The low K_{Enol} values of β-sulfonyl-substituted amides

Ahmad Basheer,[a,b] Masaaki Mishima,[c] and Zvi Rappoport[a]*

[a] *Institute of Chemistry and the Lise Meitner Minerva Center for Computational Quantum Chemistry, The Hebrew University, Jerusalem 91904, Israel*
[b] *SALiS Center for Student Active Learning in Science, The Academic Arab College for Education in Israel, Haifa 33145, Israel*
[c] *Institute for Materials Chemistry and Engineering, Kyushu University, Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan*
E-mail: zvi.rappoport@gmail.com

Dedicated to Prof. Michael Orfanopoulos of the University of Crete, Greece on the occasions of his 67th birthday and his retirement

DOI: http://dx.doi.org/10.3998/ark.5550190.p008.927

Abstract

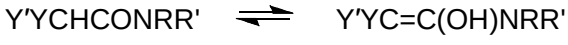
Amides substituted by one β-sulfonyl group and another β-sulfonyl, β-ester or β-CN group, form very low percentages of the corresponding enols, lower than for the β,β-diester and β-cyano, β-ester substituted systems, despite the equal or weaker electron delocalizing ability of the latter groups which help to stabilize the enols more than that of the sulfonyl group. This cannot be attributed to the non-planarity of the enols, since the calculated structures are planar. It is suggested that the sulfonyl-substituted amides are more stabilized than the β-ester- or β-cyano-substituted amides. An amide substituted by β–nonafluorosulfonyl, β–acetyl groups enolizes on the acetyl group, forming a strong, nearly symmetrical intramolecular hydrogen bond. The use of 600 MHz NMR spectroscopy can extend the range of observable enols.

Keywords: β–Sulfonylenols, β–sulfonylamides, X-ray structures, H-bonding

Introduction

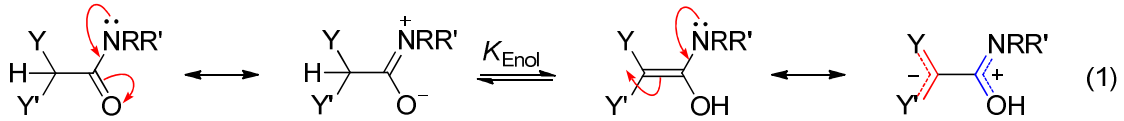
Amides substituted by two β-electron-withdrawing groups (EWGs) Y,Y′ **1** frequently give appreciable percentages of their tautomeric enols **2** with K_{Enol} = [**2**]/[**1**] ≥ 7 in $CDCl_3$.[1-13] Examples of favorable Y,Y′ combinations include CO_2R, CN,[2,6-9] CN, CN,[6,7] CO_2R, $CO_2CH_2CF_3$;[6,7] $(RO)_2P{=}O$, CO_2R',[11] CONRR', CN[12] or CSNRR', CN.[13] Surprisingly, the NO_2,

CO_2Et combination gives a relatively low K_{Enol} = 0.10[2] which is close to that for Y = Y′ = CO_2Me.[1]



1 **2**

A recent preliminary experiment With Y = $CONH_2$, Y′ = $MeSO_2$, R = R' = H showed no enol, which by our (300 and 400 MHz) NMR detection method means that $K_{Enol} \leq 0.02$.[14] These results are somewhat surprising, since mostly the better EWGs (to which NO_2 and RSO_2 belong) give higher K_{Enol} values, although quantitative correlation between K_{enol}, (or pK_{Enol} = -log K_{Enol}) and parameters measuring the extent of electron-withdrawal such as pK_a(CH_2YY') was not found.[10] Such correlation may be expected since in the **1**/**2** equilibria (Eq. 1), the enol **2a** is stabilized by the zwitterionic structure **2b** which contributes significantly to the enol structure.



1a **1b** **2a** **2b**

We assume that the lack of a general pK_{Enol} *vs*. pK_a(CH_2YY') correlation is significantly affected by the left-hand side of Eq. 1 which includes stabilization of the amide by structure **1b** superimposed on destabilization by electrostatic repulsion between the C=O and the C-Y and C-Y′ dipoles, effects which are not correlated with the pK_a's.

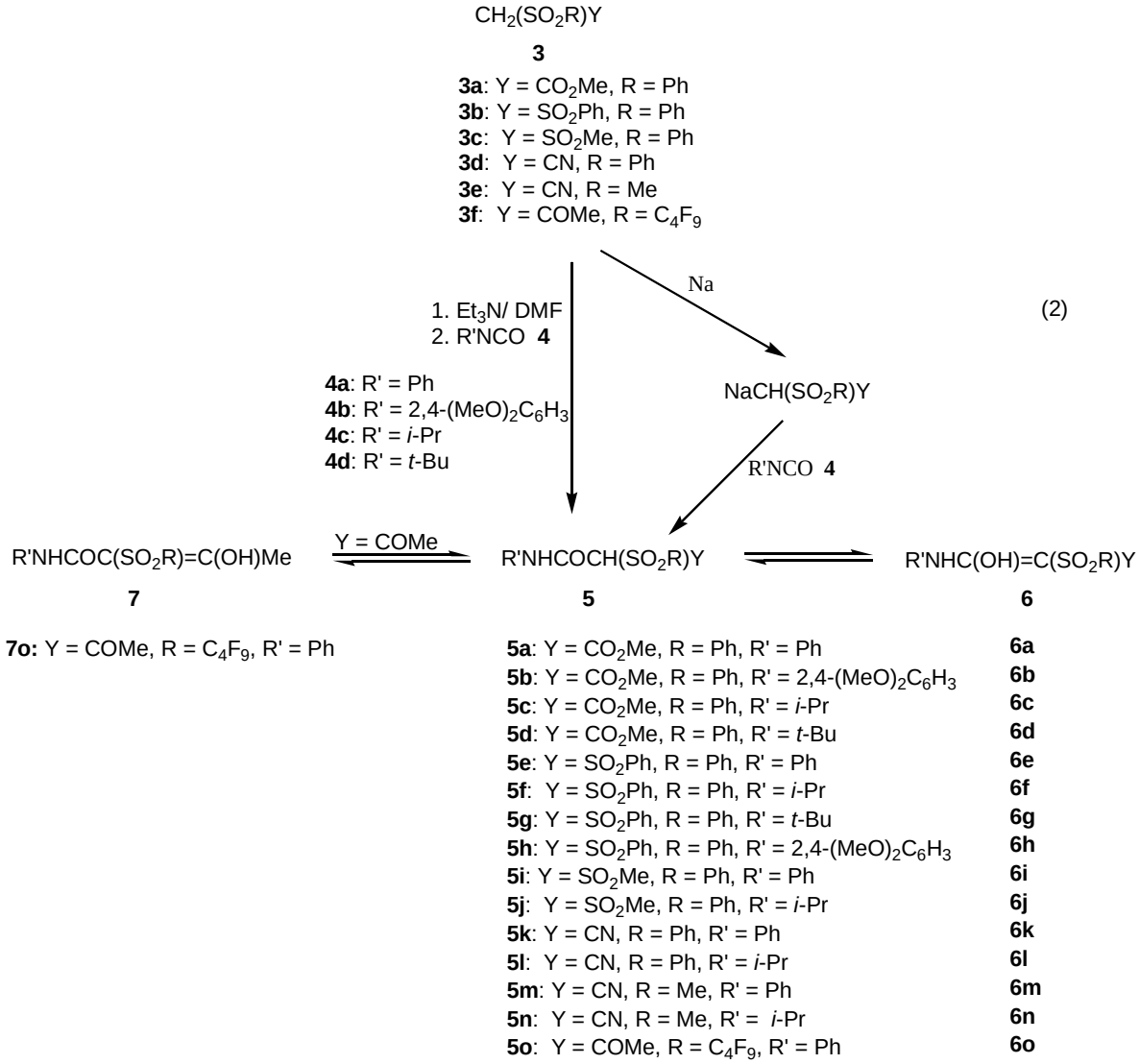
In the present paper we want to find out if the observed low K_{Enol} compared with the intuitively expected ones for *β*-sulfonyl-substituted amides reflects a low extent of promotion of the enolization. We prepared several amides substituted by RSO_2, $R'SO_2$; RSO_2, CO_2R' and RSO_2, CN EWGs pairs, and tried to observe the derived enols, calculate their K_{Enol} values, and explain the observations by computation.

Results and Discussion

Synthesis

Fifteen "formal"[15] Y′,Y-substituted amides **5a-o** which can be formed in a mixture with the isomeric enols **6a-o** were prepared by the method used previously for preparing (EWG')(EWG)CHCONRR' systems[1-13] The active methylene compounds **3a-c** were converted into their sodium salts by reaction with metallic Na in THF, and the salts reacted without isolation with aryl or alkyl isocyanates **4** to give the amides **5a-j** (Eq. 2). The cyano-substituted systems **5k-n** were prepared from **3d-f** and **4** in the presence of Et_3N in dry DMF (Eq. 2). A single keto carbonyl substituted system (Y = COMe, **5o**) was likewise prepared. In this system a

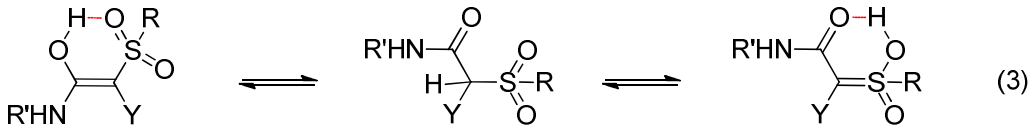
competitive enolization between the COMe and CONHR carbonyls may give enol **7**, and hence the product was assigned as **5o**/**6o**/**7o**. Only **5e**[16,17] and **5k**[16] are known compounds.



