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Remote Modulation of Amine Basicity by a Phenylsulfone and a Phenylthio Group

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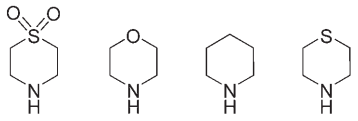
The sulfone group is an important module in medicinal chemistry. It shares its high electron withdrawing effects with groups like CF_3 or CN.[1] However, unlike the CF_3 group whose introduction into a given scaffold typically increases lipophilicity by half a log*P* unit,[2] or the nitrile group, which results in a marked lipophilicity reduction only when introduced into saturated structural domains, a sulfone unit more or less lowers the lipophilicity of a compound independently of its structural location.[3] All three groups affect the basicity of nearby basic functional groups. Whereas this is well documented for the CF_3 and CN groups,[4] relatively little experimental information is available for the specific effects of a sulfone group. In particular, the basicity-reducing effects of a remote SO_2 unit as a function of topological distance to a saturated amine is, to the best of our knowledge, not documented in the literature.

The marked electron withdrawing power and basicity-lowering effect of a sulfone group in a saturated system is best illustrated by the very weak basicity of hexahydro-1,4-thiazine-1,1-dioxide (**1**), the sulfone analogue of morpholine (**2**, Figure 1). The reduction of the amine basicity, ΔpK_a, by approximately six log units relative to piperidine (**3**) can be interpreted in terms of an amine basicity-lowering effect of almost three log units through each of the two σ-branches[5] in the six-membered ring, exerted by the SO_2 group in the β-position to the amine function. The effect of the SO_2 group is thus approximately two to almost three times that of, respectively, an alkoxy or thioether group in the β-position to a saturated amine unit, such as in morpholine (**2**) or hexahydro-1,4-thiazine (thiomorpholine, **4**). This basicity-lowering effect is comparable to the corresponding basicity decrement exerted by a cyano group on a saturated amine and somewhat larger than that of a CF_3 group in the β-position (Table 1). This is qualitatively consistent with the Hammett σ-parameters for the SO_2, CN, and CF_3 groups.[1] Hence, because of the basicity modulation by remote CN groups, as documented in Table 1, we speculated



	1	**2**	**3**	**4**
pK_a	5.4	8.5	11.1	9.0
ΔpK_a	–5.8	–2.6	0	–2.1
½ ΔpK_a	–2.9	–1.3	0	–1.1

Figure 1. Experimental pK_a values of hexahydro-1,4-thiazine-1,1-dioxide (**1**, presented herein), morpholine (**2**), piperidine (**3**), and thiomorpholine (**4**).[3]

Table 1.
Approximate basicity-lowering effects (ΔpK_a) for saturated (primary, secondary, and tertiary) amines by CN and CF_3 groups at different topological distances from the amine.[a]

NC-$(CH_2)_n$-N	*n*	ΔpK_a	CF_3-$(CH_2)_n$-N	*n*	ΔpK_a
	1	−5.7		1	−5.1
	2	−3.0		2	−2.1
	3	−1.5		3	−1.0
	4	−0.7		4	−0.3

[a] Estimated from pK_a values available in Ref. [4] (see Supplementary Material).

that an SO_2 group may also affect the basicity of an amine, even when located at rather remote positions. To assess such effects more quantitatively, we investigated a series of prototype phenylsulfone **5a**–**8c** and phenylthio amines **5d**–**8f** and determined their pK_a values in water under standard conditions (Scheme 1 and Table 2). For reasons of comparison we also prepared phenylsulfoxide **7g**.

The phenylsulfones **5a** and **6a** and phenylsulfides **5d** and **6d** are commercially available,[6] whereas the higher homologues **7a**–**f** and **8a**–**f** were synthesized as outlined in Scheme 1. Reaction of thiophenol (**9**) with bromo-chloro-alkanes **10** and **11** in the presence of potassium carbonate as base in DMF provided chloro sulfides **12** and **13**, which were oxidized by a 2.4-fold excess of *meta*-chloro-perbenzoic acid in chloroform to the corresponding phenylsulfones **14** and **15** in yields of 84% and 72%, respectively.[7] Conversion of the terminal chloride group with ammonium hydroxide, methylamine, or dimethylamine in ethanol with microwave-assisted heating to 130 °C provided smooth access to target structures **7a**–**c** and **8a**–**c**, respectively. Following similar procedures, the primary, secondary, and tertiary amines **7d**–**f** and **8d**–**f** were prepared from phenylsulfide intermediates **12** and **13**, respectively. All final compounds were purified either by silica gel chromatography or preparative HPLC. Conducting the oxidation of phenylsulfide **12** with only 1 equiv of *m*-CPBA afforded racemic sulfoxide **16** in a yield of 64% (Scheme 1). Subsequent reaction with dimethylamine gave, after purification by thin layer chromatography, a clean sample of target structure **7g**, albeit in a low yield of only 13%.

