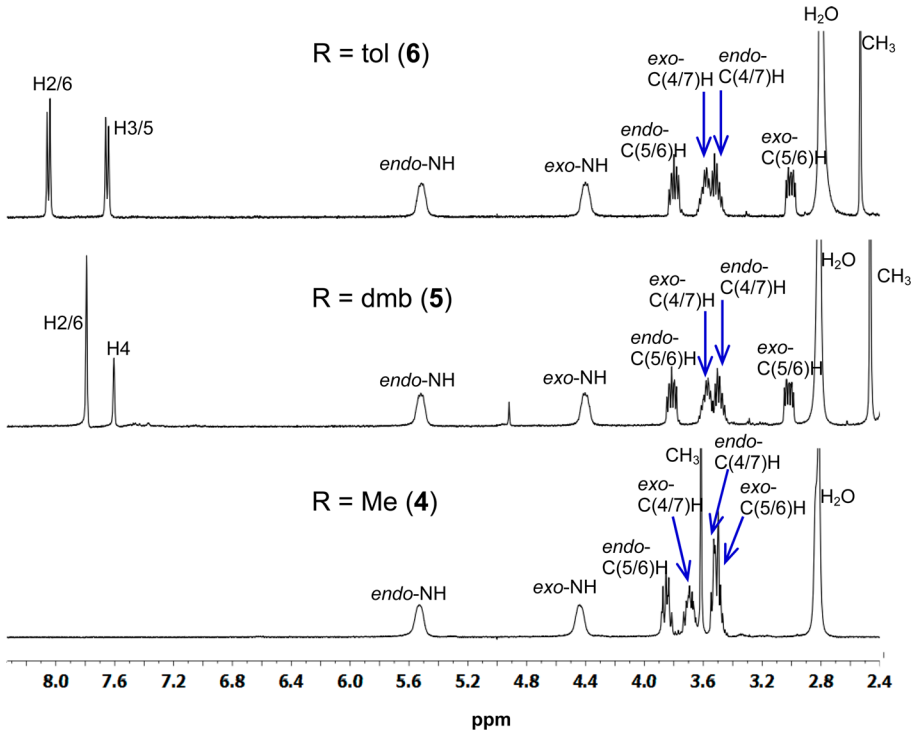

Figure 4. ^1H NMR spectra of $[Re(CO)_3(N(SO_2R)dien)]PF_6$ complexes (**4**–**6**) in acetone-d_6 at 25 °C.

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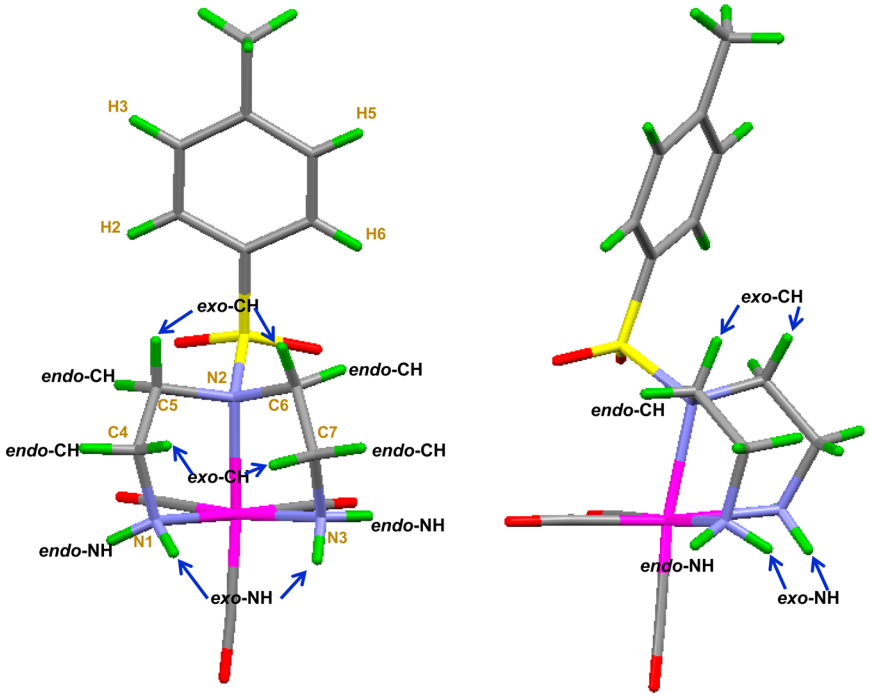
Chart 1. Front (Left) and Side (Right) Views of $[Re(CO)_3(N(SO_2tol)dien)]PF_6$ (6), Showing the Designation of *endo*- and *exo*-CH and *endo*- and *exo*-NH Protons