Structures in solution

In addition to the amide **5**, the enols **6** which may have an *E*- or *Z*-configuration, the sulfonyl group itself can be a potential enolization site, giving species **8**. The three species are shown in Eq. 3, with *Z*-**6** and **8** as hydrogen bonded species. The relative stability of the enol **8** was probed by B3LYP/6-31+G* (B3LYP/6-31G**) calculations. The cyanosulfonyl enols **8** derived from **5l** and **5n** showed no stable structure. A barrierless proton transfer gave the amides **5l** and **5n**. The ester- or the acetyl-substituted species (**5a**, **5c**, **5o** and the $PhSO_2$ analogue of **5o**) also did not give stable structures **8**. Proton transfer from the enols **8a** and **8c** first converged to the intramolecularly hydrogen bonded enol of ester **9** which was at a minimum, by transferring the proton to the adjacent ester group. It then further transferred the proton to the amido carbonyl to

give the enols **6a** and **6c** on the amide carbonyl. The latter were 10.9 (12.3) and 12.5 (13.7) kcal/mol less stable than **6a** and **6c**, respectively. In contrast, the enols formed from proton transfer to the acetyl group were stable, and indeed the enol **7** was actually the product isolated. Only the enols *i*-PrNHCOC=C[RS(=O)OH]SO_2R, R = Me, Ph (**8f**) (their calculated structures are given in Figure S1 in the Supporting Information) remain computationally stable but they were 19.5 (17.0) and 14.8 (15.5) kcal/mol, respectively, less stable than the isomeric enols **6**. Comparisons between enolizations at the three sites of acetyl-substituted sulfonylamides **7**, R' = *i*-Pr, Y = COMe showed that enolization on the acetyl carbonyl to give **7** is comparable to enolization on the amido oxygen. For the known analogue with R = C_4F_9 the enolization is 0.6 (0.2) kcal/mol more favored to give **7** than on the amide group to give **6**, which agrees with the observed product **7**.



(3)

***Z*-6** **5** **8**

6a: Y = CO_2Me, R = Ph, R` = Ph
6c: Y = CO_2Me, R = Ph, R` = *i*-Pr
6f: Y = SO_2Ph, R = Ph, R` = *i*-Pr
9: PhNHCOC(SO_2R)=C(OH)OCH_3

^{1}H and ^{13}C NMR spectra were the probes used for structural determination in solution. Most of the compounds display in the 300 or 400 MHz spectra only the signals for the amide tautomers **5a-n** in both $CDCl_3$ and DMSO-d_6. Most characteristic are the CH and NH signals in the ^{1}H spectra and the CH and C=O signals in the ^{13}C spectra. Only compounds **5b** and **5c** display, at the very low field of 15-16 ppm, weak signals in CCl_4 or in $CDCl_3$ which are ascribed to the enol OH signal of **6b** and **6c**, respectively, and accompanying NH signals with the same intensity at 8-10 ppm. The % enol in these cases is at most 2-4%, *i.e.*, K_{Enol} = 0.04 (CCl_4) and 0.03 ($CDCl_3$) for **5b**/**6b** and 0.03 (CCl_4) and 0.02 ($CDCl_3$) for **5c**/**6c**, but the integration of the small OH signal is not very reliable. In an attempt to obtain a more reliable integration and to detect lower percentages of the enol, if any, the ^{1}H NMR spectra of most of amides **5** were measured in CCl_4 or in $CDCl_3$ with a 600 MHz instrument. The increased sensitivity enabled us to see the OH signals of **6a, 6b**, **6d** and **6i** more clearly and with a better integration than that in the 400 MHz instrument, and to determine enol percentages of 0.08-0.84%. Moreover, in cases where signals for the enols were not observed, we assume that 0.05% of the enol could have been observed. A drawback is that a weak broad signal at *ca*. 14.50 ppm, which is ascribed to an unknown impurity, was observed in all the spectra of **5**/**6** in $CDCl_3$ and in $CDCl_3$ itself and may have prevented the observation of the OH signals of other enols. Small signals which appear in the region of the enol NH signals of other systems were occasionally observed in these cases, but

their assignment is only tentative. Consequently, it is difficult to estimate the precision of the K_{Enol} values, except that the values are low. The fact that the % of enol **6a** is higher in CCl_4 than in $CDCl_3$ as was observed with other enols[12] increases the reliability of the assignment. The data are given in Table 1 and spectra are shown in the Supporting Information.

Table 1. Composition of **5a-n/6a-n** and **5o/6o/7o** in several solvents at room temperature[a]

Compd.	Solvent	Amide (%)	δ(CH)	δ(NH), [δ(NH)][b]	δ(OH)	K_{Enol}	pK_{Enol}
5a/6a[d]	$CDCl_3$	99.57	4.96	9.03	16.27	0.0043	2.36
	$CDCl_3$	100[c]	4.96	8.96		≤0.005	≥ 2.3
5b/6b[c]	CCl_4	99.16	4.73	9.26	16.3	0.0085	2.1
	$CDCl_3$	99.39	5.08	9.35, [10.82]	16.14	0.0061	2.2
	DMSO-d_6	100	6.08	9.63		≤0.005	≥ 2.3
5c/6c	CCl_4	97[e]	3.81	6.08, [8.10]	14.98	0.031	1.51
	$CDCl_3$	98[e]	4.84	6.99, [8.05]	15.60	0.02	1.7
	DMSO-d_6	100	5.34	8.19		≤0.005	≥ 2.3
5d/6d	CCl_4	100	4.75	7.00		≤0.005	≥ 2.3
	$CDCl_3$	100[c]	4.75	7.00		≤0.005	≥ 2.3
5d/6d[c]	$CDCl_3$	99.32	4.75	7.00	15.71	0.068	2.16
5e/6e	$CDCl_3$	100	5.27	8.75		≤0.005	≥ 2.3
	DMSO-d_6	100	6.37	10.43		≤0.005	≥ 2.3
5f/6f	$CDCl_3$	100	5.26	6.84		≤0.005	≥ 2.3
5g/6g	$CDCl_3$	100	5.06	6.77		≤0.005	≥ 2.3
5i/6i	$CDCl_3$	99.92	5.27	8.42		0.0008	3.1
	DMSO-d_6	100	6.07	10.62		≤0.005	≥ 2.3
5j/6j	$CDCl_3$	100	5.05	6.43		≤0.005	≥ 2.3
	DMSO-d_6	100	5.82	8.36		≤0.005	≥ 2.3
5k/6k	$CDCl_3$	100	5.03	8.29		≤0.005	≥ 2.3
5l/6l	$CDCl_3$	100	4.63	6.19		≤0.005	≥ 2.3
5m/6m	$CDCl_3$	100	4.88	8.13		≤0.005	≥ 1.7
5n/6n	$CDCl_3$	100	4.76	6.31		≤0.02	≥ 2.3
5o/6o/7o	$CDCl_3$	0		9.80	19.08	≥50	≤ -1.7
	THF-d_8	0		9.86	19.05	≥50	≤ -1.7
	DMSO-d_6	[f]	[f]	10.52	[f]	≤0.02	≥ 1.7

[a] Measured with 600 MHz NMR spectrometer unless otherwise stated, except values in DMSO-d_6 which were measured with 400 MHz NMR spectrometer. [b] δ(NH) of the enol isomer. [c] Measured with 400 MHz NMR spectrometer. [d] Very weak signals were observed at 10.7 and 11.6 ppm and one of them may be due to the isomeric enol. [e] Position of OH signal is hidden by the 14.52 ppm signal at 600 MHz. [f] 100% ionization.

The **5o**/**6o**/**7o** system displays in the ^{1}H NMR spectrum in $CDCl_3$ two low field 1:1 signals at 19.08 and 9.80 ppm ascribed to OH and NH signals, respectively, of the same tautomer, as well as Me and Ph signals. The ^{13}C NMR spectra displayed two low field signals at 198.3 ppm (t, *J* 6 Hz) and 168 ppm ascribed to C_α of the enol on the COMe group and to the amide CO, respectively. The very low δ(OH) value and the similar δ values to those of the enol PhNHCOC(CO_2Et)=C(OH)Me on the acetyl group[2b] argue strongly that the species is the enol **7** (see below). The full ^{1}H and ^{13}C NMR data are given in Figure S1 of the Supporting Information.

