JOC The Journal of Organic Chemistry

Article

Absolute pKas of Sulfonamides in Ionic Liquids: Comparisons to Molecular Solvents

Zedong Wang, Xin Li, Pengju Ji, and Jin-Pei Cheng

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b02182 • Publication Date (Web): 07 Oct 2016

Just Accepted

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Absolute pK_as of Sulfonamides in Ionic Liquids: Comparisons to Molecular Solvents

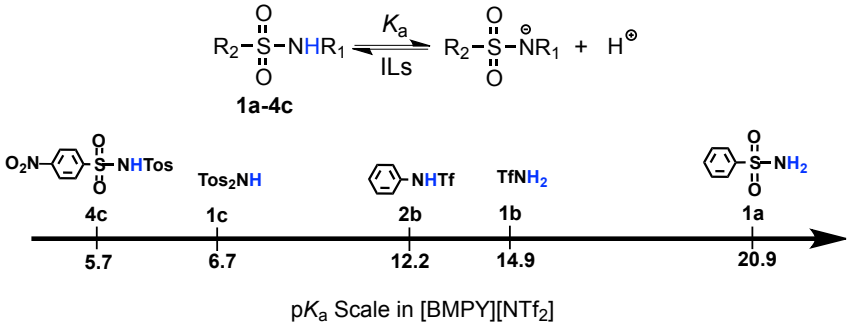
Zedong Wang,[†] Xin Li,[†] Pengju Ji,*[,‡] and Jin-Pei Cheng*[,†,‡]

[†]State Key Laboratory of Elemento-organic Chemistry, Collaborative Innovation Centre of Chemical Science and Engineering, Nankai University, Tianjin, 300071, China.

[‡]Center of Basic Molecular Science (CBMS), Department of Chemistry, Tsinghua University, Beijing, 100084, China.

jipengju@mail.tsinghua.edu.cn (P. Ji); jinpei_cheng@mail.tsinghua.edu.cn (J.-P. Cheng)

TOC



ABSTRACT

Absolute pK_as of 25 sulfonamides in four ionic liquids (ILs) were measured spectroscopically with high precision and subsequently compared with these in conventional molecular solvents. It is found that the acidity order of these sulfonamides follows: in water > in DMSO > in ILs > in acetonitrile (ACN). The well-known solvent polarity index ε fails to explain the observed stronger bond-weakening effect of ILs than that of ACN whose ε is much greater. In addition, the regression analyses show that the pK_as of sulfonamides determined in ILs linearly correlate with these in molecular solvents of distinct properties, but with various slopes. A rationale and related discussion on the effect of solvation in ILs are presented.

INTRODUCTION

Solvents are ubiquitous, and in most circumstances, are indispensable in chemistry. In a sense, the selection of solvent based on the knowledge of solvation reflects a rational development of chemistry, which, in return, can significantly improve the image of organic reactions regarding the environment

issue.[1] In recent years, as it became more and more crucial, many volatile organic solvents are listed as "unclean", and various room temperature ionic liquids (RTILs) come into play as their alternatives, in spite of a severe shortage of the knowledge on their solvation behavior.

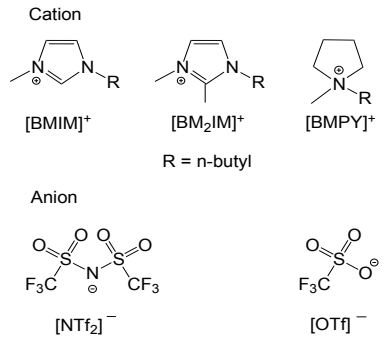
Ionic liquids are composed entirely of ions and exhibit unique properties that are significantly different from these of conventional molecular solvents.[2] As a rising mainstream medium category, ILs are labelled as green solvent[3] which have aroused enormous research interests in recent decade and have also been extensively used in industry.[4] Compared to the tremendous attentions paid on the development of their synthetic applications, fundamental aspects on the solvation phenomena of ILs are very scarce, however. As it is well known that solvents have strong impacts on the acidity of substrate by virtue of their differential strengths of solvation towards various species in solution, we believe that to study the pK_as in different media would provide quantitative understandings in this regard.

Some acidity scales in various molecular solvents have been established in past,[5] which allowed a good understanding of solvation behavior for conventional media. By contrast, acidity studies in neat ILs are far less, and the early works reported *relative* pK_as in most cases[6] that are not suitable for the solvation study. Although more recent works showed that the *absolute* acidity in ILs could be obtained electrochemically,[7] the narrow substrate scope and large uncertainty associated with irreversible electrode data make its use in solvation study problematic. However, we have recently found that the overlapping indicator method, which has been dominantly used in molecular media for most of the authentic pK_as data known today[8], can be well adopted to measure the acidities in ILs with high precision[9] and hence should be able to fulfil the current research need.