tertiary sulfonamide N donor (**4** and **6**) suggests that structures in which the chirality of the rings differs may be slightly more stable than structures having rings of the same chirality. Thus, our finding agrees with cases in which the central N is a classical sp^3 N donor, namely, that examples in which the chirality of the rings in a given structure differs ($\lambda\delta$ or $\delta\lambda$) occur more frequently than those in which the chirality is the same ($\lambda\lambda$ or $\delta\delta$).[46]

NMR Spectroscopy. The $N(SO_2R)$dien ligands and the $[Re(CO)_3(N(SO_2R)dien)]PF_6$ complexes reported here were characterized by ^1H NMR (**1**–**6**) and ^{13}C NMR (**1**, **3**–**6**) spectroscopy, usually in one or more of several solvents ($CDCl_3$, acetone-d_6, acetonitrile-d_3, and DMSO-d_6). NMR signals were assigned by analyzing the splitting pattern, integration, and data from 2D NMR experiments.

The two methylene ^1H NMR signals in $N(SO_2R)$dien ligands (**1**–**3**) are triplets integrating to four protons in $CDCl_3$ (Experimental Section and Figure S2). Selected data were obtained in acetonitrile-d_3 or in DMSO-d_6 (Experimental Section and Figure S3). The $C(5/6)H_2$ triplet for **2** (R = dmb) and for **3** (R = tol) is slightly upfield from the $C(5/6)H_2$ triplet for **1** (R = Me) in $CDCl_3$ (Figure S2). Shift values for the $C(4/7)H_2$ triplet are similar for all three ligands. These observations are attributed to the anisotropic sulfonamide aromatic groups, which are close to the $C(5/6)H_2$ groups but far from the $C(4/7)H_2$ groups. Similar results were obtained for **1** and **3** in acetonitrile-d_3. The two protons in each methylene group are not sterically similar because the sulfonamide N lies out of the plane defined by the S and the two C atoms attached to N; the apparent magnetic equivalence in the NMR spectra indicates that inversion at the sulfonamide nitrogen leads to time averaging, as discussed previously for the $N(SO_2R)$dpa ligands.[35]

The spectra of the respective complexes, on the other hand, are consistent with each of the four protons in the chelate ring giving rise to a multiplet. For example, the methylene group ^1H NMR signals observed in acetonitrile-d_3 changed from two triplets (at 3.07 and 2.79 ppm) for the $N(SO_2tol)$dien ligand (**3**) to four multiplets [at 3.51, 3.16 (two overlapped), and 2.59 ppm; see the Experimental Section and Supporting Information, Figure S4] for $[Re(CO)_3(N(SO_2tol)dien)]PF_6$ (**6**). The least amount of overlap of the multiplets for complexes **4**–**6** was found in acetone-d_6 (Figure 4). Thus, as expected, the apparent magnetic equivalence of methylene protons in the free ligands is lost in **4**–**6**. Similar changes in signals for methylene protons upon coordination of ligands have been reported for $[Re(CO)_3(N(SO_2R)dpa)]PF_6$ complexes[35] and for $[Re(CO)_3(N(H)dien)]PF_6$.[46]

We designate the magnetically distinct protons in $-CH_2-$ or $-NH_2$ groups as *endo*-H or *exo*-H protons, on the basis of the orientation of the proton either toward (*endo*) or away (*exo*) from the carbonyl ligands (Chart 1). Note that the chelate rings in these complexes are puckered, and the corresponding protons in the two chelate rings are not equivalent in the solid state. However, the chelate rings are fluxional, and time averaging leads to only one signal for each type of CH or NH proton, or six ^1H NMR signals for the $N(C(5/6)H_2-C(4/7)H_2-NH_2)_2$ tridentate framework moiety.