Solid State Structures

The solid state structure of "formal"[15] **5c**, crystallized from EtOAc/petroleum ether and **5o**, crystallized from $CDCl_3$ were determined by single crystal X-ray crystallography. The ORTEPs and the full data for both compounds are given as CIF's in the Supporting Information. The bond lengths for **5c** [**C**(1)-**C**(2)O_2Me 1.516(8) Å, **C**(1)-**C**(4)=O 1.528(7) Å, MeO-**C**(2)-**O**(1) 1.177(7) Å and *i*-PrNH-**C**(4)-**O**(2) 1.225(5) Å] indicates that the structure is **5c**. Each molecule is intermolecularly hydrogen bonded to a second **5c** molecule by N-H···O bond forming a homopolymeric network. The data resemble that of the calculated structure and that for amide $MeSO_2CH(CONH_2)_2$.[14]

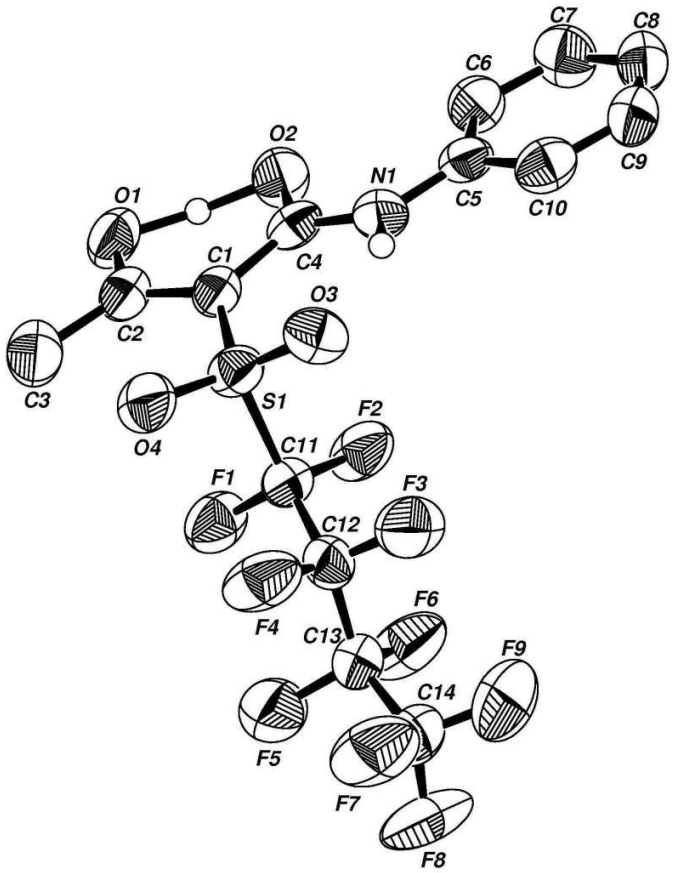
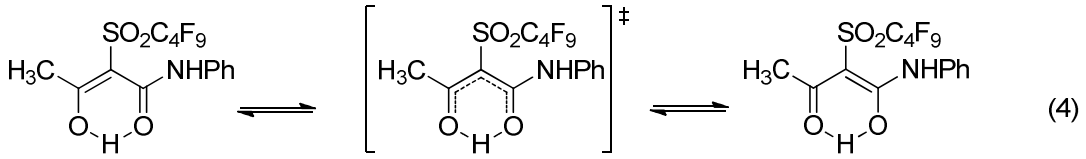


Figure 1. ORTEP structure of compound **7o**.

In contrast, the solid state structure of **5o**/**6o**/**7o** (*cf.* ORTEP of **7o** in Figure 1) shows C(1)-C(2), C(1)-C(4), C(2)-O(1) and C(4)-O(2) bond lengths of 1.428(9), 1.468(9), 1.290(8) and 1.261(8) Å. The C(1)-S(1) bond length of 1.706(7) Å is 0.1 Å shorter than the value of 1.803(5) Å in **5c**. The O(1)-H, and O(1)···H bond lengths and distances are 1.19 and 1.24 Å, respectively and <O(1)HO(2) = 160.3º. The very long C(1)-C(2) double bond indicates a single bond character for the zwitterionic enol structure. The C(1)-O(1) bond is a single C-O bond, in line with the enol sub-structure C=C(Me)-O-H of **7o**. The O-H which is *cis* to the amide group, forms a non-linear hydrogen bond with a O···O nonbonding distance of 2.40 Å, indicating a strong hydrogen bond. The small difference of 0.05, 0.04 and 0.029 Å between the O-H and O···H, C(1)-C(4) and C(1)-C(2), and C(4)-O(2) and C(2)-O(1) distances, respectively, indicate a high symmetry at room temperature (Figure S1). This is in contrast with the calculated data at B3LYP/6-31+G*, (B3LYP/6-31G**) especially at the hydrogen bond which show a much larger difference between the O-H and O···H bond lengths which are respectively 1.037(1.058) Å and 1.473(1.398) Å for **7o**, and 1.050(1.061) Å and 1.436(1.350) Å for **6o** (Figure 2b). Superposition of the two structures gives an almost symmetrical hydrogen bond of 1.26 (1.24) and 1.25(1.20) Å. This raises the possibility that the static unsymmetrical structures of **7o** and **6o** at low temperature have a low barrier for reversible hydrogen transfer between the acetyl and the amide oxygens, leading to the observed close to symmetric hydrogen bond. A similar structure with a less symmetric hydrogen bond was obtained for the enol derived from the formal amide $PhNHCOCH(COMe)CO_2Et$.[1] A similar difference between calculated and observed hydrogen bond parameters was reported for enols of cyanomalonamides.[12] A second intermolecular N(1)-H···O(3) hydrogen bond exist between the amidic NH and one of the sulfonyl oxygens (N-H 1.06 Å, H···O(3) 1.81 Å, N···O 2.71Å, < N(1)HO(3) 139.8º). We note that a competitive enolization on the COR and CONRR' carbonyls was earlier demonstrated by isolating both solid enols in the 2-carbanilido-1,3-indanedione system.[18] The calculated structures of **5c** and **7o** are given in Figure 1. The calculated B3LYP/6-31+G* thermodynamic data for the barriers of eq. 4 in kcal/mol, kcal/mol and e.u. are ΔH 91.43, ΔG 0.97 and ΔS 1.50 for **7o** → Transition state and 0.52, 0.29 and 0.80 for the corresponding **6o** → Transition state, respectively.



(4)

Enol of acetyl, **7o** Enol of amide, **6o**

O···H-O values

The results given above, especially the absence of enol signals even in the 600 MHz spectra indicate that the *β*-sulfonyl-substituted amides, substituted by another *β*-sulfonyl, *β*-ester or *β*-cyano group undergo an inefficient enolization, in contrast with the other Y,Y′ pairs mentioned

above. This can be ascribed to three reasons. (a) The sulfonyl together with the other Y group are weaker resonatively EWG than these Y,Y′ groups, and hence amide stabilization due to structure **1b** overcomes enol stabilization due to structure **2b**. Precedents for such behavior are known for several Y,Y′ pairs.[2] (b) Steric interaction between the β-substituents twist them out of planarity from the C=C(OH)NRR′ plane, thus reducing the maximum resonative stabilization of the enol, which is achieved at full planarity (*cf.* structure **2b**). Precedents for this behavior in diester-substituted systems were shown by computations.[10] (c) Amide destabilization of sulfonyl-substituted systems is lower than in the corresponding esters. The low enolization ability will be discussed in comparison with other EWGs, especially ester groups, in terms of these points.

The electron-withdrawing ability of R'SO_2, CO_2R, NO_2 and CN groups can be compared by using substituent parameters, especially σ_R^- values which measure negative charge delocalizing ability. Slightly differing values are available in the literatue, and our values are taken from a recent compilation.[19] For CO_2Me, CO_2Et, CN, NO_2, $MeSO_2$ and $PhSO_2$ the σ_p values are 0.44, 0.44, 0.65, 0.77, 0.70 and 0.68, σ_p^- are 0.74, 0.74, 1.02, 1.29, 1.13 and 0.95 and σ_R^- values are 0.30, 0.31, 0.26, 0.37, 0.35 and 0.22, respectively. Consequently, a $MeSO_2$ is a better resonatively negative charge delocalizing than CO_2R or CN, which is only exceeded by that of a NO_2 group. A $PhSO_2$ group is less EWG than a $MeSO_2$. Based on this argument alone, the $MeSO_2$ group should give higher K_{Enol} values than corresponding systems with CO_2R EWGs.

Several observed ratios

The problem of quantitative comparison is that for most of the sulfonyl-substituted systems the K_{Enol} values are $\leq$ 0.005. Consequently, for observable sulfonyl-substituted enols in $CDCl_3$, a CO_2Me group exceeds enol-promotion ability than SO_2Ph or CN as shown by the following ratios K_{Enol}[PhNHCOCH(CO_2Me)$_2$]/K_{Enol}[PhNHCOCH(CO_2Me)SO_2Ph] = 17.4, and for the *N*-*i*-Pr analogue > 5. For K_{Enol}[*i*-PrNHCOCH(CN)CO_2Me]/K_{Enol}[*i*-PrNHCOCH(CN)SO_2Ph] = > 9000 and two methoxycarbonyl groups are better than two RSO_2 groups: K_{Enol}[PhNHCOCH(CO_2Me)$_2$]/K_{Enol}[PhNHCOCH(SO_2Me)SO_2Ph] = 88. It is clear that it is difficult to observe trends with the few available accurate values. A more extensive comparison will be achieved by calculating many more K_{Enol} values by the DFT method.

