

# Acidity Inversions of $\alpha$ -NO<sub>2</sub> and $\alpha$ -SO<sub>2</sub>CF<sub>3</sub> Activated Carbon Acids as a Result of Contrasting Solvent Effects on Transfer from Water to Dimethyl Sulfoxide Solutions

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Measurements of  $pK_a$  values for the ionization of  $\alpha$ -X-substituted ethyl acetates (**1**, X = NO<sub>2</sub>; **2**, X = CN; **3**, X = SO<sub>2</sub>CF<sub>3</sub>) in H<sub>2</sub>O–Me<sub>2</sub>SO mixtures and pure Me<sub>2</sub>SO show a unique response of the acidity of the SO<sub>2</sub>CF<sub>3</sub> derivative to the solvent changes, thereby resulting in a remarkable inversion in the acidifying effects of the strongly electron-withdrawing NO<sub>2</sub> and SO<sub>2</sub>CF<sub>3</sub> groups on going from H<sub>2</sub>O to Me<sub>2</sub>SO. Overall, the results obtained provide strong evidence that the powerful electron-withdrawing effect of the SO<sub>2</sub>CF<sub>3</sub> group is by far the result of polarization effects rather than other factors such as negative hyperconjugation.

Considerable evidence has been accumulated that carbanions  $\alpha$  to nitro and carbonyl groups derive much of their stability by rehybridization from sp<sup>3</sup> to sp<sup>2</sup>, thus allowing delocalization of charge to the more electronegative atoms.<sup>1</sup> In contrast, the role of conjugative effects in determining the stability of carbanions adjacent to cyano groups has been under more scrutiny, and it is only recently that a number of studies have appeared which leave no doubt that the polar effect of the CN group is by far the major factor governing the stability of  $\alpha$ -cyanocarbanions.<sup>2–4</sup> The situation for  $\alpha$ -sulfur-stabilized carbanions, especially  $\alpha$ -sulfonyl carbanions, is still a subject of much debate.<sup>5</sup> While it is well recognized that conjugate d–p  $\pi$ -bonding cannot play a significant role, it remains less clear how charge polarization effects and negative hyperconjugation can effectively compete in determining the stability of these species.<sup>6–13</sup>

Inasmuch as there is a direct relationship between the electronic mode of action and the acidifying effect of a

substituent, it is a noteworthy feature that the literature contains a number of conflicting reports regarding the relative electron-withdrawing effects of the SO<sub>2</sub>CF<sub>3</sub> and NO<sub>2</sub> groups. On the basis of the  $pK_a$  values of 4-X- and 3-X-substituted benzoic acids—the conventional reference in Hammett's scale—Yagupolskii and Sheppard have found that SO<sub>2</sub>CF<sub>3</sub> is notably more electron-withdrawing than a NO<sub>2</sub> group:  $\sigma_m = 0.76$  and  $\sigma_p = 0.96$  for X = SO<sub>2</sub>CF<sub>3</sub>;  $\sigma_m = 0.74$  and  $\sigma_p = 0.78$  for X = NO<sub>2</sub>.<sup>14,15</sup> The SO<sub>2</sub>CF<sub>3</sub> group was also reported to be more activating than a NO<sub>2</sub> group in nucleophilic aromatic substitutions and related  $\sigma$ -adduct formation processes.<sup>16,17</sup> However, in contrast with these results, Bordwell has reported that ((trifluoromethyl)sulfonyl)methane is 1.5  $pK_a$  units less acidic than nitromethane in Me<sub>2</sub>SO solution.<sup>18</sup> A similar  $pK_a$  difference is observed in comparing unsubstituted benzyltriflone (C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>SO<sub>2</sub>CF<sub>3</sub>) to phenylnitromethane (C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>NO<sub>2</sub>) in the same solvent.<sup>18,19</sup> On the other