^1H NMR Assignments. ^1H NMR signals of the protons in the terminal NH_2 groups of previously reported $[Re(CO)_3(L)]^n$ compounds (L = simple tridentate ligands similar to diethylenetriamine with two terminal $-NH_2$ groups)[46,50] are well-resolved. The *endo*-NH signal has a more downfield chemical shift than the *exo*-NH signal; solvent has access to the exposed *endo*-NH protons, but solvent access to the *exo*-NH protons is impeded by the chelate rings.[46,50] The signal of the exposed *endo*-NH protons is shifted downfield by NH-solvent H-bonding. Both the shifts and the characteristic shift separation between these signals (Δ = ~1.5 ppm in DMSO-d_6) are useful for assigning such NH NMR signals.[46,50]

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In this work, two broad ^{1}H NMR signals of [Re(CO)$_3$(*N*(SO$_2$tol)dien)]PF$_6$ (**6**) (5 mM) in DMSO-d_6 at 4.28 and 5.70 ppm decreased in size when D$_2$O was added, indicating that they are NH signals. The signals are connected by a strong COSY cross-peak, as expected for an NH$_2$ group (Figure S5). The downfield signal at 5.70 ppm and the relatively upfield signal at 4.28 ppm, each integrating to two protons with Δ = ∼1.5 ppm, can be assigned as *endo*-NH and *exo*-NH signals, respectively.[46,50]

Similar Δ values of ∼1.5 ppm (DMSO-d_6), ∼1.1 ppm (acetone-d_6), and ∼1.0 ppm (acetonitrile-d_3) were observed between the downfield and upfield NH signals for all three complexes studied here (Table 3). This consistency aided in

Table 3. ^{1}H NMR Shifts (ppm) of *exo*- and *endo*-NH and *exo*- and *endo*-CH Signals for [Re(CO)$_3$(*N*(SO$_2$R)dien)]PF$_6$ Complexes in Various Solvents at 25 °C

signal	R = Me (**4**)	R = dmb (**5**)	R = tol (**6**)
	DMSO-d_6		
exo-NH	4.27	4.28	4.28
endo-NH	5.65	5.72	5.70
endo-C(5/6)H	3.45	3.41	3.42
exo-C(4/7)H	3.23	3.14	3.14
endo-C(4/7)H	3.10	3.00	3.01
exo-C(5/6)H	2.97	2.65	2.66
	acetone-d_6		
exo-NH	4.45	4.40	4.40
endo-NH	5.54	5.52	5.51
endo-C(5/6)H	3.85	3.81	3.81
exo-C(4/7)H	3.69	3.58	3.55
endo-C(4/7)H	∼3.50	3.50	3.52
exo-C(5/6)H	∼3.50	3.02	3.02
	acetonitrile-d_3		
exo-NH	3.44	3.41	3.37
endo-NH	4.46	4.52	4.51
endo-C(5/6)H	3.50	3.52	3.51
exo-C(4/7)H	∼3.18	∼3.16	∼3.16
endo-C(4/7)H	∼3.18	∼3.16	∼3.16
exo-C(5/6)H	3.00	2.60	2.59

assigning the *endo*-NH and *exo*-NH signals in complexes **4**–**6** (Table 3, Figure 4). Although X-ray quality crystals for compound **5** have not been isolated, the ^{1}H NMR patterns and shifts of its chelate ring signals in all solvents used match the corresponding ^{1}H NMR data for the crystallographically characterized compound **6** (Table 3 and Figure 4). These ^{1}H NMR chemical shifts provide strong evidence that **5** has a structure very similar to that of **6**. The NH signals of **6** in different solvents (Figure 5) are shifted downfield as the H-bonding ability of the solvent increases. Thus, significant downfield chemical shifts are observed in acetone-d_6 and DMSO-d_6, in contrast to the relatively upfield chemical shifts observed in acetonitrile-d_3 (Table 3 and Figure 5), owing to the weak interactions of that solvent with the NH groups. The highest Δ value (∼1.5 ppm) occurs in DMSO-d_6 because it has the greatest H-bonding ability among the three solvents.