DFT calculations of K_{Enol} values

The calculated thermodynamic parameters and pK_{Enol} values for all our systems, a few others, as well as several values for diesters, a cyano ester and dicyano substituted systems, and systems activated by only the single groups SO_2R (R = Me, Ph, C_4F_9), CO_2R (R = Me, CH_2CF_3) and CN, as well as R'$NHCOCH_3$ systems [R = *i*-Pr, *t*-Bu, Ph and 2,4-$(MeO)_2C_6H_3$] at both B3LYP/6-31+G* and B3LYP/6-31G** are given in Table 2. Earlier calculated ΔH, ΔG and pK_{Enol} values for $(MeO_2C)_2$CHCONHPh at B3LYP/6-31G** are respectively -5.7 and -2.7 kcal/mol and 1.98.[1]

Table 2. Energies (kcal/mol) and and entropies (e.u.) difference between enol and amide calculated at B3LYP/6-31+G* (B3LYP/6-31G**) in kcal/mol

pK_{Enol}	ΔE	ΔH	ΔG	ΔS
i-PrNHC(OH)=C(SO_2Ph)$_2$	3.4 (-0.7)	5.0 (0.8)	-5.3 (-4.9)	3.66 (0.57)
i-PrNHC(OH)=C(SO_2Me)$_2$	4.3 (1.0)	6.1 (2.3)	-5.9 (-4.4)	4.46 (1.71)
i-PrNHC(OH)=C($SO_2C_4F_9$)$_2$	-8.9 (-8.8)	-8.9 (-9.1)	-0.3 (0.9)	-6.49 (-6.64)
i-PrNHC(OH)=C(SO_2Me)SO_2Ph[a]	0.7 (-2.7)	1.9 (-0.7)	-4.1 (-6.4)	1.37 (-0.54)
i-PrNHC(OH)=C(SO_2Me)SO_2Ph[b]	0.8 (-2.3)	2.2 (-0.3)	-4.7 (-6.7)	1.60 (-0.23)
i-PrNHC(OH)=C(CO_2Me)SO_2Ph	0.6 (-2.9)	1.8 (-2.0)	-3.9 (-2.9)	1.33 (-1.50)
i-PrNHC(OH)=C(COMe)SO_2Ph	-2.3 (-6.9)	-1.4 (-5.8)	-3.1 (-3.8)	-1.04 (-4.25)
i-PrNHCOC(SO_2Ph)=C(OH)Me	-3.2 (-7.0)	-2.2 (-5.7)	-3.2 (-4.3)	-1.65 (-4.18)
i-PrNHC(OH)=C(COMe)$SO_2C_4F_9$	-7.8 (-10.8)	-5.5 (-9.1)	-7.6 (-5.9)	-4.06 (-6.64)
i-PrNHCOC($SO_2C_4F_9$)=C(OH)Me	-8.2 (-10.8)	-6.2 (-9.3)	-6.8 (-5.2)	-4.51 (-6.80)
i-PrNHC(OH)=C(CN)SO_2Me	1.5 (-1.3)	1.9 (-1.2)	-1.2 (-0.4)	1.37 (-0.85)
i-PrNHC(OH)=C(CN)SO_2Ph	1.1 (-1.8)	1.5 (-1.5)	-1.3 (-0.7)	1.12 (-1.12)
t-BuNHC(OH)=C(CO_2Me)SO_2Ph	3.3 (-0.6)	4.9 (0.8)	-5.2 (-4.7)	3.60 (0.57)
PhNHC(OH)=C(SO_2Me)$_2$	4.0 (0.3)	5.2 (0.9)	-4.1 (-1.9)	3.78 (0.67)
PhNHC(OH)=C(SO_2Ph)$_2$	5.0 (1.9)	6.1 (2.6)	-3.7 (-2.4)	4.49 (1.94)
PhNHC(OH)=C($SO_2C_4F_9$)$_2$	-4.4 (-5.2)	-3.6 (-4.6)	-2.7 (-2.0)	-2.64 (-3.36)
PhNHC(OH)=C(SO_2Me)SO_2Ph[a]	2.3 (-1.2)	3.0 (-0.4)	-2.4 (-2.7)	2.19 (-0.27)
PhNHC(OH)=C(SO_2Me)SO_2Ph[b]	2.5 (-0.9)	3.4 (-0.2)	-3.1 (-2.2)	2.48 (-0.16)
PhNHC(OH)=C(CO_2Me)SO_2Ph	-1.6 (-5.2)	-0.5 (-4.1)	-3.5 (-3.7)	-0.38 (-3.01)
PhNHCOCH(SO_2Ph)=C(OH)OMe	0.4 ([c])	1.8 ([c])	-4.5 ([c])	1.30 ([c])
PhNHC(OH)=C(COMe)SO_2Ph	1.2 (-4.1)	2.6 (-2.9)	-4.5 (-4.1)	1.89 (-2.10)
PhNHCOCH(SO_2Ph)=C(OH)OMe	-0.1 ([c])	1.4 ([c])	-4.8 ([c])	1.01 ([c])
PhNHC(OH)=C(COMe)$SO_2C_4F_9$	-7.1 ([d])	-6.1 ([d])	-3.5 ([d])	-4.45 ([d])
PhNHCOCH($SO_2C_4F_9$)=C(OH)Me	-8.0 (-10.4)	-6.8 (-9.7)	-4.2 (-2.4)	-4.95 (-7.12)
PhNHC(OH)=C(CN)SO_2Me	4.6 (1.4)	5.3 (1.4)	-2.3 (-0.2)	3.89 (1.05)
PhNHC(OH)=C(CN)SO_2Ph	5.2 (1.8)	5.1 (2.0)	0.7 (-0.6)	3.70 (1.45)
2,4-$(MeO)_2C_6H_3$NHC(OH)=C(SO_2Ph)$_2$	7.9 (3.2)	8.9 (5.2)	-3.1 (-6.4)	6.50 (3.79)
2,4-$(MeO)_2C_6H_3$NHC(OH)= C(CO_2Me)SO_2Ph	3.2 (-1.6)	4.6 (-0.3)	-4.8 (-4.5)	3.40 (0.20)
$MeSO_2C(CONH_2)$=C(OH)NH_2[e]	-2.0 (-5.8)	-0.8 (-4.8)	-4.0 (-3.2)	-0.58 (-3.56)
$MeSO_2C(CONH_2)$=C(OH)NH_2[a]	1.0 (-2.1)	2.2 (-1.0)	-4.2 (-3.6)	1.62 (-0.74)
i-PrNHC(OH)=C(CO_2Me)$_2$	-2.7 (-7.6)	0.0 (-4.4)	-9.0 (-10.7)	0.0 (-3.2)
i-PrNHC(OH)=C(CO_2Me)$CO_2CH_2CF_3$	4.6 (-8.4)	-2.2 (-6.2)	-8.1 (-7.7)	-1.6 (-4.5)
i-PrNHC(OH)=C($CO_2CH_2CF_3$)$_2$	-5.2 (-8.9)	-2.5 (-6.9)	-8.9 (-6.7)	-1.9 (-5.0)
i-PrNHC(OH)=C(CN)CO_2Me	-4.4 (-7.9)	-2.7 (-6.3)	-5.9 (-5.5)	-2.0 (-4.6)

Table 2 (continued)

pK_{Enol}	ΔE	Δ*H*	Δ*G*	Δ*S*
i-PrNHC(OH)=C(CN)$CO_2CH_2CF_3$	-6.0 (-9.2)	-4.1 (-7.3)	-6.3 (-6.3)	-3.0 (-5.3)
i-PrNHC(OH)=C(CN)$CO_2CH(CF_3)_2$	-7.1 (-9.9)	-4.4 (-7.0)	-9.0 (-9.8)	-3.2 (-5.1)
i-PrNHC(OH)=$C(CN)_2$	2.7 (0.1)	3.4 (0.9)	-2.4 (-2.6)	2.5 (0.7)
PhNHC(OH)=$C(CO_2Me)_2$	-1.6 (-6.2)	0.2 (-4.2)	-5.8 (-6.6)	0.1 (-3.1)
PhNHC(OH)=C(CO$_2$Me)$CO_2CH_2CF_3$	-3.1 (-6.9)	-1.0(-6.2)	-7.1 (-2.4)	-0.7 (-4.6)
PhNHC(OH)=$C(CO_2CH_2CF_3)_2$	-4.0 (-7.7)	-1.1 (-6.6)	-9.7 (-3.6)	-0.8 (-4.8)
PhNHC(OH)=C(CN)CO_2Me	-3.1 (-6.6)	-1.7 (-5.5)	-4.9 (-3.7)	-1.2 (-4.0)
PhNHC(OH)=C(CN)$CO_2CH_2CF_3$	-4.5 (-7.2)	-3.7 (-6.7)	-2.8 (-1.7)	-2.7 (-4.9)
PhNHC(OH)=C(CN)$CO_2CH(CF_3)_2$	-5.9 (-8.8)	-3.9 (-7.4)	-6.8 (-4.7)	-2.9 (-5.4)
PhNHC(OH)=$C(CN)_2$	3.5 (1.2)	3.7 (1.6)	-0.4 (-1.4)	2.7 (1.2)
i-PrNHC(OH)=CH_2	31.2 (30.0)	32.0 (31.4)	-2.7 (-4.6)	23.5 (23.0)
t-BuNHC(OH)=CH_2	27.7 (30.9)	27.3 (30.4)	2.1 (1.4)	20.0 (22.3)
PhNHC(OH)=CH_2	28.5 (31.2)	29.5 (31.6)	-3.3 (-3.8)	21.6 (23.2)
2,4-$(MeO)_2C_6H_3$NHC(OH)=CH_2	31.4 (30.1)	31.7 (30.7)	-1.1 (-2.0)	23.3 (22.5)
H_2NC(OH)=CH_2	30.8 (28.2)	31.8 (30.2)	-5.5 (-6.6)	23.3 (22.1)
H_2NC(OH)=CHSO_2Ph	16.5 (13.4)	16.8 (13.6)	2.0 (-2.0)	12.3 (10.0)
H_2NC(OH)=CHSO_2Me	15.3 (2.9)	15.9 (12.8)	-2.0 (-2.0)	11.7 (9.4)
H_2NC(OH)=C$HSO_2C_4F_9$	10.9 (9.0)	11.6 (9.6)	-2.4 (-2.0)	8.5 (7.0)
H_2NC(OH)=CHCO_2Me	1.5 (-1.6)	3.0 (-0.5)	-4.8 (-3.8)	2.2 (-0.3)
H_2NC(OH)=C$HCO_2CH_2CF_3$	-1.6 (-3.8)	-0.2 (-3.6)	-4.5 (-0.8)	-0.2 (-2.6)
H_2NC(OH)=CHCN	19.8 (17.5)	20.5 (18.3)	-2.1 (-2.6)	15.0 (13.4)

[a] Hydrogen-bonding with an oxygen atom of the SO_2Me group. [b] Hydrogen-bonding with an oxygen atom of the SO_2Ph group. [c] Untable structure, converged to the enol on the amide. [d] Unstable structure, converged to the enol on the acetyl oxygen. [e] Hydrogen bonding with an oxygen on the amide group.