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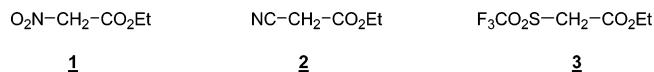
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hand, it has been reported that  $\text{CH}_3\text{SO}_2\text{CF}_3$  is 7 pK units more acidic than  $\text{CH}_3\text{NO}_2$  in the gas phase, in contrast with the generally observed situation that acidities in the gas phase and  $\text{Me}_2\text{SO}$  follow a similar order.<sup>20</sup>

In view of the increasing use of the  $\text{SO}_2\text{CF}_3$  group as a basis for the design of new electron-acceptor supersubstituents,<sup>21</sup> it is essential to further clarify the electronic mode of action of this substituent. As an approach to this problem, we are presently developing systematic solvent effect studies of the ionization of structurally related sets of  $\alpha$ -X-substituted carbon acids.<sup>19</sup> Among other systems, we have looked at the ionization of the three  $\alpha$ -X-substituted ethyl acetates **1–3**, where the effect of the



$\text{COOEt}$  group is opposed to that of a  $\text{NO}_2$ , a  $\text{CN}$ , or a  $\text{SO}_2\text{CF}_3$  group, respectively. The results obtained have prompted us to report on *the overwhelming importance of the solvent* in determining the relative electron-withdrawing capabilities of the  $\text{NO}_2$  and  $\text{SO}_2\text{CF}_3$  groups.

## Results

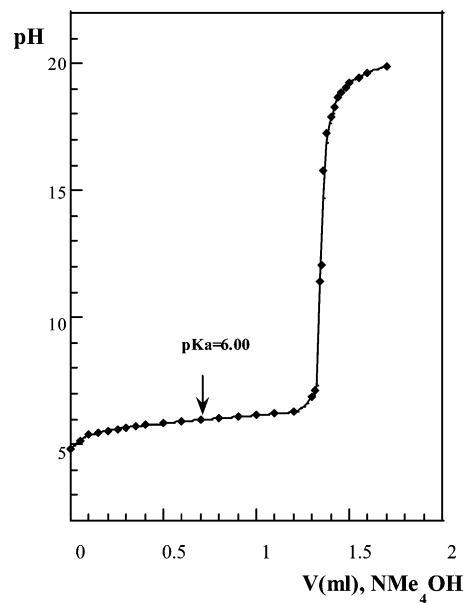
**Acidity Measurements in Water and  $\text{H}_2\text{O}-\text{Me}_2\text{SO}$  Mixtures.** The acidity constants of **1** and **3** in aqueous solution as well as in the various  $\text{H}_2\text{O}-\text{Me}_2\text{SO}$  mixtures studied were sufficiently strong to be reliably measured through potentiometric titration of ca. 0.01 M solutions ( $I = 0.1$  M  $\text{KCl}$  or  $\text{NMe}_4\text{Cl}$ ) of these carbon acids by a 0.1 M  $\text{NMe}_4\text{OH}$  solution at  $T = 25^\circ\text{C}$ . An example of the titration curves thus obtained is given in Figure 1. In the case of the less acidic compound **2** the  $\text{pK}_a$  values were preferably determined through eq 1, measuring the

$$\text{pH} - \text{pK}_a = \log \frac{[\text{C}^-]}{[\text{CH}]} \quad (1)$$

pH values of various buffer solutions made up from this carbon acid itself (CH). These buffer solutions were prepared so that the molarity of the carbanionic species ( $\text{C}^-$ ) was equal to 0.01 M at all buffer ratios employed, keeping the ionic strength constant at 0.1 M ( $\text{KCl}$  or  $\text{NMe}_4\text{Cl}$  added). To avoid buffer failure in water and  $\text{H}_2\text{O}-\text{Me}_2\text{SO}$  (70/30 v/v), only buffers with  $[\text{C}^-]/[\text{CH}]$  ratios equal to 1/1, 1/2 and 1/3 were used in these solvents. As shown in Figure S1 (Supporting Information) for the 10/90 (v/v)  $\text{H}_2\text{O}-\text{Me}_2\text{SO}$  systems, the acidity of **2** could also be determined directly by titration in solvent mixtures containing  $\geq 50\%$   $\text{Me}_2\text{SO}$ . The  $\text{pK}_a$  values thus obtained were in very good agreement with those determined from the buffer procedure. The  $\text{pK}_a$  values of **1–3**, as determined from titration curves or eq 1, are listed in Table 1.

