Sulfonyl *vs.* carbonyl group: which is the more electron-withdrawing?

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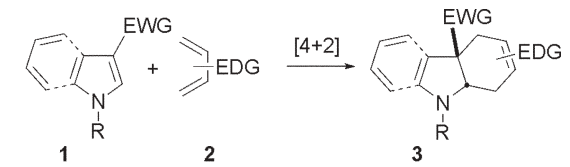
Unexpectedly high reactivity of nitrogenated aromatics protected as amides or carbamates, when compared to sulfonamides, can be explained by a decrease of the aromaticity due to a greater ability of the carbon-centered groups to achieve delocalisation of the nitrogen lone pair, resulting in stronger global withdrawing effects.

Nitrogen protection is a cornerstone of organic synthesis. Among the prevalent groups, the sulfonyl (SO_2R), carbonyl (COR) and alkoxycarbonyl (CO_2R) have all proven essential in the synthesis of peptides, nucleotides and alkaloids, for instance.[1] Their effect relies on their electron-withdrawing nature which leads to a diminution of the nucleophilic and basic properties of the nitrogen atom. Obviously, this influence extends beyond the atom bearing the protecting group. Numerous examples indeed correlate the withdrawing character of the corresponding protected substrates with their reactivity.[2]

The electronic effects of these protecting groups (inductive (*F*) and resonance (*R*) parameters) are generally quantified by Hammett constants.[3] On this scale, sulfonyl groups undoubtedly appear as much more electroattracting than carbonyl ones (Table 1), and this feature has been experimentally translated in many cases over the years. Comparison of the equilibrium acidities of either carboxamides/sulfonamides or β-oxo-ketones/-sulfones,[4] the usual choice for mesylate or tosylate as better leaving groups than acetates or carbonates in nucleophilic substitution reactions, or the relative rates of solvolysis of 1-phenethyl esters,[5] all fit this conclusion. The electrophilic character thus appears to closely correlate the electron-withdrawing effect of the protecting group.

Discrepancies in the results from our program focusing on the use of nitrogenated aromatics **1** (indoles and pyrroles) as electron-poor dienophiles in Diels–Alder cycloadditions,[2,6,7] provided an opportunity to have a closer look at this correlation (Scheme 1). In this normal electron demand process, the electrophilic, dienophilic partner reacts through its LUMO, and postulating that the more withdrawing the nitrogen substituent, the more reactive the heteroaromatic, seems obvious.



Scheme 1

The basic requirement of tethering an electron-withdrawing substituent on the aromatic nitrogen was fulfilled by transforming indole **4a** (R = H) into amides **4b–f**. Reacting indoles **4b–f** with Danishefsky diene **5**, chosen as model enophile, for 8 h led, after hydrolysis, to a first set of results (Table 2, entries 1–5). Entries 1–3 expectedly indicate that conversions are in accordance with the electronegativities of the sulfonyl groups, the trifluoromethanesulfonyl (triflyl) protected substrate **4d** giving the best results. Replacing the sulfonyl unit with acetyl resulted, however, in an increased, 88% conversion (87% isolated yield) (entry 4). The popular *tert*-butoxycarbonyl (Boc) group led to a similar 87% conversion (entry 5). Carrying out these experiments for 48 h increased the completion of the cycloadditions and confirmed the

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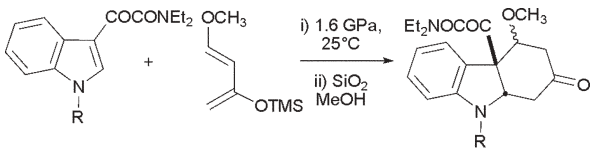
Table 1 Reported evaluation of withdrawing effects

Entry	R	F^a	R^a	$pK_a{}^b$	$pK_a{}^c$	k^d/s^{-1}
1	$COOCH_3$	0.34	0.11	—	—	—
2	$COCH_3$	0.33	0.17	25.5	14.2	3.1×10^{-9}
3	SO_2CH_3	0.53	0.19	17.5	12.5	67
4	SO_2CF_3	0.74	0.22	9.7	—	3.0×10^{5}

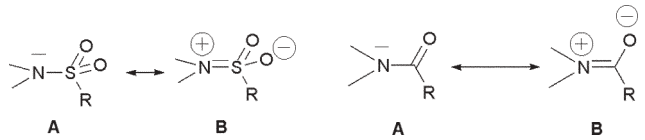
[a] Hammett and modified Swain–Lupton constants.[3] [b] pK_a of NH_2R in DMSO.[4] [c] pK_a of $PhCOCH_2R$ in DMSO.[4] [d] Solvolysis rate of 1-phenethylesters.[5]

Table 2 Cycloadditions between indoles **4** and diene **5**



Entry	4	R	*t*/h	Conv.[a] (%)	*endo*/*exo*	Yield (%)
1	**4b**	Ms	8	18	75/25	—[b]
2	**4c**	Ts	8	31	75/25	—[b]
3	**4d**	Tf	8	66	90/10	60
4	**4e**	Ac	8	88	90/10	87
5	**4f**	Boc	8	87	90/10	75
6	**4b**	Ms	48	43	85/15	31
7	**4c**	Ts	48	72	75/25	69
8	**4d**	Tf	48	100	90/10	99
9	**4e**	Ac	48	100	90/10	95
10	**4f**	Boc	48	100	90/10	96

[a] Conversion. [b] Not isolated.