The *endo*-NH and *exo*-NH ^{1}H NMR signals' assignments provide a starting point that allows us to exploit our structural data to achieve complete and unambiguous assignment of the ethylene ^{1}H NMR signals, which are rarely well-resolved for coordinated ligands having such chelate rings.[50] To demonstrate our assignment strategy of assigning the multiplets to a

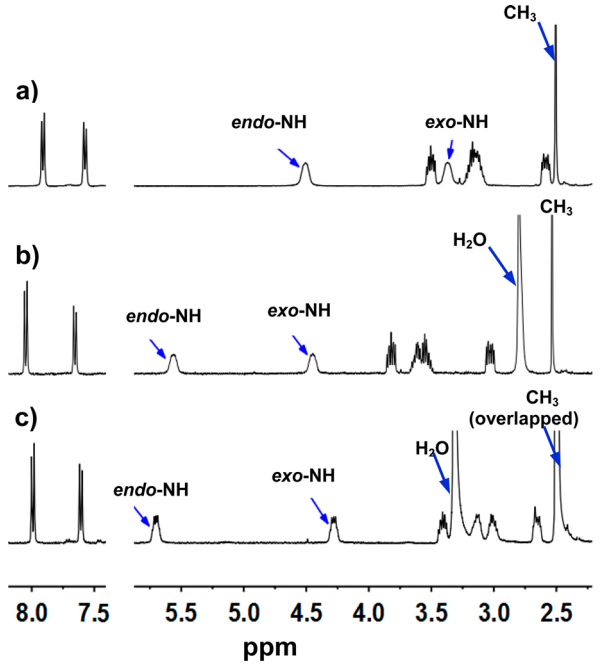

Figure 5. ^{1}H NMR spectra of [Re(CO)$_3$(*N*(SO$_2$tol)dien)]PF$_6$ (**6**), illustrating the relative position of NH signals observed at 25 °C in (a) acetonitrile-d_3, (b) acetone-d_6, and (c) DMSO-d_6.

specific *endo*-CH or *exo*-CH proton (Chart 1), we use [Re(CO)$_3$(*N*(SO$_2$tol)dien)]PF$_6$ (**6**) in acetone-d_6 because of the low degree of overlap of signals for the ethylene group (Figure 4). The atom-numbering system used in this discussion appears in Figure 1. Cross-peaks in COSY spectra (Supporting Information, Figure S5) and ROESY spectra (Figure 6 and Supporting Information, Figure S6) identify a multiplet as a

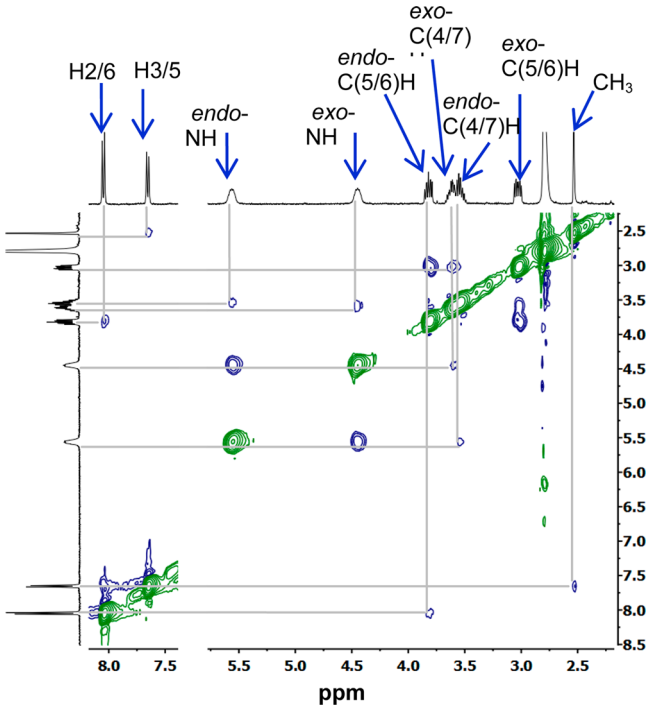

Figure 6. ^{1}H–^{1}H ROESY spectrum of [Re(CO)$_3$(*N*(SO$_2$tol)dien)]-PF$_6$ (**6**) in acetone-d_6 at 25 °C. An expanded version of this figure is in Supporting Information (Figure S6).