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**FIGURE 1.** Potentiometric determination of the  $\text{pK}_a$  value of ethyl ((trifluoromethyl)sulfonyl)acetate (**3**) in 10/90 (v/v)  $\text{H}_2\text{O}-\text{Me}_2\text{SO}$  at  $25^\circ\text{C}$ : titration of a  $1.44 \times 10^{-2}$  M solution (9.78 mL) of **3** by a 0.1 M  $\text{Me}_4\text{NOH}$  solution.

**TABLE 1.**  $\text{pK}_a$  Values for Ionization of **1–3** and Related Carbon Acids in  $\text{H}_2\text{O}$ ,  $\text{Me}_2\text{SO}$ , and Various  $\text{H}_2\text{O}-\text{Me}_2\text{SO}$  Mixtures<sup>a</sup>

compd	$\text{H}_2\text{O}$	30% $\text{Me}_2\text{SO}$	50% $\text{Me}_2\text{SO}$	70% $\text{Me}_2\text{SO}$	90% $\text{Me}_2\text{SO}$	$\text{Me}_2\text{SO}$
<b>1</b> <sup>b</sup>	5.82 (5.75) <sup>c</sup>	5.78	6.00	6.55	8.31	9.08
<b>2</b> <sup>b</sup>	10.17	10.63	10.83	11.30	11.68	12.48 (13.10) <sup>d</sup>
<b>3</b> <sup>b</sup>	6.83	6.36	5.84	5.56	6.00	6.40
<b>4</b> <sup>e</sup>	10.28		11.32	12.44	14.80	17.20 <sup>f</sup>
<b>5</b>	19.27 <sup>g</sup>					26.50 <sup>f</sup>
<b>6</b> <sup>h</sup>	4.97		5.17		6.69	
<b>7</b> <sup>i</sup>	9.11		9.12		11.10	13.30 <sup>f</sup>

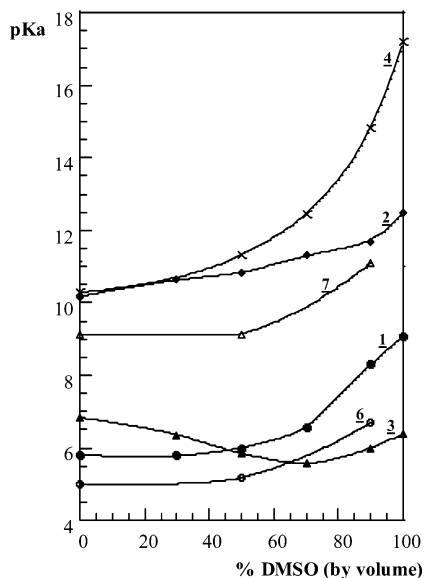
<sup>a</sup>  $T = 25^\circ\text{C}$  unless otherwise stated. <sup>b</sup> This work. <sup>c</sup> Reference 37. <sup>d</sup> Reference 38. <sup>e</sup> Reference 25 at  $20^\circ\text{C}$ . <sup>f</sup> Reference 18. <sup>g</sup> Reference 26. <sup>h</sup> Reference 27; at  $20^\circ\text{C}$ . <sup>i</sup> Reference 30; at  $20^\circ\text{C}$ .

**Acidity Measurements in  $\text{Me}_2\text{SO}$ .** The acidity of **1** in  $\text{Me}_2\text{SO}$  was measured spectrophotometrically by taking into account the fact that the conjugate carbanion **C-1** exhibits strong absorption in a region ( $\lambda_{\text{max}} = 317$  nm) where neither **1** nor the amine buffers required to study the ionization process absorb. From the determination of the  $[\text{C}^-]/[\text{CH}]$  ratio in various triethylamine ( $\text{pK}_a = 9.00$ ), morpholine ( $\text{pK}_a = 9.15$ ), and piperidine ( $\text{pK}_a = 10.85$ ) buffers,<sup>22</sup> the  $\text{pK}_a$  value of **1** was readily obtained from eq 1:  $\text{pK}_a(\text{Me}_2\text{SO}) = 9.08$ .