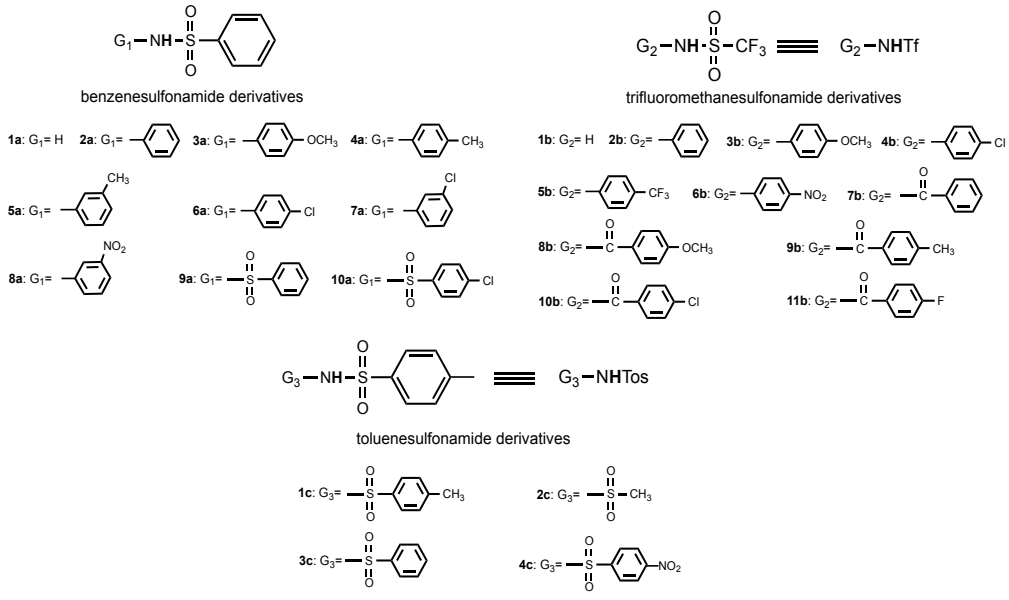
Sulfonamides are important compounds in pharmaceutical and agricultural chemicals industry. A large number of drugs, such as antimicrobials and diuretics, and several novel herbicides, bear this sulfonamide moiety. This is mainly due to their unique structure that resembles the tetrahedral intermediate involved in many acyl substitutions and stabilized by proteases and esterases.[10] Sulfonamide is known to be more acidic than carboxamides. The knowledge on sulfonamide acidities is important to pharmaceutical industry because it delivers valuable information on the mechanisms of drug actions and metabolisms. The acidities of sulfonamides have been investigated extensively in the conventional molecular solvents.[11] However, till present almost no attention has been paid on the

acidities of N–H bonds in IL. On the other hand, recent seminal study shows that developing IL drugs and use of ILs as a drug delivery medium may bring a revolution to pharmaceutical industry.[12] This, from another angle, points out the need of the information on sulfonamides acidities in ILs, especially on their relations to the solvation strength of different types of media in a more quantitative manner.

Towards this end, here we have measured 68 absolute acidity values of 25 sulfonamides in 4 ILs (Scheme 1) with high precision with the standard deviation (SD) of $\leqslant \pm 0.05$ pK units. A variety of structurally different sulfonamides (Scheme 2), such as benzenesulfonamides (**1a**-**8a**), trifluoromethylsulfonamides (**1b**-**6b**) and several more acidic sulfonamides (**9a**-**10a**, **7b**-**11b** and **1c**-**4c**), were included in this work. The measured pK_a data (Tables 1) are compared with the known acidities in molecular solvents by regression analysis, which revealed insightful and interesting information regarding the change on the solvation strength by ILs and molecular media.



Scheme 1. Cations and anions of the ILs used in this study, the ILs are: [BMIM][OTf], [BMIM][NTf_2], [BMPY][NTf_2] and [BM_2IM][NTf_2]



Scheme 2. The structures of sulfonamide derivatives (**1a**-**4c**) involved in this work

RESULTS AND DISCUSSION

Table 1 shows that the acidity scale of these N−H acids spreads over 15 pK units, which covers by far the largest energetic span and substrates collection for one R−H acid family in ILs, and provides with rich information of the effect of structural change on the N−H acidity in ILs. For examples, an additional sulfonyl group causes a dramatic increase of the acidity of **1a** (20.9) by as large as 14 orders of magnitude compared to that of **9a** (6.3), while a carbonyl group makes the acidity of **7b** (6.7) 1.6×10^8 times stronger than **1b**, due to their strong inductive as well as resonance stabilization effect on the sulfonamide nitrogen anion. This is supported by the fact that the carbon acid, $PhSO_2CH_2SO_2Ph$ (pK_a = 19.2 in [BMPY][NTf_2][9a]) is much less acidic than its analogue **9a** in ILs, apart from the fact that the electronegativity of N is greater than C atom, the large acidity difference ($\Delta pK_a \approx 13$) may also be as a consequence of a significant p-d π-resonance between the anion center and sulfonyl group of sulfonamides.[14]

