Chemical and Spectroscopical Evidence for an Electron-Transfer Mechanism in the Reaction of Arenesulfonyl Chlorides with Anions

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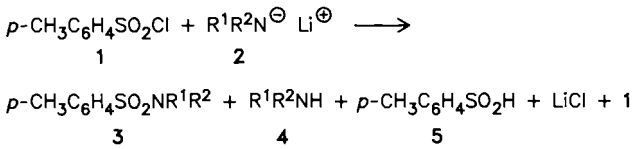
The reaction of amide and amidate anions 2 with *p*-toluenesulfonyl chloride (1) under different reaction conditions gives rise to the total or partial reduction of the acyl halide to *p*-toluenesulfinic acid (5) and acylation compounds in variable amounts depending on the crowding at the anionic center. This indicates that a Single-Electron Transfer (SET) mechanism is involved in the reactions of 1 with anions. Unpaired electron species are detected by ESR in the course of the reactions.

It is well-established that sulfur-substituted aromatic rings such as aryl sulfones[1], arenesulfonates[2], or arenesulfonamides[3] are able to accept one electron under thermal or photochemical conditions when allowed to react with anions or other chemical and electrochemical electron sources. By contrast, the behavior of arenesulfonyl chlorides as single-electron acceptors, in spite of their extended use in organic synthesis, has not been investigated so far although they should be expected to accept a single electron from anions as efficiently or even more than the above mentioned sulfur-containing groups. Arenesulfonyl chlorides are reduced by usual reductors (hydride or sulfite anions) with great ease and also by anions such as acetylide, enolate, sulfide, mercaptide, thiosulfate, cyanide, dithionite, arsenite, iodide, and dithiocarbonate[4] in reactions that have not been investigated in depth from a mechanistic point of view.

For these reasons, we decided to investigate the reactivity of *p*-toluenesulfonyl chloride (1) with nucleophiles $Nu^{\ominus}M^{\oplus}$ (2) such as amide and amidate[5] anions, species that might behave alternatively as two-electron or single-electron donors[6].

The reaction of nucleophiles 2 with *p*-toluenesulfonyl chloride under different reaction conditions gave rise to total or partial reduction of the acyl halide to *p*-toluenesulfinic acid (5) (Scheme 1) in all the instances. Results are summarized in the Table. All compounds were characterized by ^{1}H- and ^{13}C-NMR spectra by comparison with original samples synthesized by previously reported methods[7]. *p*-Toluenesulfinic acid and its salts were determined by redox titration with 0.1 N aqueous potassium permanganate. The reductor character of the solutions was previously checked by treatment of an aliquot with copper(II) chloride that results in the immediate precipitation of copper(I) chloride.

Scheme 1



	R^1	R^2
a	$(CH_3)_2CH$	$(CH_3)_2CH$
b	$PhCH_2CH_2$	H
c	CH_3CO	$PhCH_2$
d	CH_3CO	Ph
e	CH_3CO	$c\text{-}C_6H_{11}$
f	CH_3CO	$(CH_3)_3C$

The steric hindrance at the anionic center on 2 (runs 1, 2 and 9, 10 in Table) was the predominant factor to determine the course of the reaction. Hindered nucleophiles such as LDA (**2a**), lithium *N*-cyclohexylacetamidate (**2e**) or lithium *N*-*tert*-butylacetamidate (**2f**) gave exclusively the reduction of 1 and the recovery of the starting amine or amide (**4a**, **4e**, or **4f**), respectively, after the usual aqueous workup procedure. It is to be noted that compounds **3a**, **3e**, and **3f** can not be obtained either by the usual tosylation procedures described in the bibliography.

Table. Reaction of *p*-toluenesulfonyl chloride with amide and amidate anions

run	2	reaction conditions[a]	yield (%) 1	3	4	5
1	a	RT/THF (B)[b]	10	–	100	90
2	a	−70°C/THF (A)[c]	25	–	100	75
3	b	RT/THF (B)[b]	–	60	40	40
4	b	−50°C/THF (B)[b]	–	90	10	10
5	b	RT/THF (A)[c]	30	30	70	40
6	b	−50°C/THF (A)[c]	3	87	13	10
7	c	RT/THF (B)[b]	20	60	40	20
8	d	RT/THF (B)[b]	33	22	78	45
9	e	RT/THF (B)[b]	40	–	100	60
10	f	RT/THF (B)[b]	10	–	100	90

[a] RT = room temp.; (A) mode of addition A; (B) mode of addition B. – [b] pH of the reaction mixture was neutral. – [c] pH of the reaction mixture was basic.