The  $\text{pK}_a$  values of **2** and **3** in pure  $\text{Me}_2\text{SO}$  were also determined spectrophotometrically, measuring the pH of buffer solutions made up from these two carbon acids with reference to two indicators of known  $\text{pK}_a(\text{Me}_2\text{SO})$  values, i.e. 2,4-dinitrodiphenylamine ( $\text{pK}_a = 12.74$ ;  $\lambda_{\text{max}} = 435$  nm) and 2,4,4',6-tetranitrodiphenylamine ( $\text{pK}_a = 6.07$ ;  $\lambda_{\text{max}} = 480$  nm).<sup>22,23</sup> Buffer solutions of **2** or **3** with

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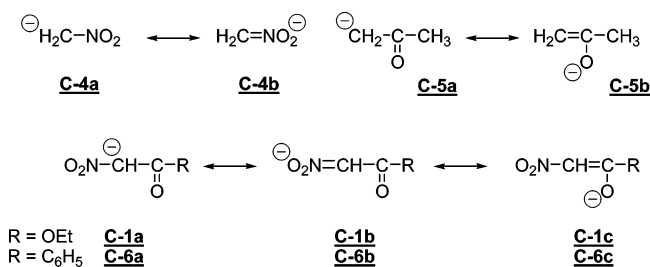


**FIGURE 2.** Effect of a H<sub>2</sub>O–Me<sub>2</sub>SO transfer on the acidity of compounds **1–3**: comparison with related carbon acids (see text for numbering).

[C<sup>−</sup>]/[CH] ratios equal to 1/3, 1/2, 1/1, 2/1, and 3/1 were prepared by addition of potassium dimsyl in Me<sub>2</sub>SO solution so that the molarity of the anionic C<sup>−</sup> species, i.e. **C-2** or **C-3**, was in all cases equal to 0.01 M. Under these experimental conditions, the pK<sub>a</sub>(Me<sub>2</sub>SO) values of **2** and **3** were calculated from eq 1.

## Discussion

Figure 2 shows the contrasting changes in the acidity of **1–3** on transfer from H<sub>2</sub>O to Me<sub>2</sub>SO. While the acidity of **1** and **2** is regularly decreased, that of **3** is increased significantly as the Me<sub>2</sub>SO content of the solutions is increased to 70–80% Me<sub>2</sub>SO (ΔpK = 1.27). Despite a slight decrease beyond this composition, the acidity of **3** is greater in pure Me<sub>2</sub>SO than in pure water solution. Regarding **1** and **2**, the observed pK<sub>a</sub> variations can be readily discussed with reference to the general situation found for α-nitro and α-carbonyl carbon acids.<sup>2,3,6,18,24,25</sup> As is well-known, such carbon acids give rise to conjugate carbanions which can be largely identified as the respective nitronate or enolate structures, e.g. **C-4b** for the nitromethane carbanion or **C-5b** for the acetone carbanion.<sup>2,3,6,18,25</sup> These correspond to a large transfer of the