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C(4/7)H or C(5/6)H signal. In the solid state, the *endo*-NH protons have a shorter average distance to the *endo*-C(4/7)H protons (2.20 Å) than to the *exo*-C(4/7)H protons (2.71 Å), and the *exo*-NH protons have a shorter average distance to the *exo*-C(4/7)H protons (2.22 Å) than to the *endo*-C(4/7)H protons (2.43 Å). Thus, from NH−CH NOE cross-peak intensities, the CH multiplets at 3.52 ppm and 3.55 ppm are assigned to the *endo*- and *exo*-C(4/7)H protons, respectively. The average distance from the *exo*-C(4/7)H protons is shorter to the *exo*-C(5/6)H protons (2.30 Å) than to the *endo*-C(5/6)H protons (2.85 Å). In the ROESY spectrum, a strong NOE cross-peak from the *exo*-C(4/7)H multiplet to the most upfield multiplet at 3.02 ppm thus assigns the multiplet to the *exo*-C(5/6)H protons. Similarly, an NOE cross-peak from the *endo*-C(4/7)H multiplet to the most downfield multiplet at 3.81 ppm assigns this multiplet to the *endo*-C(5/6)H protons. The tosyl methyl singlet (2.53 ppm) of **6** has an NOE cross-peak to the tosyl doublet at 7.65 ppm, unambiguously assigning it to the tosyl H3/5 protons and the other tosyl doublet to H2/6. The latter is more downfield (8.05 ppm), consistent with the proximity of the H2/6 protons to the sulfonamide group, shown in previous work on the $[Re(CO)_3(N(SO_2tol)dpa)]PF_6$ analogue to have an electron-withdrawing inductive effect.[35] A strong H2/6-to-*endo*-C(5/6)H NOE cross-peak and a very weak H2/6-to-*exo*-C(5/6)H cross-peak is consistent with the shorter H2/6-to-*endo*-C(5/6)H average distance (2.60 Å) compared to the H2/6-to-*exo*-C(5/6)H average distance (2.81 Å), thus confirming the assignment of the *endo*-C(5/6)H and *exo*-C(5/6)H signals (Table 3).

^{1}H NMR Shift Interpretation. The *exo*-C(5/6)H signal is more upfield for **5** and **6** than for **4** in acetone-d_6 (Figure 4). In **6** (Figure 2 and Chart 1), the relative average distance from the centroid of the tosyl ring to the *exo*-C(5/6)H protons (which point toward the center of the ring) is shorter (3.45 Å) than the distance (4.09 Å) to the *endo*-C(5/6)H protons (Chart 1). Thus, the anisotropic effect of the aromatic ring of the R group explains the unusual upfield shift of the *exo*-C(5/6)H multiplet at 3.02 ppm in acetone-d_6 for **5** and **6**. This explanation is supported by the fact that the *exo*-C(5/6)H signal is not so upfield for **4**, a complex in which R lacks an aromatic ring. This same trend, with the methylene *endo*-CH signal downfield from the *exo*-CH signal and the latter signal appearing more upfield when R has an aromatic ring (tol) than when R = Me, was reported for the $[Re(CO)_3(N(SO_2R)dpa)]X$ complexes.[35]

Coordination of a ligand normally leads to downfield ^{1}H NMR shift changes attributable to the metal inductive effect. Upon coordination to Re^I of the free $N(SO_2R)$dien ligands **1** and **3** in acetonitrile-d_3, the downfield shift for signals of the C4/7 protons is ∼0.4 ppm. For example, the C(4/7)H_2 triplet for **1** shifts from 2.76 ppm downfield to ∼3.18 ppm for the overlapping C(4/7)H signals of $[Re(CO)_3(N(SO_2Me)dien)]PF_6$ (**4**). A corollary of the relationships of the distance of the *exo*-C(5/6)H protons to the aromatic groups mentioned above for **6** is that the *endo*-C(5/6)H protons are farther from R, and the shift of the *endo*-C(5/6)H signal for **4** and **6** is not influenced by the R group. Hence, compared to the C(5/6)H_2 triplets of **1** and **3**, the *endo*-C(5/6)H signals of **4** and **6** are shifted downfield (∼0.4 ppm to ∼3.5 ppm in acetonitrile-d_3). Remarkably, upon coordination of $N(SO_2Me)$dien to form **4**, the *exo*-C(5/6)H signal (expected to shift downfield by ∼0.4 ppm owing to inductive effects) is shifted slightly upfield (0.14 ppm) compared to the free ligand triplet, even though R = Me is not anisotropic. Presently, there are not enough other complexes with assigned signals for us to interpret the factors influencing shift, but the upfield shift may be caused by the SO_2 group anisotropy. Also, although the reaction of free amines with acetone prevents comparison using acetone-d_6, in DMSO-d_6 (the other solvent rather different from acetonitrile-d_3 that we used for the complexes), the same pattern of shift changes was observed upon coordination of **1** to form **4**, including the slight upfield shift of the *exo*-C(5/6)H signal (Figure S3). Thus, solvent effects are probably not causing the unexpected upfield shift.