The influence of the experimental conditions was examined in the reaction of **2b** with 1 (see runs 3–6 in the Table). A different 3:5 ratio was observed depending on the addition rate of the nucleophiles 2 over 1. Slow addition (mode A) leads to mixtures of compounds 3, 4, and 5 and partial recovery of the acyl halide (1), the final pH of the reaction mixture being neutral or only slightly basic (see Table). On the other hand, fast addition (mode B) results in the consumption of 1 and a neutral or slightly acidic pH of the resulting reaction mixture. In any case, the use of low temperatures increases the yield in tosylation product 3.

All the experimental results summarized above may be rationalized as evidences for the formation of intermediate unpaired spe-

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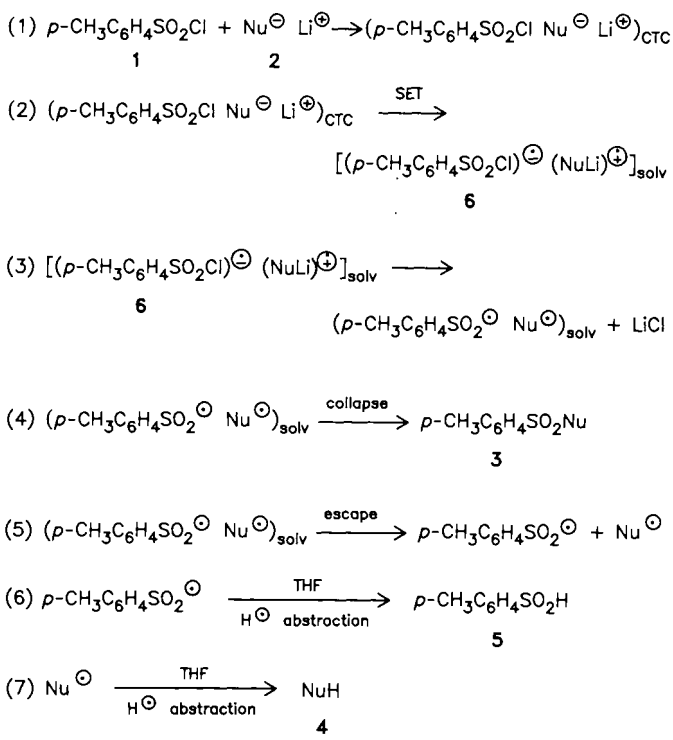
cies in the reaction. The following Electron-Transfer (ET) mechanism is proposed for these processes (Scheme 2). Anions **2** transfer one electron to the acyl halide **1** giving rise to the formation of a radical-ion pair **6** (steps 1 and 2). This pair undergoes the extrusion of lithium or sodium chloride in the solvent cage (step 3), and the resultant radicals collapse to afford the tosylated product **3** (step 4). The escape of the radicals from the solvent cage would lead to the recovery of the parent amine or amide **4** and the formation of *p*-toluenesulfinic acid (**5**) upon hydrogen abstraction by the radicals from the solvent (steps 5 and 6). The participation of THF as hydrogen donor is ascertained by the fact that 2-hydroxytetrahydrofuran[5] is isolated after usual aqueous workup of the reaction mixture.

Scheme 2



According to the proposed mechanism, the steric crowding at the basic center implies the higher stability of the corresponding radicals and increases the difficulty for the coupling reaction to give **3**. Hence, the products **4** and **5**, derived from hydrogen abstraction, are favored in this case. On the other hand, the slow mixing of the arenesulfonyl chloride **1** and the anions **2** gives rise to the arenesulfinic acid **5** in the solution, and the subsequent portions of base added are neutralized. In these conditions one equivalent of **1** can neutralize two equivalents of **2**, and hence, the recovery of **1** reaches its maximum, and the final pH of the reaction mixture is slightly basic, which corresponds to the formation of the lithium salt of **5**. When the reagents are mixed at once, the neutralization of the base by **5** is less effective as expected. This fact results from the total conversion of **1** and also from the neutral or slightly acidic pH of the reaction mixture. An increase of the reaction temperature leads to an enhanced yield in reduction products resulting from the easier diffusion of the radicals from the solvent cage.

Evidence for the formation of unpaired electron species derived from the proposed ET mechanism was also found by spectroscopic methods in the reactions of **1** with **2**. Reactions were carried out at low temperature in the ESR spectrometer cavity. The THF solution of **2** was placed in an ESR sample tube and cooled to −100°C. Then **1**, dissolved in THF, was added and the mixture carefully stirred at the same temperature. The sample was then frozen by cooling at 100 K in the spectrometer cavity and the ESR spectrum recorded, showing an unresolved signal that suggests unequivocally the existence of transient radicals in the course of the reaction, and supports the chemical evidence found for the proposed ET mechanism. The starting solutions were previously monitored by ESR under the same conditions to ascertain that the observed signals result from the interaction of compounds **1** and **2**.