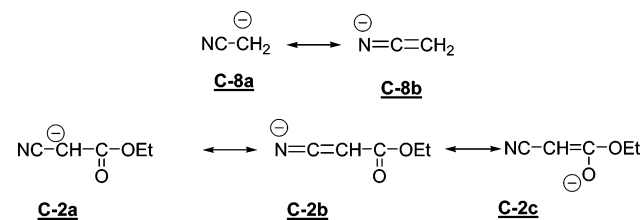


negative charge onto the electronegative oxygen atoms of the π-acceptor NO<sub>2</sub> and C=O groups. Inasmuch as the

effect of changing from water to Me<sub>2</sub>SO is to suppress the favorable effect of hydrogen-bonding solvation on the stability of such oxyanionic structures,<sup>3,18,19</sup> the acidity of the parent carbon acids is expected to concomitantly decrease. This behavior is nicely illustrated by a comparison of the measured pK<sub>a</sub> values for nitromethane (**4**) and acetone (**5**) in pure water and Me<sub>2</sub>SO solutions. Thus, we have pK<sub>a</sub>(H<sub>2</sub>O) = 10.20 and pK<sub>a</sub>(Me<sub>2</sub>SO) = 17.20 for **4** (see also Figure 1)<sup>18,25</sup> and pK<sub>a</sub>(H<sub>2</sub>O) = 19.27 and pK<sub>a</sub>(Me<sub>2</sub>SO) = 26.70 for **5**.<sup>18,26</sup>

Interestingly, the general situation described above is subject to significant modulation by specific structural features. This is the case here for ethyl nitroacetate **1** which benefits from the activation of both a NO<sub>2</sub> and a C=O group. As shown by Bernasconi for benzoyl-nitromethane (**6**), the participation of the carbonyl group in the delocalization of the negative charge of an α-keto α-nitro carbanion is substantial; i.e., both resonance structures **C-6b** and **C-6c** contribute to the stability of the carbanion **C-6**.<sup>27,28</sup> Obviously, a similar situation is likely to occur for **1**, with both structures **C-1b** and **C-1c** being major contributors to the carbanion **C-1**. As a result, the charge of **C-1**, as does that of **C-6**, is somewhat more dispersed and therefore less prone to hydrogen-bonding solvation than in the case of the nitromethane carbanion **C-4** or the acetone carbanion **C-5**. It follows that the acidity of **1** and **6** becomes rather similarly decreased on transfer from water to Me<sub>2</sub>SO but to a reduced extent relative to that of **4**: pK<sub>a</sub>(H<sub>2</sub>O) = 5.82 and pK<sub>a</sub>(90% Me<sub>2</sub>SO) = 8.31 for **1** and pK<sub>a</sub>(H<sub>2</sub>O) = 4.97 and pK<sub>a</sub>(90% Me<sub>2</sub>SO) = 6.69 for **6**. A rather analogous solvent effect is operating in the case of acetylacetone (**7**), where the presence of the two C=O groups also goes along with dispersion of negative charge in the related carbanion: pK<sub>a</sub>(H<sub>2</sub>O) = 9.11 and pK<sub>a</sub>(90% Me<sub>2</sub>SO) = 11.10.<sup>30</sup>

It has been recently demonstrated that only a relatively small fraction of the stabilization of an α-cyano-substituted carbanion can be attributed to the transfer of negative charge from carbon to nitrogen, despite the greater electronegativity of nitrogen as compared to that of carbon.<sup>2,4,31</sup> In particular, ab initio calculations have revealed that 60% of the negative charge is retained at the α-carbon in the cyanomethyl carbanion **C-8**; i.e., the



resonance structure **C-8a** with the carbon–nitrogen triple bond is substantially favored relative to the ketenimine structure **C-8b** with the two cumulative double

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(28) As a measure of the π-acceptor character of NO<sub>2</sub> and carbonyl groups: σ<sub>R</sub>(NO<sub>2</sub>) = 0.16; σ<sub>R</sub>(PhCO) = 0.16; R<sup>−</sup>(NO<sub>2</sub>) = 0.62; R<sup>−</sup>(PhCO) = 0.52; (σ<sub>P</sub><sup>−</sup> − σ<sub>m</sub>)(NO<sub>2</sub>) = 0.56; (σ<sub>P</sub><sup>−</sup> − σ<sub>m</sub>)(PhCO) = 0.45.<sup>27,29</sup>

