A Controlled-Oxidation Synthesis of Substituted Aryl 1-Methyl-4-nitro-5-imidazolyl Sulfones

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Aryl imidazolyl sulfones bearing pendant hemisuccinamido groups for conjugation to biopolymer transport systems were synthesized from sulfide precursors. The peroxide-effected oxidation at sulfur was invariably accompanied by some cleavage-oxidation of the carboxamido groups to nitro functionalities, a process which could be minimized by careful control of the reaction conditions.

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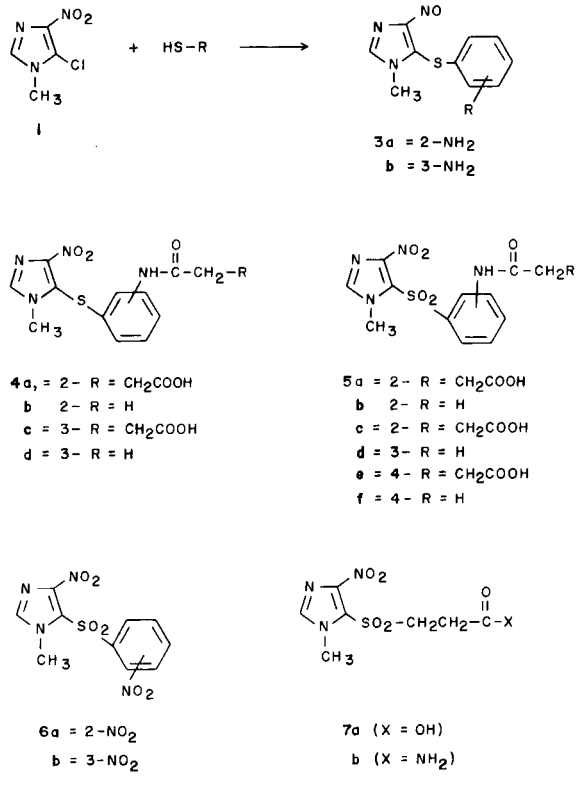
Misonidazole [1-(2-nitroimidazol-1-yl)-3-methoxypropan-2-ol] and other readily reduced nitro-substituted imidazoles are promising promoters of lethality in radiation therapy of hypoxic tumors in animals and humans [1,2]. However, peripheral neurotoxicity, arising because of their marked uptake in neural tissues compromises their general clinical utility [3]. One approach, which has yet to develop a clinically successful agent, has been the synthesis of new candidate analogs with reduced lipophilicity but unaltered reduction potentials [4,5].

A second alternative would be to conjugate an appropriate nitroimidazole radiation sensitizer to a tumor-specific monoclonal antibody or to a biocompatible polymer to take advantage of immunorecognition by cell surface antigens or differential endocytosis by malignant masses. These approaches have been suggested and, although untried, have strong literature precedent [6,7].

Prerequisites would be the availability of a nitroimidazole from a structural class of high sensitizer potential with a pendant side chain, preferably an aliphatic carboxyl, for conjugation to the bio-macromolecule. The higher the sensitizer enhancement effect the lower would be the intracellular concentration necessary to kill the cell [1]. Since within any given class the one-electron reduction potential at *p*H 7 (E_7^1) often correlates with sensitizer enhancement, an optimum choice would be the most electron affinic (least negative reduction potential) agent available [8,9].

Recent research in sensitization of hypoxic Chinese hamster V79 cells has pointed to 1-methyl-4-nitro-5-sulfonylarylimidazoles as an especially potent class [10,11]. None of the available analogs, however, bears a conjugatable pendant moiety. A three- or four-carbon carboxylic acid side chain, *e.g* a hemisuccinate, constitutes a nearly ideal handle for attaching small-molecule therapeutics to biopolymers and a convenient conjugation procedure is available [12,13]. The known radiosensitizers in this class have been synthesized by displacement of the chloro group in 1-methyl-4-nitro-5-chloroimidazole (**1**) by an alkyl or aryl thiol with subsequent oxidation to the sulfones [14].

Scheme I



The target radiosensitizing nitroimidazoles sought for our study (**5a,c**, and **e**) could not be obtained in this fashion.