The methyl ^{1}H NMR signal of $N(SO_2Me)$dien (**1**) shifted downfield upon coordination of **1** to form $[Re(CO)_3(N(SO_2Me)dien)]PF_6$ (**4**) in both acetonitrile-d_3 (0.47 ppm) and DMSO-d_6 (0.66 ppm) (Experimental Section and Supporting Information, Figure S3). These downfield shifts can be attributed to the Re^I inductive effect. We previously attributed a similar downfield shift (∼0.76 ppm) observed for $[Re(CO)_3(N(SO_2Me)dpa)]PF_6$ to the Re^I inductive effect.[35] A slightly greater downfield shift (∼1.03 ppm) relative to the free ligand reported for the $[Re(CO)_3(N(Me)dien)]PF_6$ complex in DMSO-d_6[46] can be explained by the transmission of the inductive effect through just two bonds (N−C and C−H) versus three bonds in **4** (N−S, S−C, and C−H).

^{13}C NMR Shift Interpretation. Unlike ^{1}H NMR signals, the shifts of ^{13}C NMR signals are not very dependent on solvent effects (e.g., as discussed for the NH signals) or on aromatic ring anisotropic effects (e.g., as discussed for *exo*-C(5/6)H signals). Instead, ^{13}C NMR signals are influenced more significantly by other factors, with signals of aliphatic carbons most frequently being shifted downfield by metal inductive effects. Analysis of ^{13}C NMR shifts can often provide insight into the effect of a diamagnetic metal center on the ligand. Therefore, we undertook the unambiguous assignment of the ^{13}C NMR signals of selected ligands and complexes, as described in Supporting Information. The ^{13}C NMR signals of the chelate ring carbons shift downfield, as expected, by 4 to 5 ppm upon coordination of the tridentate ligands **1** and **3** to form complexes **4** and **6**, and the shifts for the C4/7 and C5/6 signals of **4** are very similar to the shifts for these signals of **6** (data for acetonitrile-d_3 are reported in Table S1).

The methyl group ^{13}C NMR signal for the free $N(SO_2Me)$-dien ligand (**1**) appears at 37.87 ppm, but it is shifted considerably *upfield* for $[Re(CO)_3(N(SO_2Me)dien)]PF_6$ (**4**) (33.02 ppm, Table S1 in Supporting Information). The almost 5 ppm upfield change in shift when **1** forms **4** is unusual in that ^{13}C NMR shifts are influenced mainly by through-bond effects, such as the metal inductive effect expected to produce a downfield shift. For example, a significant ∼14 ppm downfield ^{13}C NMR shift was observed for the methyl group of $[Re(CO)_3(N(Me)dien)]PF_6$ (56.48 ppm) compared to the methyl group in the free $N(Me)$dien ligand (42.72 ppm) in acetonitrile-d_3.[51] Because of the unexpected upfield direction of the shift change of the methyl ^{13}C NMR signal of **4**, we measured the ^{13}C NMR shift of the methyl signal of $[Re(CO)_3(N(SO_2Me)dpa)]PF_6$ in DMSO-d_6 (32.88 ppm), a value ∼6.5 ppm upfield compared to the methyl signal in the free $N(SO_2Me)$dpa ligand (39.24 ppm).[51] We attribute the observed unusual upfield shift for **4** to the fact that the sulfonamide N undergoes an sp^2-to-sp^3 rehybridization upon coordination to Re^I in both **4** and $[Re(CO)_3(N(SO_2Me)$-$dpa)]PF_6$.