The following conclusions, based on the B3LYP/6-31+G* (B3LYP/6-31G**) values arise from Table 2: (a) For *i*-PrNHCOCH(SO_2Ph)COMe Δ*G* for enolization on the acetyl group is 0.8 (-0.1) kcal/mol more negative than on the amide carbonyl. A value of 0.8 was calculated for the *N*-Ph analogue, but the B3LYP/6-31G** value is not available since the enol on acetyl is not a stable structure. For the more EW $SO_2C_4F_9$ derivative the corresponding differences are 0.7 (-0.2) and 0.7 (0.2) kcal/mol for the *N*-*i*-Pr and *N*-Ph derivatives, respectively. The pK_{Enol} values at B3LYP/6-31+G* are more negative for enolization on the acetyl site, as observed experimentally for **7**, although the differences are not large. This is noteworthy since when the competition between the two groups is not intramolecular the calculated Δ*G* difference for H_2C=CHCOX prefers enolization when X = Me over that when X = NH_2 by 22 kcal/mol.[20] The acyl activated enols are among the most stable enols, judged by the pK_{Enol} values. (b) As

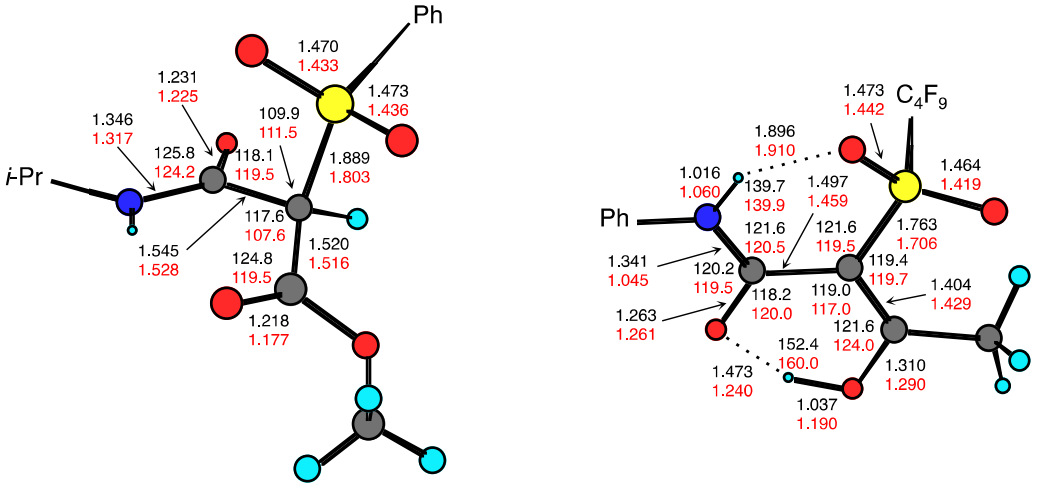
expected, the most stable enols are those substituted by two $SO_2C_4F_9$ groups, with a larger preference for the *N*-*i*-Pr derivative. The *N*-Ph, $(SO_2C_4F_9)_2$-derivative is 14.5 kcal/mol more favored than the $(PhSO_2)_2$ analogue. (c) The *N*-substituent effect on ΔG (in kcal/mol) is appreciable. For the CO_2Me, $PhSO_2$ combination the ΔG order followed is *t*-Bu 4.9 (0.8) > 2,4-$(MeO)_2C_6H_3$ 4.6 (-0.3) > *i*-Pr 1.8 (-2.0) > Ph -0.5 (-4.1). Although it may be fortuitous, the three of the four systems measured at 600 MHz are among the few which display observable enols and they are the bulkier substituents. For the SO_2Ph, SO_2Ph combination the effect is large and the order of ΔG values is 2,4-$(MeO)_2C_6H_3$ 8.9 (5.2) > Ph 6.1 (2.6) > *i*-Pr 5.0 (0.8), whereas the effect is smaller for SO_2Me, SO_2Ph [ΔG order is Ph 3.0 (-0.4) >*i*-Pr 2.2 (0.3)]. For systems with no EWG the ΔG order is *i*-Pr 32.0 (31.4) > 2,4-$(MeO)_2C_6H_3$ 31.7 (30.7) > Ph 29.8 (28.7) > *t*-Bu 27.3 (30.4). We conclude that there is no constant or observed systematic order of the effect of the *N*-substituents. (d) For *N*-Ph, Y = SO_2Ph the order of ΔG for Y′ is SO_2Ph 6.1 (2.6) > CN 5.1 (2.0) > SO_2Me 3.4 (-0.2) > COMe 2.6 (-2.9) > CO_2Me -0.5 (-4.1), and for *N*-*i*-Pr, Y = SO_2Me the order for Y′ = SO_2Ph 2.2 (-0.3) > CN 1.9 (-1.2). This order differs from the order of σ_R^- values of these groups.[21] (e) The values at B3LYP/6-31G** are consistently more negative than at B3LYP/6-31+G*. (f) For the *N*-*i*-Pr derivatives a SO_2Ph group gives a 0.8 pK_{Enol} units lower values than an SO_2Me group, both for two SO_2R groups or CN, SO_2R combinations. However, for the *N*-Ph group the trend for the two SO_2R groups is inverted by 0.8 units. Interestingly, when both SO_2Me and SO_2Ph are in the same compound the pK_{Enol} values for the both *N*-Ph and *N*-*i*-Pr derivatives are significantly lower by 2.0 and 1.3 kcal/mol than when for two identical SO_2R groups. The σ_R^- values quoted above suggest that order of electron withdrawal is $SO_2Ph \geq SO_2Me$.[8] (g) The order of EWGs according to σ_R^- values, *i.e.*, $MeSO_2 > CO_2Me > CN > PhSO_2$[20] is not reflected in the order of the calculated pK_{Enol} values, assuming additivity of substituent effects. By calculating the difference ΔpK_{Enol} value for two groups, based on the pK_{Enol} of pairs of Y,Y′-substituted systems, and making the extreme assumption of additivity of substituent effects, *i.e.*, either that the effect of identical group in the compared two pairs is cancelled if two systems are compared, or that the ΔpK_{Enol} values should be divided by two if the groups Y or Y′ appear twice in each pair different values were calculated from different pairs. The following ΔpK_{Enol} values for CO_2Me - SO_2Ph are obtained based on the following two pairs of Y,Y′ groups: -1.83 (2 CO_2Me – 2SO_2Ph), -1.33 (2 CO_2Me – CO_2Me, SO_2Ph), -0.44 (CO_2Me, CN – SO_2Ph, CN), -2.33 (CO_2Me, SO_2Ph – 2SO_2Ph), for the *N*-*i*-Pr derivative and -4.90 (CO_2Me, CN – SO_2Ph, CN) for the *N*-Ph derivative and -3.1 (CO_2Me, SO_2Ph – 2SO_2Ph) for the *N*-2,4-$(MeO)_2C_6H_3$ derivative. The CO_2Me – SO_2Me values are -2.33 (2CO_2Me – 2SO_2Me), -3.37 (CO_2Me, CN – SO_2Me, CN), for the *N*-*i*-Pr compounds and -5.09 (CN, CO_2Me – CN, SO_2Me) for the *N*-Ph compound. The CN – SO_2Ph values are -0.58 (2CN – 2SO_2Ph) and -1.68 for (CN, CO_2Me – SO_2Ph, CO_2Me), for the *N*-Ph derivative, and CN – SO_2Me value of -0.98 (2CN – 2$MeSO_2$) for the *N*-*i*-Pr derivative. For CO_2Me – CN, the pair 2CO_2Me – 2CN gives -1.25 for the *N*-*i*-Pr derivative. The crude ability of the groups to promote enolization obtained from these values is therefore CO_2Me > CN > SO_2Ph > ? SO_2Me. (h) Finally, the difference between the calculated gas phase K_{Enol} values and the observed values in CCl_4 is not large: For **5b**/**6b** and

5c/**6c** the experimental Δ*G* values are 1.9 and 2.0 kcal/mol, compared with the respective calculated values in Table 2 of 1.8 and 4.6, respectively.