Scheme 2

above trend (entries 6–10).[8] Surprisingly, the Boc group thus appears to be at least as efficient as the triflyl substituent in activating this transformation (compare entries 3 with 5, and 8 with 10).

Within the frame of Lewis formalisms, two mesomeric contributions **A**, corresponding to a lone pair fully localised on nitrogen, and **B**, involving n-delocalisation toward the R group, are generally written to account for the overall electronic structures of N-protected derivatives (Scheme 2). Intuitive comparison of both sulfonamide and amide/carbamate structures would lead one to postulate a stronger contribution of **B** in the case of the latter groups.[9] In the case of sulfur however, additional stabilising processes (*i.e.* p–d, sp^x–d delocalisation and hyperconjugation) have been proposed to explain the generally strong withdrawing effect of the sulfonyl groups.[10] This issue is somewhat reminiscent of previous studies by Cram, Corey and others on the stabilisation of carbanions by carbonyl or sulfonyl groups.[11] Later work by Wolfe theoretically demonstrated the sp^3 hybridisation of the carbanion next to the sulfonyl group;[12] this suggests the prevalence of sp^3–d overlap as the dominant stabilising effect on the carbanion in this case. However, here, the involvement of the nitrogen lone pair in the aromaticity of the five-membered ring results in its sp^2 hybridisation, regardless of the electron-withdrawing substituent tethered on the heteroatom.

To bring light on this issue, examination of the relative structural and behavioral influence of both carbonyl and sulfonyl groups, when substituting the nitrogen atom of a model 3-formylpyrrole, was carried out by computational means (Gaussian 98 at the B3LYP/6-31+G** level of theory) (Fig. 1).[13–16]

Quantitative evaluation of the N-substituent effect on the activation energy was first undertaken by means of transition state localisation for the cycloaddition between butadiene and the model 3-formylpyrroles **7a** and **7b**.[17] The exothermicities of the reactions were found to amount to 9.0 and 9.6 kcal mol^{-1}, respectively. For both processes, the differences between the activation energies of the *endo* and *exo* processes are small, within 0.3 kcal mol^{-1}. The most favoured transition states are found to be 25.8 kcal mol^{-1} above the reactants for **7a** and 27.9 for **7b**. These data are in accordance with the experimental results and come to support the choice of the model pyrrolic system.

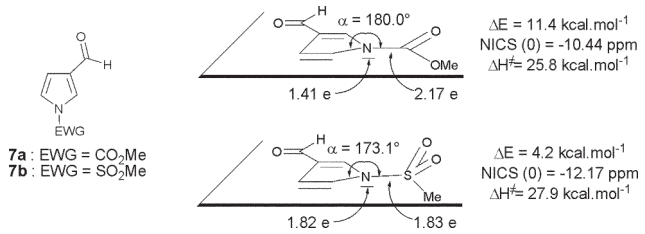


Fig. 1 Calculated electron localization function (ELF) basin population, α, Δ*E*, NICS and $\Delta H^{\neq}$ of model 3-formylpyrroles **7**.

The structures of N–X bonds in carbamates (X = C) and sulfonamides (X = S) were represented in terms of the angle (α) of the N–X bond with respect to the plane defined by the nitrogen and the adjacent, cyclic carbon atoms (Fig. 1).[10] The 180° value found for **7a** is in line with the planarity of the system, while sulfonamide **7b** is characterised by a smaller angle (173°) which reflects a slight pyramidalisation at the nitrogen atom.

To energetically quantify this property, the cost (ΔE) associated to the deconjugation of the R substituent was then estimated by optimising the geometry of the full species while freezing the X = O bond perpendicular to the above plane.[18] The induced stabilisation was found to be significantly higher in the case of carbon-centered substituents (11.4 *vs.* 4.2 kcal mol^{-1}), indicative of the greater ability of the carbon-centered protecting group to achieve p–p delocalisation.[19]

Analysis of the electron population using the ELF topological analysis[20] allowed to evaluate the relative contribution of structures **A** and **B**. N–C bond population in **7a** proved greater than 2, consistent with a partial double bond character. Depletion of this value to 1.96 upon rotation of the carbamate along the N–C bond allowed us to estimate the contribution of **B** to the overall electronic structure to 9%. N–S bond population in **7b** proved much lower (1.83 e) and no significant change was observed upon rotation along the N–S bond. This suggests that, in the latter case, the contribution of mesomeric effects (among which **B**) is negligible, and inductive effects are dominant. The much higher contribution of **B** in carbamates decreases the population of the nitrogen lone pair basin (1.41 e *vs.* 1.82 e). This effect is transmitted to the remaining 3-formylpyrrole moiety: a 0.3 electron depletion was observed for **7a** when compared to **7b**.