Table 1. pK_a Values of sulfonamides (Scheme 2) in ILs and molecular solvents

Sulfonamides[a]	pK_a[b] [Bmpy][NTf_2]	pK_a[b] [Bmim][NTf_2]	pK_a[b] [Bm_2im][NTf_2]	pK_a[b] [Bmim][OTf]	pK_a water	pK_a DMSO	pK_a ACN
$PhSO_2NH_2$ (**1a**)	20.9	20.2_5	21.9	18.1	9.4[c]	15.2[d]	24.6[d]
p-MeO-PhN**H**SO_2Ph (**3a**)	18.7	18.2	19.3	16.1	8.9[e]	14.2[e]	22.9[e]
p-Me-PhN**H**SO_2Ph (**4a**)	18.4	17.7_5	19.1	15.7	8.6[e]	13.9[e]	22.6[e]
m-Me-PhN**H**SO_2Ph (**5a**)	18.2	17.6	18.9	15.5	8.5[e]	13.7[e]	22.7[e]
PhN**H**SO_2Ph (**2a**)	18.0	17.4	18.7	15.4	8.2[e]	13.5[e]	22.6[e]
p-Cl-PhN**H**SO_2Ph (**6a**)	17.1_5	16.7	17.7_5	14.6	7.9[e]	12.7[e]	21.6[e]
m-Cl-PhN**H**SO_2Ph (**7a**)	16.7	16.3	17.4	14.3	7.7[f]	11.7[e]	
m-NO_2-PhN**H**SO_2Ph (**8a**)	15.7	15.3	16.2	13.3		11.2[e]	20.4[e]
TfN**H**$_2$ (**1b**)	14.9	14.4_5	15.5	12.8	6.3[g]	9.7[h]	
PhN**H**Tf (**2b**)	12.2	11.8	12.7	9.9_5	4.5[g]		
p-MeO-PhN**H**Tf (**3b**)	12.9	12.4	13.3_5	10.6	4.9[g]		
p-Cl-PhN**H**Tf (**4b**)	11.4	11.0	11.8	9.2	3.9[g]		
p-CF_3-PhN**H**Tf (**5b**)	10.6	10.2_5	11.0	8.5			
p-NO_2-PhN**H**Tf (**6b**)	9.4_5	9.0_5	9.8	7.6			
p-MeO-PhCON**H**Tf (**8b**)	7.2	6.7					11.6[i]
TosN**H**SO_2Me (**2c**)	7.2	6.6					
p-Me-PhCON**H**Tf (**9b**)	7.0	6.6					11.5[i]
Tos_2N**H** (**1c**)	6.7	6.2			1.7[k]		12.0[i,k]
PhCON**H**Tf (**7b**)	6.7	6.2_5					11.1[i]
$PhSO_2$N**H**Tos (**3c**)	6.5	6.0					
$PhSO_2$N**H**SO_2Ph (**9a**)	6.3	5.8 (9.7[l])			1.4_5[f]		11.3[j]
p-F-PhCON**H**Tf (**11b**)	6.3	5.9					10.7[i]
p-Cl-PhCON**H**Tf (**10b**)	6.3	5.8					10.4[i]
p-Cl-$PhSO_2$N**H**SO_2Ph (**10a**)	5.9	5.3					
p-NO_2-$PhSO_2$N**H**Tos (**4c**)	5.7	5.0					10.1[j]

[a]The acidic hydrogens are indicated by boldface type. [b]In pK_a units, SD: ≤ ±0.05 pK unit. [c]Reference 11e. [d]Reference 11f. [e]Reference 11g. [f]Reference 11b. [g]Reference 11a. [h]Reference 13. [i]Reference 11m. [j]Reference 11j. [k]Reference 11i. [l]Reference 7c, in [EMIM][NTf_2], where [EMIM]$^+$=1-ethyl-3-methylimidazolium, the value is a simulated one based on electrochemical measurement.

The structure and composition of the ILs in this study have pronounced effect on the N−H acidic dissociation equilibrium. Normally, the anion of IL plays a dominant role on the acidity, due to the relatively large proton solvation energy [ΔG_{Solv}*(H^+)] by anion (-258 kcal mol^{-1} for [NTf_2]$^-$), compared with that by cation on the deprotonated species of various substrates.[15] From Table 1, the acidity of individual sulfonamide decreases in a sequence of [BMIM][OTf] > [BMIM][NTf_2] > [BMPY][NTf_2] > [BM_2IM][NTf_2], which is consistent with our previous observations for other series of acids.[9] It is not difficult to understand that the acidity of these sulfonamides are more acidic in [BMIM][OTf] than in [BMIM][NTf_2]. This should be ascribed to a more localized negative charge and smaller size of [OTf]$^-$ compared to [NTf_2]$^-$, both leading to a stronger solvation of proton. The trend of pK_a change in the ILs with [NTf_2]$^-$ as the common counter anion could be rationalized on the basis of the extent of charge delocalization and the accessibility of the cation moiety towards the sulfonamide anion. For example, the observed stronger acidity of sulfonamide in [BMIM][NTf_2] than in the other two ILs with [NTf_2]$^-$ as a common anion should be due to the less hindered [BMIM]$^+$ moiety than the other two and its C_2-H that is capable of providing an H-bonding with the sulfonamide nitranion.

Table 1 also shows that the acidities of sulfonamides in various solvents follow the order, in water > in DMSO > in [BMIM][OTf] > [BMIM][NTf_2] > [BMPY][NTf_2] > [BM_2IM][NTf_2] > in ACN, which actually reflects the order of solvability for these solvents.[7b] This sequence is beyond one's expectation, however, because AILs are known for their relatively low polarity (ε = 10-15[16]), which would otherwise suggest a weaker acidity in ILs than in ACN, whose dielectric constant is much greater (ε = 36.1[17]). Nonetheless, as we recently found, the cations and anions in AILs should exist essentially as "free ions" rather than as ion-pairs[9e] (showing an "ionic liquid effect"[9c,9e,18,19]), it may not be too big a surprise to see that some classical parameters suitable for describing properties in molecular media (such as ε) may not always be so for certain properties in ILs. Thus, the presently observed but yet unanticipated unusually strong N−H bond weakening ability of the low-polarity ILs could be understood by considering that the IL's anion and cation should be able to act separately in stabilizing the proton and the incipient sulfonamide nitranion upon deprotonation by virtue of their respective solvability (via Coulombic, resonance, π-π interactions, etc.) towards ions of opposite charges. This *in situ* situation occurred in a solvation process in IL is not exactly the same as the status of an IL in a dielectric

constant measurement,[16] and thus, it should be the reason behind the unusually strong N−H bond-weakening ability of these superficially weakly-polar ILs.