Aminophenylsulfides similar to **3a** and **b** are well known to undergo oxidation at the amino in the process of sulfur oxidation to the sulfone state [15]. Zincke has shown, however, that prior acetylation of the amine permits oxidation at sulfur and that if the aminophenylsulfone is required the acetamide may be cleaved in a subsequent step [16]. We have employed the Zincke approach in the peroxide-catalyzed oxidation of the sulfide derivatives - in which the amino groups were first converted to hemisuccinates - **4a** and **4c** to **5a** and **5c** in 37% and 72% yields respectively and also in the oxidation of the acetamido sulfide deriva-

tives **4b** and **4d** to **5b** and **5d** in 44% and 19% yields respectively. Nitro byproducts, **6a** and **b**, accompanied almost all of these oxidations but the stepwise temperature elevation technique described herein gave acceptable yields of the desired amide sulfones. Furthermore, the virtual insolubility of the nitro byproducts in water permitted facile isolation of product. The *para*-acetamido derivative, **5f**, was prepared by a published method [14] and its deacetylated counterpart, 1-methyl-4-nitro-5-imidazolyl 4-aminophenyl sulfone, was prepared by acid-catalyzed cleavage of the acetyl from **5f**. To complete the set of required hemisuccinates and generate **5e** this 4-aminophenylsulfone was succinylated under more drastic conditions than those required to succinylate the sulfides **3a** and **3b**, reflecting, no doubt, the deactivating effects of the SO_2 moiety.

In order to have an aliphatic sulfone for comparison in the radiosensitizer studies, we prepared **7a** in 30% yield by oxidation of the sulfide produced in the condensation of 3-bromopropionic acid with 1-methyl-4-nitro-5-imidazolyl thiol. To aid in the selection of the best choice of these *ortho, meta,* and *para*-succinamidophenyl sulfones **5a,c,e** and the aliphatic propionic acid derivative **7a** for attachment to tumor-seeking monoclonal antibodies, we determined the E_7^1 one-electron reduction potentials. Because the transported forms of these materials on any monoclonal antibody backbone would undoubtedly be as amides of lysines, we performed the pulsed electrolysis studies on the amide counterparts **5b,d,f** and **7b**.

The procedure of Wardman and Clarke was employed to determine the E_7^1 on freshly prepared 0.90 m*M* solutions of the amides in phosphate buffer [16]. Compound **5e** was insufficiently soluble for the determination and the deacetylated analog, 1-methyl-4-nitro-5-imidazolyl 4-aminophenyl sulfone, was employed. Values of −413 mV for **5b**, −407 for the 4-aminophenyl sulfone, −309 mV for **5d** and −298 for **7b** were obtained. The reported E_7^1 value of −376 mV for the unsubstituted phenyl analog, 1-methyl-4-nitro-5-imidazolyl phenyl sulfone [18] is in agreement with the higher (less electron affinic) reduction potentials observed in this study for the aryl analogs with electron donors (*p*-amino or *o*-acetamido) in conjugation with the sulfone moiety. Similarly, the inductomeric electron-withdrawal (σ_m = 0.21) [19] of the *m*-acetamido group would be expected to lower (make more positive) the reduction potential and move the E_7^1 value closer to that observed for an aliphatic analog such as **7b**. Previous investigations with simple 4-nitro-5-sulfonylimidazoles lacking pendant conjugatable groups have shown an internal consistency of the E_7^1 measurements in predicting optimum radiation sensitization in hypoxic cells [10,20]. The obvious conclusion is that in this set the *m*-succinamidophenyl **5c** or the aliphatic side-chain analog **7a** should be selected for attachment to monoclonal antibodies or tumor-directed biopolymers. Research along these lines with the monoclonal antibody 19-9 raised to colorectal tumors is underway in our laboratories and will be reported elsewhere.

EXPERIMENTAL

Melting points, obtained on a Thomas-Hoover melting point apparatus are uncorrected. The ^{1}H-nmr spectra were obtained on a JEOL FX90Q spectrometer with TMS as the internal standard. Infrared spectra were obtained as potassium bromide discs on a Perkin Elmer 1420 spectrometer. Elemental Analyses were performed by the Robertson Microanalytical Laboratory, Florham Park, NJ.

1-Methyl-4-nitro-5-imidazolyl 2-Aminophenyl Sulfide (**3a**).