From the experimental pK_a values listed in Table 2 it is apparent that the amine pK_a decrements induced by an SO_2 group are attenuated in an approximately exponential fashion

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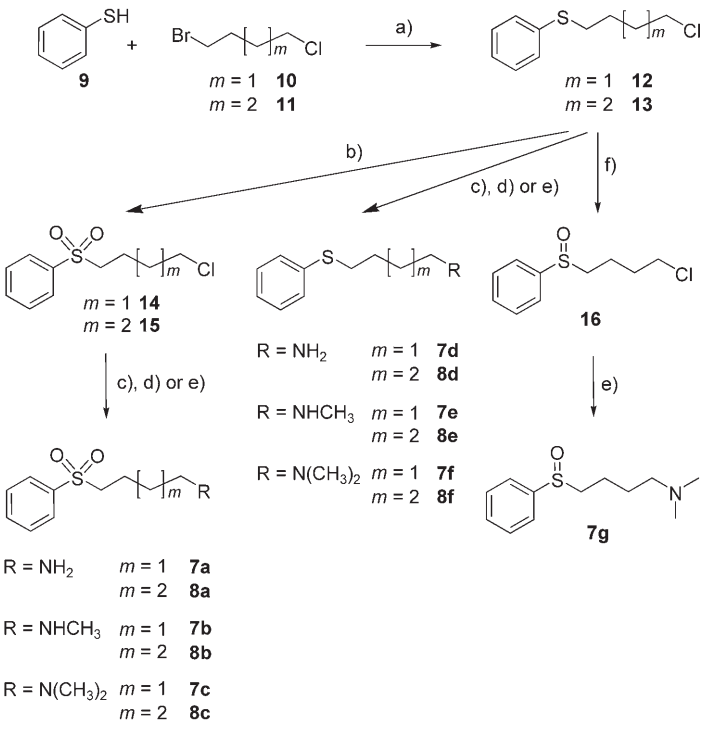

Scheme 1. a) K_2CO_3, DMF, 1 h at room temperature then 2 h at 50 °C, **12**: 95%; **13**: 86%; b) *m*-CPBA (2.4 equiv), DCM, 18 h at room temperature, **14**: 84%, **15**: 72%; c) NH_4OH (25% in water), EtOH, 1 h at 130 °C MW, **7a**: 58%, **8a**: 74%, **7d**: 9% (prep. HPLC), **8d**: 20% (prep. HPLC); d) CH_3NH_2 (41% in water), EtOH, 40 min at 130 °C MW, **7b**: 66%, **8b**: 87%, **7e**: 79%, **8e**: 67%; e) $(CH_3)_2NH$ (33% in EtOH), EtOH, 40 min at 130 °C MW, **7c**: 70%, **8c**: 87%, **7f**: 86%, **8f**: 71%, **7g**: 13% (prep. TLC); f) *m*-CPBA (1.0 equiv), DCM, 6 h at room temperature, **16**: 64%. DMF = *N*,*N*-dimethylformamide, *m*-CPBA = *meta*-chloro-perbenzoic acid, DCM = dichloromethane, MW = microwave heating, HPLC = high pressure liquid chromatography, TLC = thin layer chromatography.

Table 2.
Basicities for amines with phenylsulfone, phenylsulfoxide, and phenylthio groups at different topological distances from the amine function and estimated basicity decrements.

Parent Compound	Compd	*n*	pK_a	ΔpK_a[a]
$PhSO_2$-$(CH_2)_n$-NH_2	**5a**	2	7.8	−2.9
	6a	3	9.2	−1.5
	7a	4	10.0	−0.7
	8a	5	10.4	−0.3
$PhSO_2$-$(CH_2)_n$-$NHCH_3$	**6b**[9]	3	9.3	−1.6
	7b	4	10.2	−0.7
	8b	5	10.6	−0.3
$PhSO_2$-$(CH_2)_n$-$N(CH_3)_2$	**7c**	4	9.3	−0.9
	8c	5	9.8	−0.4
PhS-$(CH_2)_n$-NH_2	**5d**	2	9.0	−1.7
	6d	3	9.9	−0.8
	7d	4	10.4	−0.3
	8d	5	10.5	−0.2
PhS-$(CH_2)_n$-$NHCH_3$	**7e**	4	10.5	−0.4
	8e	5	10.9	−0.0
PhS-$(CH_2)_n$-$N(CH_3)_2$	**7f**	4	9.8	−0.4
	8f	5	10.0	−0.2
PhSO-$(CH_2)_n$-$N(CH_3)_2$	**7g**	4	9.4	−0.8