In order to look computationally at simpler systems with fewer interactions, the enolizations of Y-substituted N-unsubstituted acetamides H_2NCOCH_2Y, Y = SO_2R (R = Ph, Me, C_4F_9), CO_2R' (R' = CH_3, CH_2CF_3) and CN were computed. The results (Table 2, bottom) indicate that the Δ*G* and pK_{Enol} values are, as expected, significantly higher than for the Y,Y′ -disubstituted systems. The important result is that the values for sulfonyl and CN groups are much higher than for the ester groups, although among the SO_2R groups the pK_{Enol} is lower for the much more EW C_4F_9 than for Ph and Me. The differences are mainly due to the Δ*H* term, although the Δ*S* term for the esters is a few e.u. more negative than for the SO_2R. Consequently, even in the absence of mutual interactions between Y and Y′ and between Y and the N-substituent, the main experimental conclusion that an SO_2R group is a less enolization promoter than a CO_2R group remains valid. Since the enols are planar, and the pK_{Enol} values do not follow the σ_R^- values we conclude that the effect is connected with the amide, which is apparently more stabilized for the SO_2R-substituted amides than for the CO_2R-substituted amides. We believe that this (explanation c) holds also for the Y,Y′ disubstituted systems.

Calculated geometries of the enols

The calculated geometries of few of the enols are given in Figures 2 and 3. In Figure 2 few calculated and observed bond lengths and angles are compared for the amide **5c** and the enol on the acetyl group **7o** for which X-ray data are available. The crystallographic parameters are mostly similar, especially for the amide **5c**, except for the hydrogen bond parameters of **7o**, where we interpret the observed structure as resulting from a dynamic equilibrium between enols **6o** and **7o**, whereas the calculated structure represents the static most stable structure.



(**a**) **5c** (*i*-PrNHCOCH(CO_2Me)SO_2Ph) (**b**) **7o** (PhNHCOC($SO_2C_4F_9$)=C(OH)Me)

Figure 2. Calculated (black) and observed (red) bond lengths and angles for (**a**) **5c** (left) and (**b**) **7o** (right).

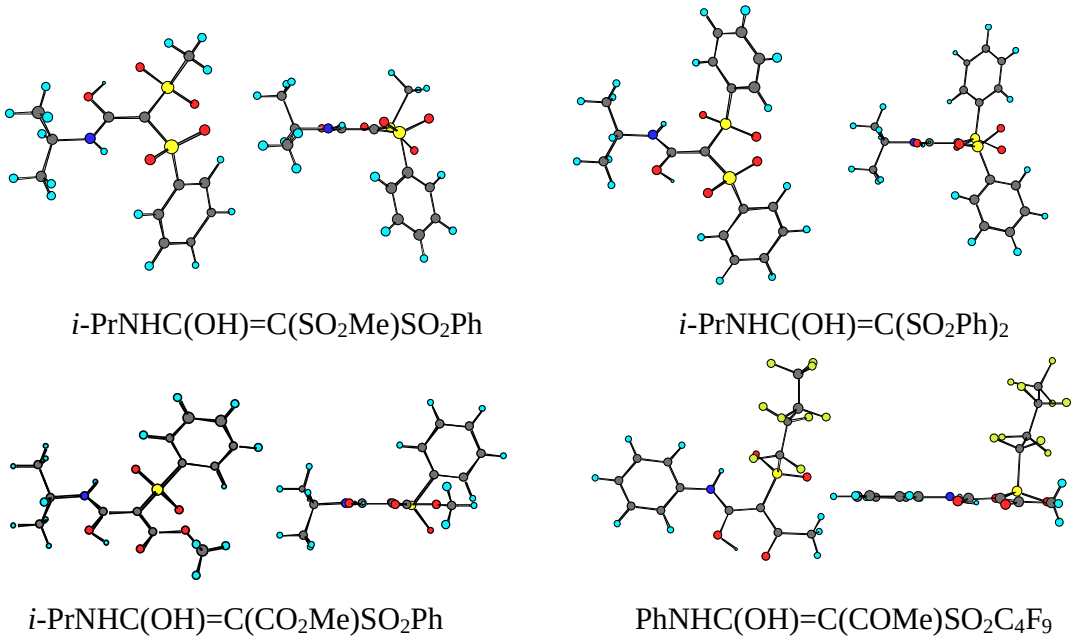


Figure 3. Calculated structure of several enols with different Y and Y′ groups. Planarity is shown by the side view on the right hand side of the structures.

In Figure 3 the calculated structures of few enols on the amide carbonyl are shown. Additional structures are given in the Supporting Information. The important conclusion is that the NHR, OH, Y, Y′ and C=C bond of the enolic moiety are all in the same plane, as demonstrated by a side view of each of the enols. This excludes suggestion (b) above that the low % of enolization is due to twisting of the β-Y,Y′ substituents from planarity. Consequently, although the full negative charge delocalizing ability of these substituents is operating to stabilize the enols, this is insufficient to observe a significant percentage of the enols.

Suggestion (c) is therefore the remaining explanation. To investigate it we need to dissect the total effect of the substituents on K_{Enol} to the separate effects on the amide and the enol. This was performed by using the bond separation isodesmic equations, in which the effect of substituents on the total amide/enol equilibria is dissected to the effect of the substituent on the stabilization of the amide (Eq. 5) and the enol (Eq. 6) in comparison with the parent system. In these hypothetical isodesmic equations the Y,Y′ groups are no longer conjugated with the substituents on Cα(NHR)OH. Eq. 7 (the difference of eqs. 5 and 6) gives the ΔG for the difference between ΔG for the Y,Y′ substituted system and the parent N-substituted acetamide and its enol. Table 3 display the results of equations 5 and 6 using ethylene as the "deconjugating" reagent, at both B3LYP/6-31+G* and B3LYP/6-31G**. Similar calculations when CH_4 is used instead of $H_2C=CH_2$ are given in the Supporting Information, while the energies of the parent reactions required for comparisons are given in Table 4.

$$Y'YCHCONHR' + H_2C{=}CH_2 \rightleftharpoons CH_3CONHR' + Y'YC{=}CH_2 \qquad \Delta G_A \quad (5)$$

$$Y'YC{=}C(OH)NHR' + H_2C{=}CH_2 \rightleftharpoons H_2C{=}C(OH)NHR' + Y'YC{=}CH_2 \quad \Delta G_E \quad (6)$$

$$\Delta G = \Delta G_A - \Delta G_E = \Delta G_{Y'Y}\,[Y'YCHCONHR' \rightleftharpoons Y'YC{=}C(OH)NHR'] - \Delta G_{HH}[CH_3CONHR' \rightleftharpoons H_2C{=}C(OH)NHR'] \quad (7)$$

Table 3. Δ*E*, Δ*H* and Δ*G* (kcal/mol) for Equations 5 and 6; A: at B3LYP/6-31+G*; B: at B3LYP/6-31G** level

Y, Y′	R	Eqn.	Δ*E*		Δ*H*		ΔG	
			A	B	A	B	A	B
SO_2Ph, SO_2Ph	*i*-Pr	5	-9.3	-8.5	-9.0	-8.2	-10.5	-10.0
		6	19.3	19.1	18.8	19.1	16.6	18.1
SO_2Me, SO_2Me	*i*-Pr	5	-6.9	-5.5	-6.6	-5.3	-8.0	-7.3
		6	20.8	23.9	20.3	23.7	18.0	21.8
$SO_2C_4F_9$, $SO_2C_4F_9$	*i*-Pr	5	-15.1	-12.0	-14.4	-11.6	-17.2	-14.3
		6	26.2	27.5	25.5	27.2	23.7	26.1
SO_2Ph, SO_2Me	*i*-Pr	5	-11.3	-9.9	-11.0	-9.6	-12.8	-10.9
		6	19.9	23.0	19.4	22.8	17.1	20.8
SO_2Ph, CO_2Me	*i*-Pr	5	-6.3	-5.0	-6.3	-5.2	-8.4	-8.1
		6	24.6	27.7	24.2	27.7	21.8	25.4
SO_2Ph, COMe	*i*-Pr	5	-5.6	-4.3	-5.5	-4.4	-7.8	-7.0
		6	27.8	31.5	28.0	32.6	25.6	30.2
$SO_2C_4F_9$, COMe	*i*-Pr	5	-7.5	-5.5	-7.4	-5.5	-9.7	-8.1
		6	31.6	34.7	31.6	35.4	27.8	32.3
SO_2Me, CN	*i*-Pr	5	-8.8	-7.8	-8.7	-7.7	-10.6	-10.2
		6	21.5	23.7	21.0	23.5	19.5	22.4
SO_2Ph, CN	*i*-Pr	5	-10.2	-9.3	-10.0	-9.3	-11.8	-11.8
		6	20.5	22.7	20.1	22.5	18.7	21.2
SO_2Ph, SO_2Ph	Ph	5	-10.2	-9.6	-9.8	-9.3	-11.2	-11.9
		6	17.3	19.8	16.9	19.6	14.4	17.6
SO_2Me, SO_2Me	Ph	5	-8.1	-7.1	-7.7	-6.7	-9.6	-9.4
		6	18.4	20.9	17.9	20.6	15.1	18.3
$SO_2C_4F_9$, $SO_2C_4F_9$	Ph	5	-19.1	-17.2	-18.4	-16.6	-20.6	-19.3
		6	22.6	23.4	21.9	23.0	19.9	21.2
SO_2Ph, SO_2Me	Ph	5	-11.3	-10.6	-11.0	-10.2	-13.1	-13.2
		6	17.8	20.4	17.3	20.1	14.7	17.5
SO_2Ph, CO_2Me	Ph	5	-10.1	-9.4	-9.8	-9.2	-11.7	-12.0
		6	22.7	25.2	22.3	25.2	19.5	22.5
SO_2Ph, COMe	Ph	5	-3.1	-2.8	-2.8	-2.7	-5.0	-5.5
		6	26.0	30.9	26.5	30.7	23.2	27.8