Next, we carried out a regression study on the sulfonamides acidities measured in the 4 ILs. All the correlations between the pK_as in any two ILs show excellent linearity with $R^2 = 0.999$ (see SI, Figure S3, one of them is shown in Figure 1). Furthermore, regression analyses between the pK_as in one representative IL ([BMPY][NTf_2]) and these in molecular solvents were performed. Remarkably, in spite of the tremendous differences in solvent properties of water, DMSO and ACN from ILs, good to excellent linearity is observed in

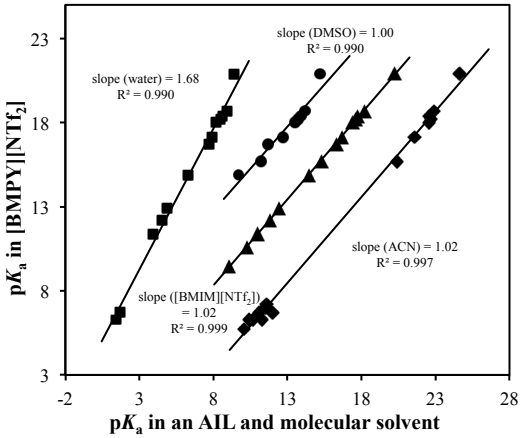


Figure 1. pK_as of sulfonamides in [BMPY][NTf_2] against these in [BMIM][NTf_2] and molecular solvent; filled square, circle, triangle and diamond represents the pK_as in water, DMSO, [BMIM][NTf_2] and ACN, respectively.

all the correlations (Figure 1). It is noteworthy that the slope of the correlation between the pK_as in [BMPY][NTf_2] and in water is significantly greater than unity (slope = 1.68), indicating a much lower sensitivity of sulfonamide acidity towards structure variation in water than in AILs. This is understandable, because the negative charge of the sulfonamide anion can be better dispersed in water than in IL due to the greater solvability of water caused mainly by its strong hydrogen-bondings. This reduces the charge density on nitrogen and weakens the influence of a structural change more significantly than the situation in ILs. On the other hand, the slopes of the correlations between the acidities in ILs (taking [BMPY][NTf_2] as example) vs. DMSO and vs. ACN are all observed to be around unity (Figure 1, slope = 1.00 and 1.02, respectively). Though this seeming coincidence in the slope values cannot be fully understood based on our present knowledge on solvation, these correlation Equations 1-3 (Scheme 3) together with those in ILs mentioned above can provide a practically very useful way for estimating unknown pK_as in these molecular and ionic solvents for relevant compounds.

$$p\mathit{K}_a\,([BMPY][NTf_2]) = 1.68\ p\mathit{K}_a\,(water) + 4.24 \qquad Eqn.1$$

$$p\mathit{K}_a\,([BMPY][NTf_2]) = p\mathit{K}_a\,(DMSO) + 4.76 \qquad Eqn.\ 2$$

$$p\mathit{K}_a\,(ACN) \approx p\mathit{K}_a\,([BMPY][NTf_2]) + 4.81 \qquad Eqn.\ 3$$

Scheme 3. The acidity correlation equations between pK_as in IL and molecular media

In summary, the absolute acidities of 25 N−H acids (altogether 68 pK_a values) were accurately measured in four ILs. The wide energetic range (>15 pK units) of the obtained data enabled regression analyses among the pK_as scales in both ILs and molecular media, which exhibit excellent linear correlations of the acidity scales both in ILs and in between the ILs and molecular solvents (water, DMSO and ACN). Such relationships allow reasonable estimates for the unknown acidities of sulfonamides in these solvents. A detailed comparison among the acidity scales in these ionic and molecular media finds an interesting trend that the ILs of low ε value can show an unusually strong ability (vs. ACN, ε = 36.1) in facilitating deprotonation. The absolute acidities and the solvation insights disclosed in this work may serve either as benchmark values or reliable references for the development of appropriate theoretical solvation models and for mechanistic analyses in ILs.

EXPERIMENTAL

General

ILs (Scheme 1)[20], carbon indicator acids (fluorene derivatives, Table S1) and the base used in this work were synthesized and purified as described in previous work.[9] In addition, ILs were dried in vacuum at 70 ^oC for 5 hours before use and were stored in desiccators under argon. The water contents of ILs are less than 10 ppm, which was determined by the Karl-Fischer titration. Sulfonamides, except otherwise noted, were commercially available and were carefully recrystallized and dried before used as substrates. The sulfonamides and indicator acids were kept in a glove box. The principle of acidity measurement by indicator overlapping method[11c, 13]is introduced as Equation 4:

$$HA + In^- \overset{K_{eq}}{\rightleftharpoons} HIn + A^-$$

$$p\mathit{K}_a = p\mathit{K}_{HIn} - \lg\mathit{K}_{eq} = p\mathit{K}_{HIn} - \lg\frac{[HIn][A^-]}{[HA][In^-]} \qquad Eqn.\ 4$$

Where HIn and HA denotes the indicator and substrate acids respectively. It is worth noting that all the acidities of indicator acids were referenced to an anchor compound whose acidity was measured by self-dissociation (SI), so the pK_as of these indicator acids are absolute values in essence. All manipulations were

carried out under dry argon using standard Schlenk techniques. The pK_a measurement started by adding 1.5 ml IL solution of base (~5 × 10^{-4} M) into an empty UV cell with a 3-way valve (Figure S1), and then the spectrum for baseline was recorded on a UV instrument. Next an IL solution of an appropriate indicator acid (HIn) with known pK_a was added dropwisely until the UV absorbance was not increasing with the addition. Then the IL solution (10^{-5} to 10^{-4} M) of substrate acid of interest (HA) was added in several portions. The weight of the UV cell and the corresponding spectrum were also recorded upon each addition. The pK_a of HA was then calculated from the change of absorbance and the amount of acid added.