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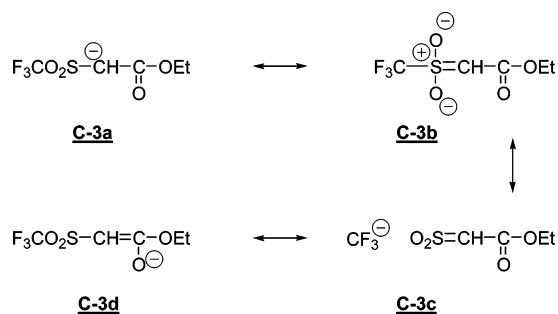
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bonds. This finding leaves no doubt that it is the competing  $\alpha$ -carbonyl group of the ester functionality (structure **C-2c**) and not the CN group (structure **C-2b**) which is playing the primary role in the delocalization of the negative charge of the ethyl cyanoacetate carbanion **C-2**. That the enolate structure **C-2c** is a major contributor to **C-2** is evidenced by the finding that the acidity decreases smoothly but regularly on going from water to Me<sub>2</sub>SO. However, as found for **1**, the effect is relatively moderate ( $\Delta pK = 2.31$ ), suggesting that stabilization of the polarizable structure **C-2a** by the dipolar aprotic solvent may overcome part of the destabilization due to the loss of hydrogen bonding (vide infra).

Obviously, the most important message of Figure 1 is the opposite response of the acidity of the trifluoromethanesulfonyl substrate **3** to the solvent change. Even though the decrease in the  $pK_a$  value brought about by the transfer from H<sub>2</sub>O to pure Me<sub>2</sub>SO corresponds to a relatively modest increase in the acidity of **3** ( $\Delta pK = 0.45$ ), the observed behavior suggests that the negative charge of the conjugate carbanion is subject to better stabilization by the dipolar aprotic solvent.<sup>13,19,32</sup> This is in accord with the idea that in this case most of the powerful electron-withdrawing effect exerted by the SO<sub>2</sub>CF<sub>3</sub> group arises from charge polarization effects; i.e., structure **C-3a** is largely favored compared to **C-3b**, **C-3c**, or **C-3d**.<sup>5,13,19</sup> As a matter of fact, we have observed that



the ionization of **3** is associated with a very strong upfield shift of the H<sub>α</sub> resonance:  $\Delta\delta(\text{H}_\alpha) = -1.95$ . Concomitantly, the C<sub>α</sub> resonance moves negligibly to low field ( $\Delta\delta(\text{C}_\alpha) = 0.61$ ). This has to be compared with the strong downfield shifts of the H<sub>α</sub> and C<sub>α</sub> resonances which are commonly found in ionization reactions giving rise to pure sp<sup>2</sup>-hybridized carbanions:  $\Delta\delta(\text{H}_\alpha)$  0.6–2 ppm;  $\Delta\delta(\text{C}_\alpha) = 20$ –50 ppm.<sup>2,19,33,34</sup> Last, the ionization of **3** induces only a weak upfield shift of the fluorine resonance ( $\Delta\delta(\text{F}) = -2.34$ ). Altogether, the results clearly indicate that a high negative charge density must be retained on the C<sub>α</sub> carbon of the trifluoromethyl carbanion, as shown in **C-3a**, supporting the above conclusion that not only the enolate structure **C-3d** but also d–p  $\pi$ -bonding (**C-3b**) and negative hyperconjugation (**C-3c**) cannot play a primary role in the stabilization of **C-3**.<sup>9–12</sup> In fact, structure **C-3a** is highly favorable in terms of polarizability of the charge, making it more susceptible to stabilization by Me<sub>2</sub>SO

than by water.<sup>30</sup> This would account for our finding of an enhanced acidity of **3** in Me<sub>2</sub>SO-rich media.

A striking manifestation of the above behavior is the observation of a solvent-induced inversion in the acidity of **1** and **3** which takes place in the 50:50 (v/v) H<sub>2</sub>O–Me<sub>2</sub>SO region. While **1** is 1 order of magnitude more acidic than **3** in water, it becomes 500-fold less acidic than **3** in pure Me<sub>2</sub>SO. Such a clear reversal in the relative acidifying effects of the NO<sub>2</sub> and SO<sub>2</sub>CF<sub>3</sub> groups within a homogeneous family of carbon acids is unprecedented.