Table 3 (continued)

Y, Y′	R	Eqn.	Δ*E*		Δ*H*		ΔG	
			A	B	A	B	A	B
$SO_2C_4F_9$, COMe	Ph	5	-9.0	-7.3	-8.6	-7.1	-11.4	-10.9
		6	28.8	32.7	29.1	32.6	25.4	29.3
CO_2Me, CN	Ph	5	-12.5	-9.2	-12.4	-9.1	-14.7	-11.7
		6	23.2	21.7	22.8	21.5	21.3	20.1
SO_2Ph, CN	Ph	5	-13.4	-10.1	-13.3	-10.0	-14.9	-13.0
		6	23.0	21.3	22.6	21.0	20.9	19.4
SO_2Ph, CO_2Me	Ar[a]	5	-5.5	-4.7	-8.4	-4.0	-11.3	-6.9
		6	26.7	24.8	26.2	24.5	25.1	23.5
SO_2Ph, SO_2Ph	Ar[a]	5	-6.2	-6.2	-5.8	-5.8	-7.2	-7.2
		6	18.2	21.2	17.7	21.0	15.7	18.3
CO_2Me, CO_2Me	*i*-Pr	5	-5.9	-5.2	-5.9	-5.3	-7.0	-6.3
		6	28.2	32.0	28.0	32.3	25.1	29.5
COMe, CO_2Me	*i*-Pr	5	-9.1	-8.3	-9.6	-9.0	-10.5	-10.0
		6	32.4	35.8	31.6	35.6	30.0	34.4
COMe, COMe	*i*-Pr	5	-6.9	-5.6	-7.3	-6.1	-8.3	-7.3
		6	30.7	33.9	29.9	34.1	28.0	33.4
CN, CO_2Me	*i*-Pr	5	-8.9	-8.3	-8.8	-8.3	-10.0	-9.9
		6	27.2	29.7	26.9	29.7	24.6	27.8
CN, COMe	*i*-Pr	5	-9.5	-8.4	-9.3	-8.3	-11.1	-10.7
		6	31.7	37.2	31.7	37.0	29.9	35.2
CO_2Me, CO_2Me	Ph	5	-5.4	-4.9	-6.0	-5.5	-6.2	-5.5
		6	26.7	30.1	26.5	30.4	23.5	27.4
COMe, CO_2Me	Ph	5	-14.0	-14.9	-14.5	-15.7	-12.8	-13.9
		6	30.1	34.7	30.1	34.1	27.7	31.9
COMe, COMe	Ph	5	-4.6	-4.2	-5.5	-5.1	-4.8	-4.2
		6	30.1	32.7	29.0	32.3	26.0	30.4
CN, CO_2Me	Ph	5	-9.2	-8.9	-9.8	-9.5	-9.8	-9.8
		6	24.9	27.0	24.4	26.9	21.7	24.4
CN, COMe	Ph	5	-11.9	-11.6	-12.1	-12.0	-12.5	-12.9
		6	29.4	35.5	29.4	34.9	27.3	32.3

[a] Ar = 2,4-$(MeO)_2C_6H_3$.

Table 4. Energy Difference (kcal/mol) between Enol and Amide Calculated at B3LYP/6-31+G* (B3LYP/6-31G**) levels

Enol	ΔE	ΔH	ΔG	pK_{enol}
i-PrNHC(OH)=CH_2	31.7(30.2)	31.2(30.0)	32.0(31.4)	-23.47(-23.02)
t-BuNH(C(OH)=CH_2	27.2(30.3)	27.7(30.9)	27.3(30.4)	-19.99(-22.32)
PhNHC(OH)=CH_2	31.0(29.6)	31.0(29.8)	29.8(28.7)	-21.88(-21.04)
ArNHC(OH)=CH_2[a]	32.2(30.6)	31.4(30.1)	31.7(30.7)	-23.27(-22.53)

[a] Ar = 2,4-$(MeO)_2C_6H_3$.

The following conclusions arise from Table 3: (a) All the ΔG (and ΔH) values for the reaction of the amides (Eq. 5) are negative, indicating that the overall interaction between the α- and β-substituents is destabilizing and they prefer to be in different molecules. (b) In contrast, all the reactions of the enols (Eq. 6) give positive ΔG and ΔH values, whose values are much larger than those of Eq. 5). (c) The values based on the B3LYP/6-31+G* basis set are less positive than those based calculated at B3LYP/6-31G**. (d) The differences are substituent dependent; for Eq. 5, the order of destabilization for *N*-*i*-Pr is CO_2Me, CO_2Me ,SO_2Me, COMe, COMe,COMe < CO_2Me, SO_2Ph ,$SO_2C_4F_9$,COMe, CO_2Me,CN < CO_2Me, COMe < SO_2Me,CN < CO_2Me,CN < SO_2Me, SO_2Ph < SO_2Ph,CN < SO_2Ph,SO_2Ph. With Y′ = COMe, Y= $SO_2C_4F_9$ gives a more negative values than SO_2Ph. For *N*-Ph the order is: COMe,COMe < CO_2Me,CO_2Me < CO_2Me,CN < $SO_2C_4F_9$,COMe < SO_2Ph, CO_2Me < SO_2Ph,SO_2Ph < SO_2Ph,CO_2Me < COMe,CN < CO_2Me,COMe. (e) The ΔG values for enols (Eq. 6) are consistently higher for CO_2Me-activated systems than by sulfonyl systems. The order of ΔG values when R' = *i*-Pr is: CO_2Me, COMe > CN, COMe > COMe, COMe > CO_2Me, CO_2Me > CO_2Me, CN > SO_2Me, COMe > CO_2Me, SO_2Ph > SO_2Me, CN > SO_2Ph, CN > SO_2Me, SO_2Ph > SO_2Ph, SO_2Ph >$SO_2C_4F_9$, COMe. For the *N*-Ph derivatives the order is: CO_2Me, COMe > COMe, CN > COMe,COMe >$SO_2C_4F_9$, COMe > CO_2Me, CO_2Me > CO_2Me, SO_2Ph > CO_2Me, CN > SO_2Ph, SO_2Ph.

Experimental Section

General. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded as described previously.[22] Precursors for synthesis, solvents and deuterated solvents for NMR measurements were purchased from a commercial supplier and used without further purification.

Calculations. The geometries were fully optimized a the B3LYP/6-31+G* and B3LYP/613G** levels of theory, with normal convergence using the Gaussian 03 program,[23] Vibrational normal mode analyses were performed at the same level to ensure that each optimized structure was a true minimum on the potential energy surface, no imaginary frequency, and to calculate the thermal correction needed to obtain the Gibbs free energies. *H*, *G* and *S* values obtained at

298.25 K are given in the Supplementary information along with Cartesian coordinates of the optimized structures at respective levels of theory.

Chemicals. **5a-j**/**6a-j** were prepared by the reaction of the active methylene compounds with sodium followed by reaction with the organic isocyanate. The procedure of the preparation of **5c**/**6c** is representative of that for all derivatives.

Sodium pieces (0.12 g, 5 mmol) were added to a solution of methyl phenylsulfonylacetate (1.07 g, 5 mmol) in dry THF (20 mL) and the mixture was stirred overnight. The colorless precipitate was dissolved on addition of isopropyl isocyanate (0.5 mL, 5 mmol) and the mixture was heated at reflux for 2 h. The solvent was evaporated giving the yellow solid sodium salt, which was dissolved in DMF (5 mL) and the solution was poured into ice-cooled 2N HCl solution (50 mL). The colorless precipitate formed was filtered, washed with cold water (100 mL) and dried in air to give 1.13 g (3.78 mmol, 76%) of the product. Suitable crystals of **5c**, mp 182-3 ^{o}C for X-ray diffraction were obtained by dissolving the crude solid in ethyl acetate and slow evaporation at rt. Anal. Calcd for $C_{13}H_{17}NO_5S$: C, 52.12; H, 5.69; N, 4.68. Found: C, 52.36; H, 5.87; N, 4.66%. ^{1}H NMR ($CDCl_3$, 298 K) display signals for 98:2 amide **5c** / enol **6c** mixture. (**5c**) δ: 1.16 (d, *J* 6.2 Hz), 3.79 (s), 3.99 (octet, *J* 6.6 Hz), 4.84 (s), 6.99 (d, *J* 6.2 Hz), 7.59 (t, *J* 7.4 Hz), 7.72 (t, *J* 8.1 Hz), 7.92 (d, *J* 9.1 Hz). (**6c**) δ: 8.05 (s), 15.60 (s), all other signals overlap the **5c** signals. ^{13}C NMR ($CDCl_3$, 298 K) δ(**5c**): 22.1 (q, *J* 126.8 Hz), 22.1 (q, overlaps), 42.6 (d, *J* 141.0 Hz), 53.8 (q, *J* 148.7 Hz), 75.5 (d, *J* 144.4 Hz), 129.2 (d, *J* 164.5 Hz), 129.3 (d, *J* 165.5 Hz), 134.9 (dt, J_d 163.0 Hz, J_t 6.8 Hz), 136.9 (t, *J* 9.2 Hz), 157.4 (m), 163.4 (m).