This compound was prepared from **1** and **2** (R = 2-aminophenyl) by the procedure of Bennett and Baker in 70% yield, mp 131-133°, lit mp 129-132° [14].

1-Methyl-4-nitro-5-imidazolyl 3-Aminophenyl Sulfide (**3b**).

A solution prepared from 0.750 g (4.64 mmoles) of 1-methyl-4-nitro-5-chloroimidazole (**1**) and 13 ml of anhydrous ethanol in a round bottom flask equipped with a gas inlet tube and a reflux condensor was heated to 50° in an oil bath. 3-Aminothiophenol **2**, (R = 3-aminophenyl) (0.581 g, 4.64 mmoles) dissolved in 2 ml of absolute ethanol was added in a single portion. A dense precipitate formed. The precipitate was stirred magnetically while a slow stream of ammonia gas was passed through the reaction medium. The solution volume was maintained at ca. 15 ml by addition of ethanol. The initial yellow solid dissolved, a homogeneous solution resulted, and a white precipitate of ammonium chloride formed during the 3 minutes of gas flow at 50°. The oil bath heater was removed and the ammonia gas stream was continued for 30 minutes after which the solution was agitated for 12 hours and filtered to remove the ammonium chloride. Evaporation of the solvent to a reduced volume and chilling precipitated the crude **3b** which was recrystallized from 95% ethanol to orange-yellow needles, 0.921 g, 79%, mp 177-179°.

Anal. Calcd. for $C_{10}H_{10}N_4O_2S$: C, 47.99; H, 4.03; N, 22.39. Found: C, 47.86; H, 4.08; N, 22.10.

1-Methyl-4-nitro-5-imidazolyl 2-Succinamidophenyl Sulfide (**4a**).

A solutionof 0.300 g (1.20 mmoles) of **3a** in 30 ml of anhydrous refluxing benzene was treated to the addition of 0.120 g (1.20 mmoles) of succinic anhydride in a single portion. The reaction mixture was refluxed for 3 hours, cooled to room temperature, filtered to remove the product, and the mother liquor concentrated and chilled to produce a second product crop. The crude solid was thoroughly triturated with warm benzene and dried *in vacuo* to give 0.289 g (69%) of **4a**, mp 177-178°.

Anal. Calcd. for $C_{14}H_{14}N_4O_5S$: C, 47.99; H, 4.03; N, 15.99. Found: C, 47.76; H, 3.77; N, 15.49.

1-Methyl-4-nitro-5-imidazolyl 3-Succinamidophenyl Sulfide (**4c**).

A suspension of 1.00 g (4.00 mmoles) of **3b** in 10 ml of anhydrous THF was brought to reflux and treated to the addition of 0.400 g, 4.00 mmoles, of succinic anhydride in a single portion. The reactants were heated at reflux with magnetic stirring for 7 hours during which time a homogeneous solution resulted. The solution was evaporated to ca 5 ml and chilled to precipitate 1.073 g, 77%, of **4c** as a pale yellow solid, mp 190-191°.

Anal. Calcd. for $C_{14}H_{14}N_4O_5S$: C, 47.99; H, 4.03; N, 15.99. Found: C, 47.83; H, 3.95; N, 16.24.

1-Methyl-4-nitro-5-imidazolyl 3-Acetamidophenyl Sulfide (**4d**).

A mixture of 1.00 g (4.00 mmoles) of **3b**, 5 ml (45 mmoles) of acetic anhydride, and 0.328 g (4.00 mmoles) of sodium acetate was stirred at reflux for 3 hours. The medium was chilled at ice bath temperature and filtered. The filtrate was washed with cold water and dried *in vacuo* to yield 91% of the title compound, mp 183-185° (from ethanol).

Anal. Calcd. for $C_{12}H_{12}N_4O_3S \cdot 2H_2O$: C, 43.91; H, 4.87. Found: C, 44.27; H, 4.43.

1-Methyl-4-nitro-5-imidazolyl 2-Succinamidophenyl Sulfone (**5a**).