Synthesis of picric derivatives as indicators[21]

a. 3-chloropicric acid (Scheme S1, **C**):

To a 100 ml 3-neck round bottom flask charged with 2.5 g (19.5 mmol) 3-chlorophenol, under an acetone/dry ice bath, 10 ml concentrated sulfuric acids (98% w/w, 0.183 mol) was added slowly, then the temperature of reaction mixture was raised cautiously to 90 ^{o}C and kept at this temperature for 40 mins before the temperature was cooled down to 0 ^{o}C by a water and ice bath (NaCl/icewater). Again under the acetone/dry ice bath, with cautions 10 ml fuming nitric acid (90% w/w, 0.214 mol) was added dropwisely, then the reaction temperature was allowed to rise to 80 ^{o}C and was held at this temperature for 50 mins. After system was cooled down to ambient temperature, the reaction mixture was then poured into ice water, the brown yellowish precipitates were collected and recrystallized from water once and CCl_4 twice to give a yellowish solid 2.3g. Yield: 45%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 127.9.

b. 3, 5-dichloropicric acid (Scheme S1, **D**):

The starting material was 3,5-dichlorophenol, synthetic procedures were similar to these for 3-chloropicric acid (**C**) describe above, which gave a yellow solid with a yield of 38%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.58 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.6, 143.1, 127.7, 121.0.

Synthesis of sulfonamides

The commercial available (**1a** and **1b**) and prepared sulfonamides (**2a**-**8a**, **2b**-**4c**) were carefully recrystallized at least 3 times and stored in glove box before used in pK_a measurement. The synthetic procedures for the sulfonamides used in this work can be found elsewhere.[22]

PhNHSO$_2$Ph (**2a**), yield: 72%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 7.80 (d, J = 7.2 Hz, 2H), 7.60–7.48 (m, 3H), 7.22 (t, J = 7.8 Hz, 2H), 7.14 (d, J = 7.7 Hz, 2H), 7.00 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 140.0, 138.2, 133.3, 129.7, 129.6, 127.1, 124.5, 120.5.[22b]

p-MeO-PhNHSO$_2$Ph (**3a**), yield: 58%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 7.69 (d, J = 7.1 Hz, 2H), 7.60–7.45 (m, 3H), 6.98 (d, J = 7.2 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.0, 139.9, 133.2, 130.5, 129.6, 127.1, 123.9, 114.7, 55.5.[22b]

p-Me-PhNHSO$_2$Ph (**4a**), yield: 68%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H), 7.80 (d, J = 7.1 Hz, 2H), 7.60- 7.48 (m, 3H), 7.28 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H). 10.14 (s, 1H), 7.73 (d, J = 7.1 Hz, 2H), 7.58-7.49 (m, 3H), 7.04–6.95 (m, 4H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 139.9, 135.4, 133.9, 133.3, 130.0, 129.7, 127.1, 121.1, 20.8.[22b]

m-Me-PhNHSO$_2$Ph (**5a**), yield: 69%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 7.80 (d, J = 7.2 Hz, 2H), 7.60–7.50 (m, 3H), 7.09 (t, J = 8.1 Hz, 1H), 7.16 (s, 1H), 6.98–6.88 (m, 2H), 6.82 (d, J = 7.9 Hz, 1H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) $\boldsymbol{\delta}$ 140.0, 138.9, 138.1, 133.3, 129.7, 129.4, 127.1, 125.3, 121.0, 117.5, 21.5.[22b]

p-Cl-PhNHSO$_2$Ph (**6a**), yield: 63%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H), 7.80 (d, J = 7.1 Hz, 2H), 7.60–7.48 (m, 3H), 7.28 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 139.6, 137.1, 133.5, 129.7, 129.6, 128.7, 127.1, 122.0.[22b]

m-Cl-PhNHSO$_2$Ph (**7a**), yield: 65%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.66 (s, 1H), 7.82 (d, J = 7.2 Hz, 2H), 7.63–7.50 (m, 3H), 7.24 (t, J = 8.1 Hz, 1H), 7.16 (s, 1H), 7.11 (d, J = 8.2 Hz, 1H), 7.05 (d, J = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 139.8, 139.6, 133.9, 133.6, 131.3, 129.8, 127.1, 124.2, 119.5, 118.4.[22b]

m-NO$_2$-PhNHSO$_2$Ph (**8a**), yield: 48%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 7.99 (s, 1H), 7.85 (d, J = 7.2 Hz, 2H), 7.81 (d, J = 7.9 Hz, 1H), 7.60–7.51 (m, 4H), 7.48 (t, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.6, 139.6, 139.4, 133.7, 131.1, 129.9, 127.1, 125.7, 118.8, 113.9.[22b]

PhSO$_2$NHSO$_2$Ph (**9a**), yield: 33%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.87 (s, 1H), 7.71 (d, J = 7.4 Hz, 4H), 7.51 (t, J = 7.2 Hz, 2H), 7.44 (t, J = 7.4 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.3, 131.9, 128.9, 126.8.[22c]

p-Cl-PhSO$_2$NHSO$_2$Ph (**10a**), yield: 31%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.65 (s, 1H), 7.74–7.68 (m, 4H), 7.50–7.45 (m, 3H), 7.41 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.4, 143.5, 136.5, 131.8, 128.9, 128.8, 126.8.[22c]