5k-n /**6k-n** and **5o**/**6o**/**7o** were prepared by the reaction of the active methylene compounds with the organic isocyanate in the presence of dry Et_3N in DMF.

5o/**6o**/**7o**. To a stirred mixture of 1-[(nonafluorobutyl)sulfonyl]-2-propanone (0.85 g, 2.5 mmol) and dry Et_3N (0.75 mL, 5.4 mmol) in dry DMF (5 mL) was added phenyl isocyanate (0.27 mL, 2.5 mmol) and the mixture was stirred for 1 h. The orange solution was added dropwise to a cold solution of 2N HCl (50 mL) and the colorless precipitate formed was filtered, washed with cold water (50 mL) and dried in air to give the pure enol on acetyl **7o** (1.05 g, 92%), mp 177-8 ^{o}C, which was crystallized from EtOAc/petroleum ether to give colorless crystals suitable for X-ray diffraction. Anal. Calcd for $C_{14}H_{10}F_9NO_4S$: C, 36.60; H, 2.18; N, 3.05. Found: C, 36.77; H, 2.37; N, 2.83%. ^{1}H NMR ($CDCl_3$, 298 K) δ: 2.63 (3H, s), 7.25 (1H, m), 7.36-7.45 (4H, m), 9.80 (1H, s), 19.08 (1H, s). ^{13}C NMR ($CDCl_3$, 298 K) δ: 25.6 (q, *J* 129.3 Hz), 95.0 (s), 107.2, 110.8 (t), 115.2 (t), 119.1 (t), 122.4 (d, *J* 161.2 Hz), 126.5 (d, *J* 162.8 Hz), 129.3 (d, *J* 161.8 Hz), 135.1 (t, *J* 9.8 Hz), 168.0 (s), 198.3 (s).

5k/**6k**. To a mixture of (phenylsulfonyl)acetonitrile (0.91 g, 5 mmol) and dry Et_3N (1.5 mL, 10.8 mmol) in dry DMF (5 mL) was added phenyl isocyanate (0.56 mL, 5 mmol) at rt and the mixture was stirred for 1 h. The dark brown solution formed was added slowly to a cold solution of 2N HCl (50 mL), giving a brown solid (1.39 g, 93%), which on crystallization gave colorless cotton-like fibres of **5k**, mp 220-1 ^{o}C ($CHCl_3$). Anal. Calcd for $C_{15}H_{12}N_2O_3S$: C, 59.99; H, 4.03; N, 9.33. Found: C, 59.70; H, 3.45; N, 9.16%. ^{1}H NMR ($CDCl_3$, 298 K) δ: 5.03 (1H, s), 7.22 (1H, t, *J* 7.6

Hz), 7.38 (2H, t, *J* 8.4 Hz), 7.50 (2H, d, *J* 7.6 Hz), 7.65 (2H, t, *J* 8.0 Hz), 7.81 (1H, t, *J* 7.6 Hz), 8.02 (2H, d, *J* 7.6 Hz), 8.29 (1H, s).

A similar procedure, starting from (methylsulfonyl)acetonitrile (1.19 g, 10 mmol), Et_3N (3 mL, 21.5 mmol) and phenyl isocyanate (1.08 mL, 10 mmol) gave **5m**/**6m** (2.07 g, 87%). Crystallization gave colorless cotton-like fibres, mp 214-5 ^oC (acetone). Anal. Calcd for $C_{10}H_{10}N_2O_3S$: C, 50.42; H, 4.20; N, 11.76; S, 13.45. Found: C, 50.11; H, 4.06; N, 11.49; S, 13.11%. ^1H NMR (DMSO-d_6, 298 K) δ: 3.40 (3H, s), 5.88 (1H, s), 7.28 (2H, t, *J* 8.4 Hz), 7.39 (2H, d, *J* 8.0 Hz), 7.59 (2H, d, *J* 7.6 Hz), 10.87 (1H, s).

A similar procedure was used for the preparation of compounds **5l/6l** and **5n/6n**. Their NMR and analytical data are given in Tables S1, S2 and S11 of Supporting Information.

Acknowledgements

We thank Karina Volkov for preliminary experiments, Dr. Shmuel Cohen for the X-ray data and the Israel Science Foundation for support.

Supporting Information Available

Experimental and computational details. This material is available free of charge on the Web at: http://www.arkat-usa.org/get-file/52569/. The full crystallographic data for compounds **5c** and **7o** are given as a CIF.

References and Notes

1. Mukhopadhyaya, J. K.; Sklenak, S.; Rappoport, Z. *J. Am. Chem. Soc.* **2000**, *122*, 1325. http://dx.doi.org/10.1021/ja992059f
2. Mukhopadhyaya, J. K.; Sklenak, S.; Rappoport, Z. *J. Org. Chem.* **2000**, *65*, 6856. http://dx.doi.org/10.1021/jo000293e
3. Lei, Y. X.; Cerioni, G.; Rappoport, Z. *J. Org. Chem.* **2000**, *65*, 4028. http://dx.doi.org/10.1021/jo000046a
4. Rappoport, Z.; Lei, Y. X. Yamataka,H. *Helv. Chim. Acta* **2001,** *84*, 1405. http://dx.doi.org/10.1002/1522-2675(20010613)84:6<1405::AID-HLCA1405>3.0.CO;2-G
5. Song, J.; Lei , Y. X.; Rappoport, Z. *J. Org. Chem.* **2007**, *72*, 9152. http://dx.doi.org/10.1021/jo071206m
6. Lei, Y. X.; Cerioni, G.; Rappoport, Z. *J. Org. Chem.* **2001**, *66*, 8379. http://dx.doi.org/10.1021/jo010487+
7. Lei, Y. X.; Casarini, D.; Cerioni, G.; Rappoport, Z. *J. Phys. Org. Chem.* **2003,** *16*, 525.

http://dx.doi.org/10.1002/poc.629
8. Lei, Y. X.; Casarini, D.; Cerioni, G.; Rappoport, Z. *J. Org. Chem.* **2003**, *68*, 947. http://dx.doi.org/10.1021/jo020464a
9. Basheer, A.; Rappoport, Z. *J. Org. Chem.* **2004**, *69*, 1151. http://dx.doi.org/10.1021/jo030266z
10. Mishima, M.; Matsuoka, M.; Lei, Y. X.; Rappoport, Z. *J. Org. Chem*. **2004**, *69*, 5947. http://dx.doi.org/10.1021/jo040196b
11. Song, J.; Yamataka , H.; Rappoport, Z. *J. Org. Chem.* **2007**, **7***2*, 7605. http://dx.doi.org/10.1021/jo0710679
12. Basheer, A.; Yamataka, H.; Ammal, S. C.; Rappoport, Z. *J. Org. Chem*. **2007**, *72*, 5297. http://dx.doi.org/10.1021/jo070877h
13. Basheer, A.; Rappoport, Z. *Org. Biomol. Chem*. **2008**, *6*, 1071. http://dx.doi.org/10.1039/b717556f
14. Basheer, A.; Mishima M.; Rappoport, Z. *J. Phys. Org. Chem.* **2010,** *23*, 255. http://dx.d io.org/10.1002/poc.111611
15. The term "formal" is used to emphasize that the amides appear frequently in mixtures with their enols tautomers.
16. Barnikow, G.; Krueger, K.; Hilgetag, G. *J. Prakt. Chem. (Leipzig)* **1967**, *35*, 302. http://dx.doi.org/10.1002/prac.19670350510
17. Dubenko, R. G.; Neplyuev, V. M.; Pel'kis, P. S. *Zhur. Organ. Khim*. **1968**, *4*, 453; *Chem. Abstr*., **1968**, *68*,104664.
18. Song, J.; Mishima, M ; Rappoport, Z. *Org. Lett.* **2007**, *9*, 4307. http://dx.doi.org/10.1021/ol7018554
19. Values taken from Charton, M. in *The Chemistry of Cyclobutanes*, Eds. Rappoport, Z.; Liebman, J. F., Wiley, Chichester, 2005, chap. 10, pp. 441-495. http://dx.doi.org/10.1002/0470864028
20. Sklenak, S.; Apeloig, Y.; Rappoport, Z. *J. Am. Chem. Soc.* **1998**, *120*, 10364. http://dx.doi.org/10.1021/ja980354e
21. Values taken from Shorter, J., in *The Chemistry of Sulphones and Sulphoxides*, Eds. Patai, S.; Rappoport, Z.; Stirling, C. J. M., Wiley, Chichester, 1988, chap. 10, pp. 483-540. (The σ_R^- values are 0.26 (CN), 0.337 (NO_2), 0.35 ($MeSO_2$); For the $MeSO_2$ group σ_p values are 0.68-0.73, and σ_p- are 0.822-1.16, for $PhSO_2$ σ_p 0.70-0.71 and σ_p- 0.90-0.95, for $F_2CHCF_2SO_2$ σ_p = 1.01; σ_R- for $MeSO_2$ based on ionization of anilines and phenols are 0.38 and 0.29, respectively, and 0.57 and 0.41 for CF_3SO_2).
22. Frey, J.; Rappoport, Z. *J. Am. Chem. Soc.* **1996**, *118*, 5182. http://dx.doi.org/10.1021/ja960456+
23. Gaussian 03, Revision D.01: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.;

Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.;. Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, H. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M.C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; C. Gonzalez, C.; Pople, J. A. Gaussian, Inc., Wallingford CT, 2004.