[a] ΔpK_a, relative to saturated alkylamines.[8]

as a function of topological distance to an amine, in a way similar to that observed for the cyano group. Moreover, the basicity lowering effect for a β-positioned SO_2 unit in this acyclic series[8] is fully consistent with the cyclic case (Figure 1). Quite consistent basicity-lowering effects are observed for the triples of primary, secondary, and tertiary amines with the sulfone group in either the δ- or ε-position. Estimated average pK_a decrements thus obtained are compiled in Table 3. Comparison

Table 3.
Approximate basicity-lowering effects ΔpK_a for saturated (primary, secondary, and tertiary) amines by a phenylsulfone and a phenylthio group at different topological distances.[8]

Parent Compound	*n*	ΔpK_a	Parent Compound	*n*	ΔpK_a
$PhSO_2$-$(CH_2)_n$-N	2	−2.9	PhS-$(CH_2)_n$-N	2	−1.7
	3	−1.5		3	−0.8
	4	−0.7		4	−0.4
	5	−0.3		5	−0.1

with the corresponding pK_a decrements of Table 1 underscores the similarity of effects exerted by a SO_2 and CN group at different topological distances to an amine, exceeding somewhat those of a CF_3 group. Thus, even for rather remote SO_2 groups small, but significant basicity lowering effects can be diagnosed, indicating interesting possibilities to modulate amine basicity, lipophilicity, and other important compound properties, such as amphiphilicity and potentially solubility, by introduction of a remote sulfone unit.

It is also instructive to analyze the basicity-lowering effects exerted by the corresponding phenylthio unit (see Tables 2 and 3). As expected these are considerably weaker than those observed for the corresponding sulfone group. We note again an approximately exponential attenuation by increasing topological distance, as observed in the sulfone series, but systematically shifted by one topological distance unit, that is, the phenylthio group exerts a similar basicity decrement as a phenylsulfone unit placed one bond unit further apart from the amine function. The basicity decrement given here for a β-positioned phenylthio unit (−1.7) is comparable to, but expectedly somewhat smaller than that derived from the *N*,*N*-dimethyl-β-acetylthio-ethylamine (8.3,[10] ΔpK_a = −1.9) and larger than that derived from β-methylthio-ethylamine (9.5,[11] ΔpK_a = −1.2); the latter corresponds nicely to the basicity decrement observed for thiomorpholine (**4**).

Finally, we also wish to report the pK_a value and corresponding pK_a decrement of the sulfoxide obtained for the derivative **7g** (Table 2). Although this is a singular case, the fact that the basicity lowering effect of a phenylsulfoxide unit is essentially the same as that of the corresponding phenyl-sulfone group is worth noting. It is consistent with the observation that the lipophilicity-lowering effect of a sulfoxide is known to be of similar magnitude as that of a sulfone, in contrast to the much smaller effects typically exerted by a sulfide unit.[12] This finding is also consistent with Hammett σ_m-parameters (or Taft's σ^*-parameters) for $PhSO_2$, PhSO, and PhS groups of 0.62 (3.25), 0.51 (3.24), and 0.17 (1.87), respectively.[1]

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There are continuous efforts in developing and refining pK_a prediction tools.[13] Their potential success depends largely on publicly available pK_a data. Unfortunately, there is still a paucity of pK_a data in the literature, and certain structural domains are not sufficiently covered.[14] Essentially no data are available in the literature on the basicity-modulating effects of a sulfone unit at different topological distances to a saturated amine, and the information on thioalkylamines is quite limited. Our data document the marked basicity-lowering effects by a phenylsulfone unit even when located at rather remote positions to an amine, and the corresponding, but reduced effects of a phenylthio group.