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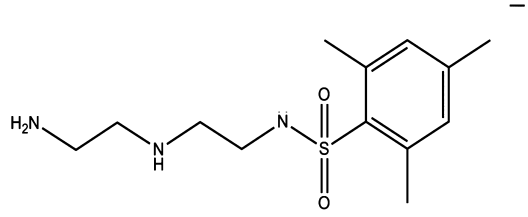
Challenge Reactions of $[Re(CO)_3(N(SO_2tol)dien)]PF_6$ (6) in DMSO-d_6. No change was observed in the ^1H NMR signals of **6** (5 mM), even after 6 months, indicating that **6** is robust. However, addition of diethylenetriamine to 5 mM solutions of **6** to create solutions that were 50 mM or 10 mM in diethylenetriamine led to the elimination of all peaks for **6** by the next day and after about 6 days ($t_{1/2}$ ~28 h), respectively. In both cases, the final ^1H NMR spectrum exhibits peaks for the $N(SO_2tol)$dien ligand (**3**) and for the known $[Re(CO)_3(N(H)dien)]PF_6$ complex.[46] No signals indicating any intermediates were observed. The complete displacement of the coordinated $N(SO_2tol)$dien ligand of **6** by 10 mM diethylenetriamine establishes that although the Re−N bonds involving the central donor of $N(SO_2R)$dien ligands have normal lengths, the donor ability of the central sulfonamide nitrogen atom is lower than that of the central nitrogen atom of diethylenetriamine.

A related study[38] was reported for the neutral $Re(CO)_3(tmbSO_2\text{-dien})$ complex. The coordinated unsymmetrical monoanionic NNN donor ligand, $tmbSO_2\text{-dien}^-$ (Chart 2), employed in that study has a 2,4,6-trimethylbenzenesulfonyl

Chart 2. $tmbSO_2\text{-dien}^-$ Monoanionic Ligand.[38]



($tmbSO_2$) group linked to one of the terminal N atoms of diethylenetriamine. The terminal donor of the free ligand prior to coordination is a secondary sulfonamide of the type $(RSO_2)R'NH$. When 10 molar equiv of diethylenetriamine was added to a solution of $Re(CO)_3(tmbSO_2\text{-dien})$ (3 mM, DMSO-d_6), no coordinated $tmbSO_2\text{-dien}^-$ ligand was displaced, even after the solution was heated at ~60 °C.[38] Thus, the deprotonated monoanionic $tmbSO_2\text{-dien}^-$ ligand is clearly a better ligand than neutral $N(SO_2tol)$dien.

If the central tertiary sulfonamide donor in $N(SO_2tol)$dien were coordinated weakly enough to the Re in $[Re(CO)_3(N(SO_2R)dien)]PF_6$ complexes, a good monodentate ligand might be able to substitute for the coordinated sulfonamide group. Therefore, we conducted a challenge experiment in which the strongly basic, potentially monodentate 4-Me_2Npy ligand was added to $[Re(CO)_3(N(SO_2tol)dien)]PF_6$ (**6**). No ^1H NMR spectral changes were observed over many days, even with a 10-fold excess of 4-Me_2Npy. Such evidence indicates that the central sulfonamide bond is strong enough to stay coordinated to Re, even in the presence of an excess of a strong monodentate ligand. Also, the results show that the $[Re(CO)_3(N(SO_2tol)dien)]PF_6$ complex is resistant to strong base, an advantage over $[Re(CO)_3(N(SO_2Me)dpa)]PF_6$, which decomposes readily in the presence of base.[35]

Solubility of $[Re(CO)_3(N(SO_2tol)dien)]PF_6$ (6) in Water. A mixture of 5 mg of $[Re(CO)_3(N(SO_2tol)dien)]PF_6$ (**6**) and 450 μL of D_2O gave a clear solution when heated in a boiling water bath for 30 min. The ^1H NMR spectrum of this solution, which compares favorably with spectra of **6** in other solvents (Figure 4), has four methylene multiplets, whereas the $N(SO_2tol)$dien ligand has two methylene triplets in D_2O. These results established that **6** dissolved unchanged to an extent much greater than is required for radiopharmaceuticals and that **6** is robust even in a hot aqueous solution. Furthermore, another experiment conducted using 5 mg of **6** also showed complete dissolution (observed visibly and by ^1H NMR spectroscopy) of **6** in a 450 μL:20 μL of D_2O/DMSO mixture (95.7%:4.3%). In contrast, similar NMR experiments carried out using the previously reported $[Re(CO)_3(N(SO_2Me)dpa)]PF_6$ complex[35] show that even the $[Re(CO)_3(N(SO_2R)dpa)]PF_6$ complex having the smallest R group is insoluble in D_2O or in D_2O/DMSO (95.7%:4.3%).