A three-necked, 50 ml round bottom flask equipped with a condensor, dropping funnel, and magnetic stirring bar, was charged with 0.368 g (1.05 mmoles) of **4a** and 3.8 ml of glacial acetic acid. Dropwise addition of 4.0 ml of 30% hydrogen peroxide was carried out at 60° with vigorous magnetic stirring over 30 minutes during which a deep yellow solution resulted. After 6 hours at 60° the color faded and the temperature of the reaction medium was then raised in stages: to 70° for 6 hours and then to 80° for 30 minutes. The flask was removed from the oil bath heater and stirred at room temperature for 12 hours, diluted with 25 ml of water, chilled, filtered to remove a trace of nitro compound **6a**, see discussion *vide infra*, and the aqueous phase extracted exhaustively with methylene chloride. The product was obtained by evaporating the dried (sodium sulfate) organic layer and was recrystallized from boiling ethanol with the addition of cold water to give 0.147 g (37%) of **5a**, mp 157-161°; ^{1}H-nmr (DMSO-d_6): δ 2.38 (br s, 4 H, CH_2CH_2), 4.01 (s, 3 H, N-CH_3), 7.45-8.17 (m, 4 H, ArH), 9.70 (s, 1 H, imidazole-H), 10.4 (br s, 1 H, N-H).

Anal. Calcd. for $C_{14}H_{14}N_4O_7S \cdot \frac{1}{2}H_2O$: C, 42.96; H, 3.86; N, 14.32. Found: C, 42.99; H, 3.82; N, 14.44.

1-Methyl-4-nitro-5-imidazolyl 2-Acetamidophenyl Sulfone (**5b**).

The requisite 1-methyl-4-nitro-5-imidazolyl 2-acetamidophenyl sulfide (**4b**) was prepared as described in 61% yield [14]. A magnetically stirred solution of 3.5 ml of glacial acetic acid and 0.350 g (1.20 mmoles) of **4b** was maintained at 60° in an oil bath and subjected to the slow dropwise addition of 3.5 ml of 30% hydrogen peroxide over 30 minutes. The mixture was stirred and heated at 60° for 3 hours, raised to 70° for 6 hours, and the oxidation completed by heating at 80° for 30 minutes. The heat source was removed and the reaction contents agitated at ambient temperature for 12 hours. Dilution of the reaction mixture with 10 ml of water precipitated a trace, *ca* 5%, of the nitrophenyl compound **6a** which was washed well with warm water to remove any residual sulfone **5b**. The combined aqueous phases were exhaustively extracted with methylene chloride, the extracts dried with sodium sulfate, concentrated to *ca.* 2 ml and chilled to precipitate the title compound, 171 mg, 44%, mp 181.5-183.5°, from 95% ethanol; ^{1}H-nmr (DMSO-d_6): δ 1.84 (s, 3 H, CH_3CO), 4.03 (s, 3 H, CH_3N), 7.41-8.20 (m, 5 H, ArH and imidazole-H), 9.69 (s, 1 H, N-H).

Anal. Calcd. for $C_{12}H_{12}N_4O_5S$: C, 44.44; H, 3.73; N, 17.18. Found: C, 44.52; H, 3.80; N, 17.14.

1-Methyl-4-nitro-5-imidazolyl 3-Succinamidophenyl Sulfone (**5c**).

The oxidation of 0.500 g, 1.43 mmoles of **4c** with 5.0 ml of 30% hydrogen peroxide in glacial acetic acid was carried out as described above for **5a**. A 0.433 g, 72%, yield of **5c**, mp 120-122° (from ethanol) was obtained; ^{1}H-nmr (DMSO-d_6): δ 2.55 (br s, 4 H, CH_2CH_2), 3.97 (s, 3 H, CH_3), 7.50-8.41 (m, 5H, ArH and imidazole H), 10.42 (s, 1 H, NH).

Anal. Calcd. for $C_{14}H_{14}N_4O_7S \cdot \frac{1}{2}H_2O$: C, 42.96; H, 3.86; N, 14.32. Found: C, 42.66; H, 3.58; N, 14.50.

1-Methyl-4-nitro-5-imidazolyl 3-Acetamidophenyl Sulfone (**5d**).

The oxidation procedure described above for the preparation of **5b** was employed to oxidize **4d** to **5d** with the variation that the heating at 60° was carried out for 11 hours. Dilution with water precipitated 11% of the nitro compound **6b** and, by exhaustive extraction of the supernatant with methylene chloride yielded 19% of the desired acetamidophenyl sulfone, mp 143-144°; ir (potassium bromide): 3610 (NH), 3380-2700 (br OH), 1720 (COOH) and 1690 ($CONH_2$) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 2.09 (s, 3 H, CH_3CO), 3.98 (s, 3 H, N-CH_3), 7.50-8.41 (m, 4 H, ArH), 8.18 (s, 1 H, imidazole H), 10.30 (br s, 1 H, N-H).