PhNHTf (**2b**), yield: 67%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H), 7.42 (t, J = 7.7 Hz, 2H), 7.29 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 135.3, 130.0, 127.1, 123.3, 120.2 ($^{1}J_{CF}$ = 322 Hz).[22b]

p-MeO-PhNHTf (**3b**), yield: 59%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.60 (s, 1H), 7.21 (t, J = 8.3 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.6, 127.3, 126.5, 120.3 ($^{1}J_{CF}$ = 323 Hz), 55.7.[22b]

p-Cl-PhNHTf (**4b**), yield: 72%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.02 (s, 1H), 7.49 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 134.4, 131.3, 130.0, 124.8, 120.1 ($^{1}J_{CF}$ = 321 Hz).[22b]

p-CF_3-PhNHTf (**5b**), yield: 64%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.33 (s, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.3 Hz, 2H).[22b]

p-NO_2-PhNHTf (**6b**), yield: 68%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12 (s, 1H), 8.26 (d, J = 9.0 Hz, 2H), 7.46 (d, J = 9.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.5, 143.1, 125.6, 121.4, 120.1 ($^{1}J_{CF}$ = 322 Hz).[22b]

PhCONHTf (**7b**), yield: 59%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.16 (s, 1H), 7.93 (d, J = 7.3 Hz, 2H), 7.47 (d, J = 7.3 Hz, 1H), 7.40 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.9, 131.6, 129.0, 128.3.[22d]

p-MeO-PhCONHTf (**8b**), yield: 62%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.10 (s, 1H), 7.91 (d, J = 8.6 Hz, 2H), 6.98 (d, J = 8.7 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.8, 163.1, 131.4, 127.0, 120.3 ($^{1}J_{CF}$ = 322 Hz), 113.9, 55.8.[22d]

p-Me-PhCONHTf (**9b**), yield: 66%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.23 (s, 1H), 7.83 (d, J = 7.9 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.9, 142.5, 133.0, 129.3, 129.1, 120.5 ($^{1}J_{CF}$ = 322 Hz), 21.5.[22d]

p-Cl-PhCONHTf (**10b**), yield: 61%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.30 (s, 1H), 7.92 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.9, 136.7, 135.8, 130.9, 128.5, 120.6 ($^{1}J_{CF}$ = 322 Hz).[22d]

p-F-PhCONHTf (**11b**), yield: 49%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.43 (s, 1H), 7.98 (dd, J = 8.5 Hz, $^{4}J_{HF}$ = 5.9 Hz, 2H), 7.19 (t, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.8, 164.6 ($^{1}J_{CF}$ = 248 Hz), 133.5, 131.7 ($^{3}J_{CF}$ = 9 Hz), 120.6 ($^{1}J_{CF}$ = 323 Hz), 115.3 ($^{2}J_{CF}$ = 21 Hz).[22d]

$MeSO_2NHTos$ (**2c**), yield: 48%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.09 (s, 1H), 7.75 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 3.15 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 143.6, 138.5, 129.8, 127.3, 43.8, 21.5.[22c]

PhSO$_2$NHTos (**3c**), yield: 28%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.80 (s, 1H), 7.75 (d, J = 7.4 Hz, 2H), 7.63 (d, J = 8.2 Hz, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H), 7.27 (d, J = 8.1 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 143.1, 142.8, 139.9, 132.7, 129.6, 129.2, 127.1, 127.0, 21.4.[22c]

p-NO$_2$-PhSO$_2$NHTos (**4c**), yield: 25%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.76 (s, 1H), 8.21 (d, J = 8.7 Hz, 2H), 7.88 (d, J = 8.6 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 7.9 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.6, 148.7, 142.6, 141.1, 129.0, 128.3, 126.8, 124.0, 21.3.[22c]

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website. Picture of the UV-cell; expansion of the indicator acidity scale; indicators used in this work and their corresponding pK_as in ILs; UV-vis spectra for representative measurements; regression analysis; NMR spectra.

NOTES

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by National Natural Science Foundation of China (NSFC, Grant Nos. 21172118, 21390401) and Tsinghua University Initiative Scientific Research Program (Grant Nos. 20131080083, 20141081295). We thank Miss J.-J. Zhang for her assistance with the NMR experiments.

REFERENCES

(1) Reichardt, C.; Welton, T. *Solvents and Solvent Effects in Organic Chemistry*, 4th ed.; Wiley-VCH: Weinheim, **2011**.

(2) (a) Welton, T. *Chem. Rev*. **1999**, *99*, 2071. (b) Wasserscheid, P. *Nature* **2006**, *439*, 797. (c) Galinski, M.; Lewandowski, A.; Stepniak, I. *Electrochim. Acta* **2006**, *51*, 5567.

(3) (a) Earle, M. J.; Seddon, K. R. *Pure Appl. Chem*. **2000**, *72*, 1391. (b) Wheeler, C.; West, K. N.; Liotta, C. L.; Eckert, C. A. *Chem. Commun*. **2001**, 887. (c) *Ionic Liquids: Industrial Applications for Green Chemistry*, *ACS Symposium Series 818* (Eds.: R. D. Rogers, K. R. Seddon), American Chemical Society, Washington, DC, **2002**. (d) *Ionic Liquids as Green Solvents: Progress and Prospects*, *ACS Symposium Series 856* (Eds.: R. D. Rogers, K. R. Seddon), American Chemical Society, Washington, DC, **2003**. (e)

Wasserscheid, P.; Stark A. in *Green Solvents, Ionic Liquids*: *Handbook of Green Chemistry*, *Vol. 6* (Ed.: Anastas, P. T.), Wiley-VCH, Weinheim, **2014**.