SUMMARY AND CONCLUSIONS

From the present results with $[Re(CO)_3(N(SO_2R)dien)]PF_6$ complexes, in which the chelate rings are less rigid, we conclude that the M−N bond of normal length observed was not a result of the rigid tridentate framework in the $[Re(CO)_3(N(SO_2R)dpa)]X$[35] complexes. In both series of complexes, the methyl ^{13}C NMR signal of the R = Me member of the series exhibited a very unusual *upfield* shift for an aliphatic carbon signal upon coordination of the ligand. This result, attributed to the similar sp^2-to-sp^3 rehybridization of the sulfonamide N upon coordination to Re^I in both series of complexes, further establishes that coordination of the sulfonamide N is not influenced by the rigidity of the $N(SO_2R)$dpa chelate rings. The decomposition of the $[Re(CO)_3(N(SO_2R)dpa)]X$ complexes by base[35] led us to hypothesize that base was attacking the coordinated $N(SO_2R)$dpa ligand, most likely by deprotonating the CH_2 group, and that the low electrophilicity of the Z = CH_2NH_2 group of the $N(CH_2CH_2NH_2)_2$ framework would confer stability toward base. The stability of the new $[Re(CO)_3(N(SO_2R)dien)]PF_6$ complexes toward base supports these hypotheses and allowed us to conduct a challenge reaction study with the basic $N(H)$dien ligand. $N(H)$dien replaced the coordinated $N(SO_2tol)$dien ligand in $[Re(CO)_3(N(SO_2tol)dien)]PF_6$, indicating that the neutral sulfonamide N central donor in $N(SO_2tol)$dien is a somewhat weaker donor than the central traditional sp^3 N donor in $N(H)$dien. Nevertheless, the new $[Re(CO)_3(N(SO_2R)dien)]PF_6$ complexes are long-lived, even in the presence of base, and are relatively robust to heat treatment. As expected, the moderately hydrophilic character of the Z = CH_2NH_2 group of the $N(CH_2CH_2NH_2)_2$ framework also confers water solubility on the $[Re(CO)_3(N(SO_2R)dien)]PF_6$ complexes. The aqueous solubility of the new ligands and complexes is much higher than necessary for radiopharmaceutical kit formulation. Also, there are perceived advantages in using small chelate ligands when constructing bioconjugates, and the $N(CH_2CH_2NH_2)_2$ framework is relatively small. Thus, the results obtained here suggest that $N(SO_2R)$dien ligands should be explored in the development of radiopharmaceuticals, including bioconjugates.

ASSOCIATED CONTENT

Supporting Information

Crystallographic data for $[Re(CO)_3(N(SO_2Me)dien)]PF_6$ (**4**) and $[Re(CO)_3(N(SO_2tol)dien)]PF_6$ (**6**), in CIF format; figure illustrating overlay of the Re, C1, C2, and C3 atoms of **6** and $[Re(CO)_3(N(Me)dien)]PF_6$; ^1H NMR spectra of ligands **1**−**3** in $CDCl_3$; ^1H NMR spectra of **1** and **4** in DMSO-d_6; ^1H NMR spectra of $[Re(CO)_3(N(SO_2R)dien)]PF_6$ complexes (**4**−**6**) in acetonitrile-d_3; COSY spectrum of **6** in acetone-d_6; ROESY spectrum of **6** in acetone-d_6; ^{13}C NMR spectrum of **6** and assignment of ^{13}C NMR signals of **6** in acetone-d_6; aromatic

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region of the HMBC spectrum of **6** in acetone-d_6; HSQC spectrum of **6** in acetone-d_6; and a comparison of ^{13}C NMR shifts of ligands (**1** and **3**) and complexes (**4** and **6**) in acetonitrile-d_3. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: lmarzil@lsu.edu.

Notes

The authors declare no competing financial interest.

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