Experimental Section

General procedures. Compound **12**: K_2CO_3 (1.25 g, 9.08 mmol, 1.0 equiv) and 1-bromo-4-chlorobutane (**10**, 1.56 g, 9.08 mmol, 1.0 equiv) were added to a solution of thiophenol (**9**, 1.00 g, 9.08 mmol, 1.0 equiv) in DMF (10 mL) . The reaction mixture was stirred under an atmosphere of argon for 1 h at room temperature followed by an additional time period of 2 h at 50 °C to drive the reaction to completion. The crude reaction mixture was filtered and concentrated by evaporation under reduced pressure. A solution of sat. $NaHCO_3$ (50 mL) was added and the mixture extracted with DCM (3×50 mL). The combined organic phases were dried over $MgSO_4$, filtered, and the organic solvent removed by evaporation under reduced pressure providing 1.73 g (95%) of compound **12**, which was sufficiently pure to be used without further purification in the consecutive reaction step. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.70–1.94 (m, 4H), 2.88 (t, J = 7.0 Hz, 2H), 3.47 (t, J = 6.4 Hz, 2H), 7.18–7.28 ppm (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 25.42, 30.45, 32.14, 43.34, 125.07, 127.91, 128.44, 135.37 ppm. MS (EI): 200.1 $[M]^+$. Compound **14**: A solution of compound **12** (1.00 g, 4.98 mmol, 1.0 equiv) and *m*-CPBA (2.95 g, 11.96 mmol, 2.4 equiv; 70% purity) in DCM (30 mL) was stirred for 18 h at room temperature. Water (50 mL) was added and the pH of the water phase adjusted to 12 by addition of 1 M NaOH and the reaction mixture extracted with DCM (3×50 mL). The combined organic phases were dried over $MgSO_4$, filtered, and purified by silica column chromatography using a MPLC system (CombiFlash Companion, Isco Inc.) eluting with a gradient of heptane/ethyl acetate to yield 0.97 g (84%) of compound **14**. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.85–1.92 (m, 4H), 3.13 (t, J = 6.9 Hz, 2H), 3.52 (t, J = 5.9 Hz, 2H), 7.60–7.70 (m, 3H), 7.90–7.94 ppm (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 19.35, 29.89, 42.80, 54.45, 127.06, 128.36, 132.76, 138.23. MS (EI): 233.2 $[M+H]^+$. Compound **7a**: A solution of NH_4OH (25% in water; 2.17 mL, 14.12 mmol, 15.0 equiv) was added to compound **14** (0.22 g, 0.94 mmol, 1.0 equiv) dissolved in ethanol (5 mL) and the reaction mixture heated by microwave irradition to 130 °C for 90 min. Water (10 mL) was added and the pH of the water phase adjusted to 12 by addition of 1 M NaOH and the reaction mixture extracted with DCM (3×20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and purified by preparative HPLC on reversed phase eluting with a gradient of acetonitrile/water to provide 0.12 g (58%) of compound **7a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.71 (br s, 4H), 2.84 (br s, 2H), 3.08 (br s, 2H), 7.42–7.56 (m, 3H), 7.52–7.56 (br s, 2H), 7.76–7.78 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.78, 26.38, 38.77, 55.21, 127.97, 129.41, 133.85, 138.87. MS (ISP): 214.3 $[M+H]^+$. Compound **7d**: A solution of NH_4OH (25% in water; 3.43 mL, 22.27 mmol, 15.0 equiv) was added to compound **12** (0.30 g, 1.48 mmol, 1.0 equiv) dissolved in ethanol (7 mL) and the reaction mixture heated by microwave irradition to 130 °C for 40 min. Water (10 mL) was added and the pH of the water phase adjusted to 12 by addition of 1 M NaOH and the reaction mixture extracted with DCM (3×20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and purified by preparative HPLC on reversed phase eluting with a gradient of acetonitrile/water to provide 0.024 g (9%) of compound **7d**. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56–1.70 (m, 4H), 2.78 (t, J = 7.3 Hz, 2H), 2.88 (t, J = 6.8 Hz, 2H), 7.08–7.27 ppm (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 27.20, 28.26, 33.97, 40.56, 127.17, 130.04, 130.51, 137.63 ppm. MS (ISP): 182.1 $[M+H]^+$.

pK_a values were determined by potentiometric titration (SIRIUS GLpKa Analyzer) in aqueous solution, containing 0.15 M KCl to adjust ionic strength. To measure pK_a of substances by the pH-metric technique, a certain amount of sample was dissolved in the background electrolyte solution and acidified to pH 2 by addition of 0.5 M HCl. The solution was then titrated with standardized base (0.5 M KOH) to pH 12 at constant temperature (23 °C) under an atmosphere of argon to minimize absorption of atmospheric CO_2. The pK_a values were then calculated by shape analysis of the titration curve in comparison to the blank titration curve.

Keywords: amine · basicity · pK_a shifts · sulfide · sulfone

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[3] For example, based on data from the MedChem. Database (see Ref. [4]), the log*P* values for octanol/water partition of cyclopentane and tetrahydrothiophene-1,1-dioxide are 3.0 and −0.8, respectively. Likewise, the lipophilicity change in going from ethylbenzene to methylsulfonyl-benzene amounts to $\Delta\log P = -2.7$.

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[13] a) ACD/pK_a Predictor, Version 8.19, Advanced Chemistry Development, Inc., Toronto ON, Canada; b) pkalc, Version 3.1, CompuDrug Inc., Sedona AZ, USA; for a comparison of the experimental with calculated pK_a data, see Table S2 in the Supplementary Material.

[14] Whereas the most recent update (Version 6) of the MedChem. database contains some 12000 additional entries compared to the previous Version 3, less than 100 entries with new pK_a values became available.

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