Anal. Calcd. for $C_{12}H_{12}N_4O_5S$: C, 44.44; H, 3.73; N, 17.18. Found: C, 44.61; H, 3.94; N, 17.06.

1-Methyl-4-nitro-5-imidazolyl 4-Aminophenyl Sulfone.

A solution prepared from 0.50 g (1.54 mmoles) of **5f** [14] in 5 ml of ethanol, and 2.5 ml of concentrated hydrochloric acid was heated at reflux for 2 hours. Dilution with 15 ml of water precipitated the hydrochloride salt of the title compound which was filtered off and converted to the free base by addition of 4.50 g of sodium acetate in 10 ml of water. The liberated free base was filtered and recrystallized to gie 0.32 g, 74%, mp 142-143° (from ethanol:water 1:1); ir (potassium bromide): 3465 and 3375 (NH); ^{1}H-nmr (DMSO-d_6): δ 3.91 (s, 3H, CH_3N), 6.46 (br s, 2H, NH_2), 6.67 (d, 2H, C-3 ArH, J = 9.0 Hz), 7.71 (d, 2H, C-2 ArH, J = 9.0 Hz), and 8.04 (s, 1H, imidazole-H).

Anal. Calcd. for $C_{10}H_{10}N_4O_4S$: C, 42.55; H, 3.57; N, 19.85. Found: C, 42.32; H, 3.52; N, 19.68.

1-Methyl-4-nitro-5-imidazolyl 4-Succinamidophenyl Sulfone (**5e**).

The 4-aminophenyl sulfone (0.100 g, 0.35 mmole), succinic anhydride (0.175 g, 1.75 mmoles), and 5 μl of triethylamine were refluxed in 4 ml of anhydrous THF for 6.5 hours, treated to the addition of supplemental anhydride and base (0.175 g succinic anhydride and 50 μl of triethylamine) and reflux was continued for 6.5 more hours. Evaporation *in vacuo* gave a semi-solid mass which crystallized when triturated successively with 3 × 10 ml portions of water. The solid was recrystallized from ethanol to analytical purity, 59% yield, mp 186-187°; ir (potassium bromide): 3580-2550 (NH/OH), 1705 (COOH), 1690 ($CONH_2$) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 2.52 (m, 4H, CH_2CH_2), 3.98 (s, 3H, CH_3), 7.98 (dd, 4H, ArH), 8.15 (s, 1H, imidazole-H), and 10.54 (br s, 1H, COOH).

Anal. Calcd. for $C_{14}H_{14}N_4O_7S \cdot H_2O$: C, 47.99; H, 4.03; N, 15.99. Found: C, 47.76; H, 3.77; N, 15.49.

1-Methyl-4-nitro-5-imidazolyl 2-Nitrophenyl Sulfone (**6a**).

If in synthesis of **5a** or **5b** the hydrogen peroxide was in excess of the amounts indicated, the reaction temperatures during the addition of the oxidant or in subsequent stages were higher than indicated or the reaction times extended beyond those suggested, the only isolable product (in 25-40% yield) was the 1-methyl-4-nitro-5-imidazolyl 2-nitrophenyl sulfone (**6a**) mp 196-198°. Even under the experimental conditions described above, traces of **6a** invariably formed but the isolation procedure was able to produce the desired **5a** and b; ^{1}H-nmr (DMSO-d_6): δ 4.01 (s, 3 H, CH_3N), 7.99-8.48 (m, 5 H, ArH and imidazole-H).

Anal. Calcd. for $C_{10}H_8N_4O_6S$: C, 38.46; H, 2.58. Found: C, 38.60; H, 2.40.

1-Methyl-4-nitro-5-imidazolyl 3-Nitrophenyl Sulfone (**6b**).

Similar results were obtained in the oxidation **4c** and **4d** in which the 3-nitrophenyl sulfone **6b** was an invariable byproduct, mp 165-167° (from methylene chloride); ^{1}H-nmr (DMSO-d_6): δ 4.05 (s, 3 H, CH_3N), 7.85-8.80 (m, 5 H, ArH and imidazole-H).