(4) (a) Pinkert, A.; Marsh, K. N.; Pang, S.; Staiger, M. P. *Chem. Rev*. **2009**, *109*, 6712. (b) Armand, M.; Endres, F.; MacFarlane, D. R.; Ohno, H.; Scrosati, B. *Nat. Mater.* **2009**, *8*, 621. (c) Bara, J. E.; Camper, D. E.; Gin, D. L.; Noble, R. D. *Acc. Chem. Soc.* **2010**, *43*, 152. (d) Hallett, J. P.; Welton, T. *Chem. Rev*. **2011**, *111*, 3508. (e) Tang, S.; Baker, G. A.; Zhao, H. *Chem. Soc. Rev*. **2012**, *41*, 4030.

(5) For representative pK_a scales in common molecular solvents, see: (a) Serjeant, E. P.; Dempsey, B. *Ionisation Constants of Organic Acids in Aqueous Solution*, Pergamon Press, New York, **1979**. (b) Streitwieser, A. *J. Org. Chem.* **2009**, *74*, 4433 and the references therein. (c) Bordwell, F. G. *Acc. Chem. Soc*. **1988**, *21*, 456. (d) Refs. 11j, 11k and 11m.

(6) (a) Thomazeau, C.; Olivier-Bourbigou, H.; Magna, L.; Luts, S.; Gilbert, B. *J. Am. Chem. Soc.* **2003**, *125*, 5264. (b) D'Anna, F.; Vitale, P.; Noto, R. *J. Org. Chem.* **2009**, *74*, 6224. (c) Angelini, G.; De Maria, P.; Chiappe, C.; Fontana, A.; Pierini, M.; Siani, G. *J. Org. Chem.* **2010**, *75*, 3912.

(7) (a) Barhdadi, R.; Troupel, M.; Comminges, C.; Laurent, M.; Doherty, A. *J. Phys. Chem. B* **2012**, *116*, 277. (b) Fujii, K.; Hashimoto, K.; Sakai, T.; Umebayashi, Y.; Shibayama, M. *Chem. Lett*. **2013**, *42*, 1250. (c) Millań, D.; Rojas, M.; Santos, J. G.; Morales, J.; Isaacs, M.; Diaz, C.; Pavez, P. *J. Phys. Chem. B* **2014**, *118*, 4412. (d) Bentley, C. L.; Bond, A. M.; Hollenkamp, A. F.; Mahon, P. J.; Zhang, J. *J. Phys. Chem. C* **2015**, *119*, 21828. (e) Bentley, C. L.; Bond, A. M.; Hollenkamp, A. F.; Mahon, P. J.; Zhang, J. *J. Phys. Chem. C* **2015**, *119*, 21840. (f) Kanzaki, R.; Kodamatani, H.; Tomiyasu, T.; Watanabe, H.; Umebayashi, Y. *Angew. Chem. Int. Ed.* **2016**, *55*, 6266.

(8) A comprehensive Internet-based pK_a databank, *i*BonD, was established by us recently, it includes more than 30,000 equilibrium acidity data (pK_as) for about 17,000 compounds in various molecular solvents and about 6500 bond dissociation energies (BDEs) of various most important chemical bonds. For details, see: http://ibond.chem.tsinghua.edu.cn, http://ibond.nankai.edu.cn.

(9) (a) Deng, H.; Li, X.; Yuan, C.; He, J.-Q.; Cheng, J.-P. *J. Org. Chem*. **2012**, *77*, 7291. (b) Wang, Z.; Deng, H.; Li, X.; Ji, P.; Cheng, J.-P. *J. Org. Chem.* **2013**, *78*, 12487. (c) Wang, Z.; Ji, P.; Li, X.; Cheng, J.-P. *Org. Lett*. **2014**, *16*, 5744. (d) Mao, C.; Wang, Z.; Ji, P.; Cheng, J.-P. *J. Org. Chem*. **2015**, *80*, 8384. (e) Mao, C.; Wang, Z.-D.; Wang, Z.; Ji, P.; Cheng, J.-P. *J. Am. Chem. Soc.* **2016**, *138*, 5523.

(10) (a) Henry, R. *J. Bacteriol. Rev.* **1943**, *7*, 175. (b) Vullo, D.; Innocenti, A. C.; Supuran, T. in *Diuretics with Carbonic Anhydrase Inhibitory Activity: Toward Novel Applications for Sulfonamide Drugs, Drug Design of Zinc-Enzyme Inhibitors: Functional, Structural, and Disease Applications* (Eds.: Supuran, C. T.; Winum, J.-Y.), John Wiley & Sons, Hoboken, **2009**. (c) Hansen, E.; Limé, E.; Norrby, P.; Wiest, O. *J. Phys. Chem. A* **2016**, *120*, 3677.