Aromaticity of the heterocycle ring was finally estimated using the nucleus-independent chemical shifts (NICS) method,[21] the values of **7a** (−10 ppm) and **7b** (−12 ppm) reflecting the higher aromatic character of the latter. All these data are clearly consistent with the higher capability of carbonylated substituent to delocalise electrons and are in line with the higher reactivities of both carbamate and amide substrates.

The apparent discrepancy with the data in Table 1 (column 5) reflects – at least in part – the electronic nature and hybridisation of the nitrogen atom (anionic *vs.* aromatic), among others. It is also well to bear in mind the different steric hindrances generated by the various electron-withdrawing groups.

These theoretical results are thus in full accordance with the experimental ones. A more efficient delocalisation occurs with the carbonyl groups than with the sulfonyl units. The above data are indicative of weaker global mesomeric effects – including those of different nature – in the sulfonyl groups; even when inductive effects are taken into account, the sulfur-centered functional group is less efficacious in decreasing the electron density on the nitrogen atom. *Tethering a methoxycarbonyl unit on a nitrogen atom may thus render this atom more electron-deficient than would a sulfonyl group*. The impact of this clearly appears in the above experimental results and may have a bearing in other processes. All parameters being taken into account, these results suggest the higher efficiency of p–p overlap in the carbonyl substituent species, than the overall delocalisation (including p–d and sp^x–d) occuring in the sulfonyl one, even when the nitrogen is sp^2 hybridised.

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8 *Representative procedure* for the cycloaddition reactions: to a solution of indole **4d** (75 mg, 0.2 mmol) in dry dichloromethane (0.5 mL), at room temperature under argon, was added 1-methoxy-3-trimethylsilyloxy-buta-1,3-diene (78 mL, 0.4 mmol). The resultant mixture was transferred into a 1 mL Teflon high-pressure vessel. The vessel was filled up with dry dichloromethane and compressed to 1.6 GPa for 48 h. After decompression, the solvent was evaporated under reduced pressure. The residue was then stirred overnight in methanol (5 mL) in the presence of silica (100 mg). Filtration, evaporation of the solvent and purification by flash chromatography on silica (elution with cyclohexane–EtOAc (65 : 35) led to the isolation of the diastereomeric cycloadducts (97 mg (99%), 9 : 1 mixture of diastereomers). Major diastereomer: δ_H (300 MHz; $CDCl_3$) 0.93 (t, *J* 7.2, 3H), 1.06 (t, *J* 7.2, 3H), 2.38 (dd, *J* 7.5 and 18.1, 1H), 2.56 (dd, *J* 3.4 and 18.1, 1H), 2.70–2.93 (m, 2H), 3.01 (dd, *J* 6.4 and 16.2, 1H), 3.10–3.30 (m, 2H), 3.26 (s, 3H), 3.33–3.52 (m, 1H), 4.97 (dd, *J* 3.4 and 7.5, 1H), 5.48 (dd ≈ t, *J* 6.4 and 6.8, 1H), 6.89 (ddd ≈ td, *J* 7.5, 7.5 and 0.8, 1H), 7.13 (dd ≈ t, *J* 7.9 and 7.9, 1H), 7.30 (ddd ≈ td, *J* 7.5, 7.5 and 1.1, 1H), 7.35–7.48 (m, 1H); δ_C (75 MHz; $CDCl_3$) 12.3, 13.4, 39.0, 39.6, 41.6, 43.8, 57.4, 62.8, 64.7, 76.4, 115.1, 119.6 (q, *J* 323), 125.6, 126.6, 127.9, 130.4, 140.2, 165.3, 197.2, 204.1; δ_F (282 MHz; $CDCl_3$) 88.8; *m/z* (FAB) 477 (100). ν_{max}(film)/cm^{-1} 2976, 2940, 2899, 2832, 1731, 1715, 1702, 1635, 1400 and 1194. (Found: C, 50.37; H, 4.81; N, 5.79; S, 6.55. $C_{20}H_{23}F_3N_2O_6S$ requires C, 50.42; H, 4.87; N, 5.88; S, 6.73%).

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17 The nature of the TS was checked *via* harmonic frequency evaluations to show the presence of one and only one imaginary frequency. In addition, the TS structures were given small geometrical perturbations along the reaction coordinates and then further geometrical optimization was carried out to ensure they connect the reactant and product of interest.

18 Steric effects and delocalisation in the remaining S=O bond are not taken into account in these calculations.

19 The considered optimised conformations involve the most stable rotamers in **7a** and **7b**, in full agreement with data gathered in house from RX diffraction experiments on crystals of indole derivatives **4c** and **4e** and from the literature on saturated amides and sulfonamides (see ref. 10); the in-house structures will be included in a forthcoming paper.

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