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# Toward Prediction of the Chemistry in Ionic Liquids: An Accurate Computation of Absolute p$K_a$ Values of Benzoic Acids and Benzenethiols

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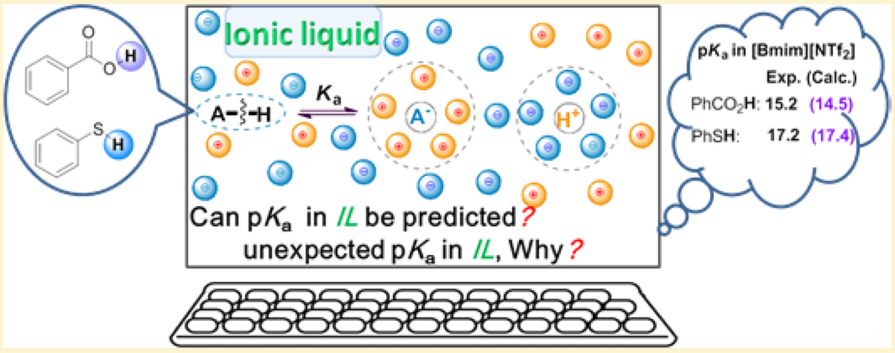
Supporting Information




**ABSTRACT:** In contrast to the great success of computational methodologies in molecular solvents, effective and accurate calculation of the fundamental bond energetic properties in ionic liquids (ILs) is essentially absent. This is largely due to the unusual complexity of handling solvation quantities of ILs and the lack of precisely determined bond parameters to serve as the authentic benchmark to calibrate the modeling methodology. Herein, we report the first accurate calculations of absolute p$K_a$ values in a commonly used IL, [Bmim][NTf$_2$], with the carefully developed "ion-biased" cluster-continuum model. Experimental p$K_a$ values of benzoic acids and benzenethiols in [Bmim][NTf$_2$] were reproduced with mean unsigned errors of only 0.3 and 0.5 p$K_a$ units, respectively, which enables theoretical approaches with a suitable strategy as a powerful tool to handle complicated problems in ILs and to eventually realize the rational design of the IL chemistry.

## INTRODUCTION

The most fundamental process in chemistry is the reorganization of chemical bonds through bond breaking and formation. Hence, energetics of bond fission, the key factor for analyzing reaction behavior, has been substantially studied with special focus on the R−H bond heterolysis free energy (p$K_a$) in molecular solvents such as water[1] and DMSO.[2] The reason for this is that most chemical transformations occurring in solution proceed initially through heterolytic cleavage of bonds, and no other physicochemical indicators can model their intrinsic driving force better than p$K_a$. In addition, it is also the primary quantity for derivation of other major modes of bond dissociation energies like homolytic bond dissociation energy (BDE),[3] p$K_a$ (HA$^{+\bullet}$),[4] hydride affinity[5] in solution, and so on.

Although significant bond energetic data have already been accumulated in the past as the quantitative guideline for rational development of chemistry,[1−6] more are still unknown, and the measurement for the majority of them may not be experimentally amenable. Thus, great efforts have been made in recent decades to develop calculation methodologies to complement the experiment.[7,8] Surprisingly, in contrast to the remarkable success of the computational handling of the problems in conventional molecular solvents such as water, DMSO, *etc.*,[7,8] until present, no theoretical protocol assumed to be applicable for the ionic liquid (IL) chemistry has been verified to accurately reproduce the experiments. This is unexpected, especially when considering that the chemistry in ILs has already attracted numerous research activities during the same period of time and has clearly demonstrated its unlimited potential to promote amazing new chemistry and industry.[9] Doubtlessly, rational exploration of the IL chemistry and its great potential as the so-called "designer's solvent" for exciting green transformation would not be eventually realized without the success of computation.[10]

From the viewpoint of physical organic chemistry, chemical reactions are governed *internally* by the energies of the bonds being broken and formed and *externally* by microenvironment variables, such as the reaction media, concentration, and temperature. To develop a rational IL chemistry, both aspects

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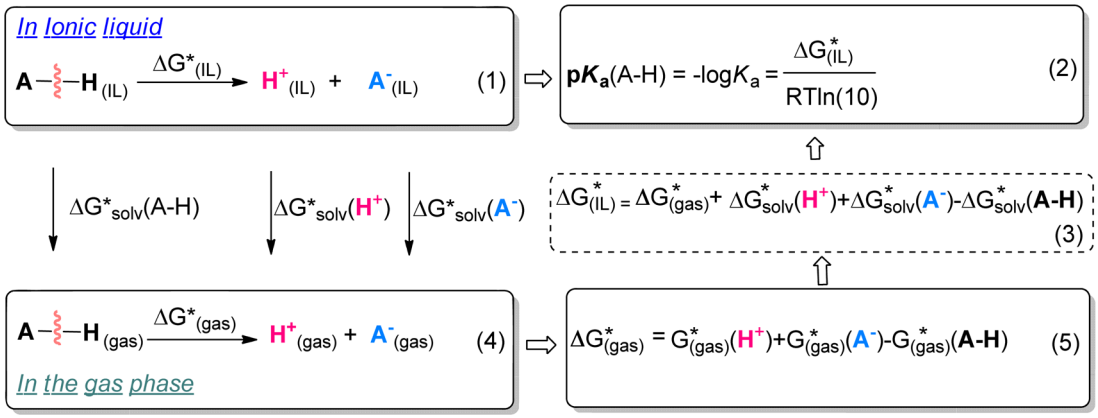