(11) (a) Trepka, R. D.; Belisle, J. W.; Harrington, J. K. *J. Org. Chem*. **1974**, *39*, 1094. (b) Exner, O.; Janák, P. *Collect. Czech. Chem. Commun.***1975**, *40*, 2510. (c) Bordwell, F. G.; Branca, J. C.; Hughes, D. L.; Olmstead, W. N. *J. Org. Chem*. **1980**, *45*, 3305. (d) Kravtsov, D. N.; Peregudov, A. S.; Petrov, E. S.; Terekhova, M. I.; Shatenshtein, A. I. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1981**, *30*, 993. (e) Ludwig, M.; Pytela, O.; Kalfus, K.; Večeřa, M. *Collect. Czech. Chem. Commun.* **1984**, *49*, 1182. (f) Ludwig, M.; Pytela, O.; Večeřa, M. *Collect. Czech. Chem. Commun.* **1984**, *49*, 2593. (g) Ludwig, M.; Pytela, O.; Javůrková, H.; Večeřa, M. *Collect. Czech. Chem. Commun.* **1987**, *52*, 2900. (h) Ludwig, M.; Pařík, P.; Kulhánek, J. *Collect. Czech. Chem. Commun.* **1995**, *60*, 841. (i) Ludwig, M.; Stverka, P. *Collect. Czech. Chem. Commun.* **1996**, *61*, 1205. (j) Leito, I.; Kaljurand, I.; Koppel, I. A.; Yagupolskii, L. M.; Vlasov, V. M. *J. Org. Chem*. **1998**, *63*, 7868. (k) Kütt, A.; Leito, I.; Kaljurand, I.; Sooväli, L.; Vlasov, V. M.; Yagupolskii, L. M.; Koppel, I. A. *J. Org. Chem*. **2006**, *71*, 2829. (l) Nadvornik, J.; Ludwig, M. *Collect. Czech. Chem. Commun.* **2001**, *66*, 1380. (m) Yagupolskii, L. M.; Petrik, V. N.; Kondratenko, N. V.; Soovaeli, L.; Kaljurand, I.; Leito, I.; Koppel, I. A. *J. Chem. Soc.*, *Perkin Trans. 2* **2002**, 1950. (n) Mansfeld, M.; Pařík, P.; Ludwig, M. *Collect. Czech. Chem. Commun.* **2004**, *69*, 1479.

(12) Shamshina, J. L.; Kelley, S. P.; Gurau, G.; Rogers, R. D. *Nature* **2015**, *528*, 188 and the reference cited within.

(13) Bordwell, F. G.; Algrim, D. *J. Org. Chem.* **1976**, *41*, 2507.

(14) It is generally accepted the acidifying effect of sulfonyl group on carbon acids is mainly due to the polarization effect rather than the resonance stabilization or negative conjugation of carbanions. For details, see: (a) Breslow, R.; Mohacsi, E. *J. Am. Chem. Soc.* **1961**, *83*, 4100. (b) Terrier, F.; Kizilian, E.; Goumont, R.; Faucher, N.; Wakselman, C. *J. Am. Chem. Soc.* **1998**, *120*, 9496. (c) Goumont, R.; Magnier, E.; Kizilian, E.; Terrier, F. *J. Org. Chem.* **2003**, *68*, 6566.

(15) The Gibbs solvation energy of proton, $[\Delta G_{Solv}^{*}(H^{+})]$, by $[NTf_2]^{-}$ anion was obtained based on a theoretical calculation, the calculation indicates that the Gibbs solvation energies of various deprotonated substrate anions by an IL cation, $[BMIM]^{+}$, are in a range of -50 to -65 kcal mol^{-1}. For details, see: (a) Xue, X.-S.; Wang, Y.;

Yang, C.; Ji, P.; Cheng, J.-P. *J. Org. Chem*. **2015**, *80*, 8997. (b) Xue, X.-S.; Yang, C.; Li, X.; Cheng, J.-P. *Org. Chem. Front.* **2014**, *1*, 176.

(16) (a) Wakai, C.; Oleinikova, A.; Ott, M.; Weingärtner, H. *J. Phys. Chem. B* **2005**, *109*, 17028. (b) Huang, M.; Jiang, Y.; Sasisanker, P.; Driver, G. W.; Weingärtner, H. *J. Chem. Eng. Data* **2011**, *56*, 1494.

(17) (a) Coetzee, J. F. *Prog. Phys. Org. Chem.* **1967**, *4*, 45. (b) Würflinger, A. *Ber. Bunsenges. Phys. Chem.* **1980**, *84*, 653.

(18) (a) Newington, I.; Perez-Arlandis, J. M.; Welton, T. *Org. Lett.* **2007**, *9*, 5247. (b) Hallett, J. P.; Liotta, C. L.; Ranieri, G.; Welton, T. *J. Org. Chem.* **2009**, *74*, 1864.

(19) Lui, M. Y.; Crowhurst, L.; Hallett, J. P.; Hunt, P. A.; Niedermeyer, H.; Welton, T. *Chem. Sci*. **2011**, *2*, 1491.

(20) Burrell, A. K.; Sesto, R. E. D.; Baker, S. N.; McCleskey, T. M.; Baker, G. A. *Green Chem.* **2007**, *9*, 449.

(21) Pearce, P. J.; Simkins, R. J. J. *Can. J. Chem.* **1968**, *46*, 241.

(22) (a) Greenfield, A.; Grosanu, C. *Tetrahedron Lett*. **2008**, *49*, 6300. (b) Kato, T.; Okamoto, I.; Tanatani, A.; Hatano, T.; Uchiyama, M.; Kagechika, H.; Masu, H.; Katagiri, K.; Tominaga, M.; Yamaguchi, K.; Azumaya, I. *Org. Lett*. **2006**, *8*, 5017. (c) Dykhanov, N. N. *Zh. Obshtsh. Khim*. **1959**, *29*, 3602. (d) Yagupolskii, L. M.; Shelyazhenko, S. V.; Maletina, I. I.; Petrik, V. N.; Rusanov, E. B.; Chernega, A. N. *Eur. J. Org. Chem.* **2001**, 1225.