Reactions of lithium and sodium alkoxides have been shown in some instances to proceed by single-electron transfer pathways[8]. For this reason we studied the reaction of the lithium alkoxides of *n*-hexanol and cyclohexanol with compound **1** under the conditions described above for amides and amidates, but we failed to detect any evidence of electron-transfer processes in this case.

From this study the ability of *p*-toluenesulfonyl chloride to act as a single-electron acceptor towards anions with the charge centered on one (**2a, b**) or two (**2c−f**) hetero atoms is clearly established by both chemical and spectroscopic methods. It does not mean that the reaction products derive in the case of the less hindered anions exclusively from the ET reaction pathway. Although radical intermediates must be invoked to explain the reduction of **1** by these anions, the tosylation products **3**, when obtained, might be generated either by this or an alternative polar mechanism that most probably accounts for reactions with alkoxides.

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Experimental

Starting amines and some amides were commercially available (Aldrich) and were used without further purification. Compounds **2c**, **2e**, and **2f** were prepared according to literature methods[7a]. Authentic samples of **3b**[10], **3c**[7b], and **3d**[7c] were prepared for comparison.

Reaction of Lithium 2-Phenylethylamide (**2b**) *with p-Toluenesulfonyl Chloride* (**1**)

General Procedure for Addition Mode A: To a solution of dry 2-phenylethylamine (5.0 mmol, 0.61 g) in anhydrous THF (10 ml) cooled at −10°C, a 1.6 N butyllithium solution in hexane (5.0 mmol, 3.13 ml) was added dropwise under argon, and the reaction mixture was allowed to stand for 15 min at the same temp. The resulting solution was then added dropwise to a solution of *p*-toluenesulfonyl chloride (5.0 mmol, 0.95 g) in dry THF (15 ml) and the mixture allowed to react for 2 h at the temp. shown in the Table. After hydrolysis with water and extraction with ether (3 × 5 ml) the organic layer was dried with Na_2SO_4 and evaporated under reduced pressure to afford a mixture of **3b**, **4b**, and unreacted **1**. The aqueous layer was also evaporated to give a solid residue characterized after crystallization by NMR as **5** [mp 85°C (ref.[9] 85°C)] or its lithium salt depending on the pH. Yields are summarized in the Table.

General Procedure for Addition Mode B: To the solution of the lithium amide in THF (25 ml) prepared as above, *p*-toluenesulfonyl chloride (5 mmol, 0.95 g) was added at once. After 2 h the reaction mixture was treated as described above.

N-(2-Phenylethyl)-p-toluenesulfonamide (**3b**): Mp 64−65°C (ref.[10] 66°C). − ^{1}H NMR ($CDCl_3$, TMS): δ = 2.2 (s, 3H), 2.75 (t, 2H), 2.95 (t, 2H), 4.6 (br. s, 1H), 7.0 (m, 7H), 7.5 (d, 2H). − ^{13}C NMR ($CDCl_3$, TMS): δ = 21.20 (q), 35.71 (t), 44.12 (t), 126.40 (d),

126.89 (d), 128.43 (d), 128.52 (d), 129.49 (d), 137.06 (s), 137.82 (s), 143.09 (s).

N-Acetyl-N-benzyl-p-toluenesulfonamide (**3c**): Mp 95°C (ref.[7b] 98°C). – ^{1}H NMR ($CDCl_3$, TMS): δ = 2.3 (s, 3H), 2.5 (s, 3H), 5.1 (s, 2H), 7.2 (d, 2H), 7.25 (s, 5H), 7.55 (d, 2H). – ^{13}C NMR ($CDCl_3$, TMS): δ = 21.22 (q), 24.53 (q), 49.29 (t), 127.45 (d), 127.65 (d), 128.31 (d), 129.50 (d), 136.53 (s), 136.59 (s), 144.62 (s), 169.00 (s).

N-Acetyl-N-phenyl-p-toluenesulfonamide (**3d**): Mp 146–147°C (ref.[7c] 149°C). – ^{1}H NMR ($CDCl_3$, TMS): δ = 2.0 (s, 3H), 2.55 (s, 3H), 7.35 (m, 7H), 7.9 (d, 2H). – ^{13}C NMR ($CDCl_3$, TMS): δ = 21.32 (q), 24.66 (q), 128.86 (d), 129.12 (d), 129.54 (d), 136.30 (s), 135.25 (s), 144.61 (s), 169.59 (s).

CAS Registry Numbers

1: 98-59-9 / **2a**: 4111-54-0 / **2b**: 38225-29-5 / **2c**: 121618-44-8 / **2d**: 56935-98-9 / **2e**: 121618-45-9 / **2f**: 121618-46-0 / **3b**: 5450-75-9 / **3c**: 121618-47-1 / **3d**: 84672-52-6 / **5**: 536-57-2

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