It should also be noted that our results reveal that there is some similarity in the behavior of the SO<sub>2</sub>CF<sub>3</sub> and CN groups. Consistent with the aforementioned idea that the latter substituent derives most of its electron-withdrawing character from a polar effect,<sup>2–4</sup> literature data report that the  $pK_a$ 's of  $\alpha$ -cyanocarbon acids exhibit a slight tendency to decrease on going from water to Me<sub>2</sub>SO.<sup>3</sup> For malononitrile, the  $pK_a$  values are essentially the same in aqueous and Me<sub>2</sub>SO solutions:  $pK_a(\text{H}_2\text{O}) = 11.14$ ;<sup>35</sup>  $pK_a(\text{Me}_2\text{SO}) = 11$ .<sup>18</sup> As a result, malononitrile is a weaker acid than ethyl cyanoacetate (**2**) in water ( $pK_a(\text{H}_2\text{O}) = 10.17$ ) but a stronger acid in Me<sub>2</sub>SO ( $pK_a(\text{Me}_2\text{SO}) = 12.48$ ).

In conclusion, we have demonstrated that the nature of the solvent is a parameter of overwhelming importance in determining the relative electron-withdrawing capabilities of the NO<sub>2</sub> and SO<sub>2</sub>CF<sub>3</sub> groups, especially when these two groups are directly bonded to the ionization site. Also, our results for **3** do not support recent theoretical studies which suggest that negative hyperconjugation might play a significant role in the stabilization of  $\alpha$ -SO<sub>2</sub>CF<sub>3</sub>-substituted carbanions.<sup>7–12</sup>

While Taft and Bordwell have previously pointed out the role of the solvent in governing the acidifying effects of a number of electron-withdrawing groups—the so-called substituent solvation assisted resonance effects (SSAR)—most of the discussion was centered on substituents attached at a para position of a benzene ring, with little attention devoted to the SO<sub>2</sub>CF<sub>3</sub> group.<sup>36</sup> In fact, the question of how the solvent can affect the relative activating effects of the NO<sub>2</sub> and SO<sub>2</sub>CF<sub>3</sub> substituents in different bonding situations remains to be elucidated, calling for similar studies with other nitro- and SO<sub>2</sub>CF<sub>3</sub>-activated acid functionalities.

## Experimental Section

**Materials.** Ethyl nitroacetate (**1**) and ethyl cyanoacetate (**2**) were of the highest quality commercially available and used without further purification. Ethyl ((trifluoromethyl)sulfonyl)acetate was prepared as described by Langlois et al.<sup>39</sup> The amines used as buffering reagents in pure Me<sub>2</sub>SO were purified according to standard procedures. Dimethyl sulfoxide was refluxed over calcium hydride and distilled, and the fractions at 32–35 °C (under 2 mmHg) were collected and stored under nitrogen. Only freshly prepared solutions were used in the spectrophotometric studies carried out in pure Me<sub>2</sub>SO.

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SO. H<sub>2</sub>O–Me<sub>2</sub>SO solutions were prepared as described previously.<sup>34,40–41</sup>

**Measurements.** All the information pertaining to the potentiometric methodology, including calibration of the cell used to carry out the pH measurements, has been reported in detail in previous works.<sup>40,41</sup> A Tacussel Isis 20000 electronic pHmeter was used for that purpose. Spectrophotometric

determinations of the p*K*<sub>a</sub> values with reference to appropriate indicators in pure Me<sub>2</sub>SO have been carried out following the procedures of Bordwell and Crampton.<sup>22,23,42</sup>

**Supporting Information Available:** Figure S1, Potentiometric determination of the p*K*<sub>a</sub> value of ethyl cyanoacetate (**2**) in 10:90 (v/v) H<sub>2</sub>O–Me<sub>2</sub>SO at 25 °C. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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