Anal. Calcd. for $C_{10}H_8N_4O_6S$: C, 38.46; H, 2.58; N, 17.94. Found: C, 38.81; H, 2.76; N, 17.84.

1-Methyl-4-nitro-5-imidazole 2-Carboxyethyl Sulfone (**7a**).

A solution of 3.18 g (20.0 mmoles) of 1-methyl-4-nitro-5-imidazolethiol [14] in 20.0 ml of 4% aqueous sodium hydroxide was treated to the dropwise addition of 3.64 g, 23.0 mmoles, of 3-bromopropionic acid. This mixture was agitated at ambient temperature for 24 hours, acidified to *p*H 3 with concentrated hydrochloric acid, and the precipitated sulfide removed by filtration. Extraction of the mother liquor with ethyl acetate followed by drying (sodium sulfate) and evaporation produced more sulfide, 2.32 g, 50%, mp 158-160° (from water). This crude sulfide was directly oxidized to the sulfone. A solution maintained at 60° of 1.00 g (4.32 mmoles) of sulfide in 10 ml of glacial acetic acid was treated to the dropwise addition of 10 ml of 30% hydrogen peroxide. After 12 hours at 60° the reaction temperature was raised to 80° for 30 minutes. The contents of the flask were then chilled to 4° for 11 hours and filtered to remove the product **7a** which was recrystallized from ethanol to give 0.67 g (59%) of the sulfone as short white needles, mp 180-182°; ir (potassium bromide): 3276-2555 (COOH), 1496 and 1369 (NO_2), 1320 and 1156 (SO_2) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.77 (t, 2H, CH_2, J = 7Hz), 3.93 (t, 2H, CH_2SO_2, J = 7 Hz), 3.89 (s, 3 H, N-CH_3), 8.16 (s, 1H, imidazole H), 12.58 (br s, 1H, COOH).

Anal. Calcd. for $C_7H_9N_3O_6S$: C, 31.94; H, 3.45; N, 15.96. Found: C, 31.81; H, 3.51; N, 15.69.

1-Methyl-4-nitro-5-imidazolyl 2-Carboxamidoethyl Sulfone (**7b**).

A solution of 0.300 g (1.14 mmoles) of **7a** in 5.0 ml of oxalyl chloride was refluxed under a nitrogen atmosphere for 5 hours, evaporated *in vacuo* to a semisolid residue and treated to the slow portion-wise addition of 20 ml of chilled concentrated aqueous ammonium hydroxide. After the aqueous ammonia had been added the reaction mixture was diluted with 20 ml of ice water, the white precipitate filtered off, washed with cold water and dried *in vacuo*. This crude product was then recrystallized from 95% ethanol to give 0.121 g, 40%, of **7b**, mp 173.5-176.5°.

Anal. Calcd. for $C_7H_{10}N_4O_5S$: C, 32.06; H, 3.84; N, 21.37. Found: C, 32.10; H, 3.88; N, 21.16.

Determination of One-Electron Reduction Potentials.

The procedure of Wardman and Clarke [17] was employed to determine the difference between the one-electron reduction potentials, measured at *p*H 7, of a quinone couple (Q/Q^-) and a 4-nitro-5-sulfonyl imidazole couple (S/S^-), a quantity known as the E_7^1 value. The quinones employed were duroquinone and 9,10-anthraquinone-2-sulfonate sodium salt. These experiments were performed on pulsed radiolysis equipment at the Center for Fast Kinetics, University of Texas-Austin, under the direction of Dr. E. L. Powers. Data were analyzed according to the method of Adams [8]. The electrochemical measurements were performed on freshly prepared 0.90 m*M* solutions of the 4-nitroimidazoles dissolved in phosphate buffer (*p*H 7.3) which had been purged with nitrogen for 15 minutes prior to pulsing. While **5f** was insufficiently soluble in the standard buffer to obtain an E_7^1, it was possible to obtain a 0.90 m*M* solution of the 1-methyl-4-nitro-5-imidazolyl 4-aminophenyl sulfone and determine its one-electron reduction potential as −407 mV. In addition, values of −413 mV for **5b**, −309 mV for **5d**, and −298 mV for **7b** were determined.

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