**Figure 1.** Thermodynamic cycle used for the p$K_a$ calculation.

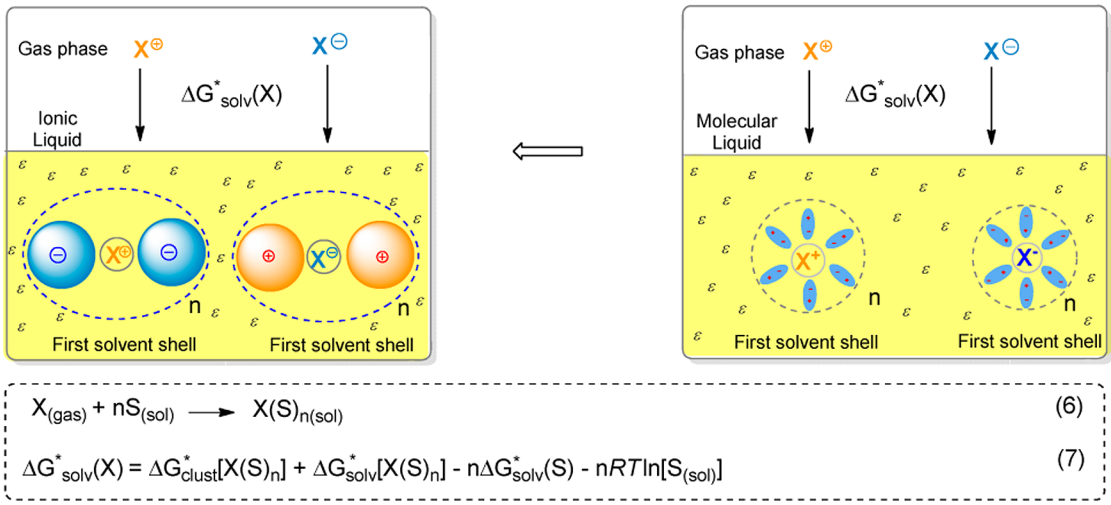


**Figure 2.** Schematic extension of the cluster-continuum model from molecular to ionic medium, where *n* is the number of the attached solvent molecules in the first solvent shell.

are the central issue, where computation can surely make an invaluable contribution in building up the fundamental understanding framework and in untangling the controversies therein. In this regard, the challenge met in exploring effective methodologies to compute the absolute bond parameters like p$K_a$ in ILs, which is fundamentally different from molecular solvent due to the charged nature of its components, becomes one of the best tests for the IL phase computation. As is well-known, a common strategy toward accurate prediction of solution p$K_a$ values is to use a thermodynamic cycle, which requires accurate computation of the gas-phase acidities and the solvation free energies.[7] In such a context, the accurate calculation of solvation free energies,[11] for example, the solvation free energy in water,[12] represents the primary challenge for predicting p$K_a$ in solution.[7] The same is true for the prediction of p$K_a$ values in ILs. As expected, the prediction of accurate solvation free energies may be more complicated for ionic species due to strong electrostatic effects arising from unbalanced localized charges.[8d] In particular, the prediction of the solvation free energy of the proton would be more challenging as its chemical structure is often unknown and difficult to model theoretically.[7] Although the issues associated with calculating the solvation free energy of the proton can be circumvented, in principle, by pursuing p$K_a$ values in a relative manner against a reference acid whose experimental p$K_a$ is known,[7a−c,e,13] this strategy suffers an unavoidable limitation in its application to other ILs because there are numerous ILs of which no experimental p$K_a$ value is available.

In the present work, we practiced a strategy to apply certain numbers of the so-called "explicit" cation or anion of ILs to modulate the inner solvation shell of the cluster-continuum model[14] to quantum mechanically describe the specific solute−solvent interactions of the proton and its conjugate anion of acid with the IL anion and cation, respectively. The rationality of the "ion-biased" cluster-continuum model (IB-CCM) has roots in recent experimental and theoretical findings where the IL cation [Bmim$^+$] and its counteranion [$NTf_2^-$] do not strongly associate with each other to form long-lived ion pairs.[15,16] Application of the IB-CCM model to compute the absolute equilibrium acidities of benzoic acids and benzenethiols in [Bmim][$NTf_2$] was demonstrated in the present work. It was shown that the developed IB-CCM is capable of accurately reproducing the p$K_a$ values with a remarkable mean unsigned error (MUE) of less than 0.5 p$K_a$ units, implying that the "dream" for ILs as the designer's solvent may eventually realized with the assistance of computation as a powerful tool. The relevant details are described, and the discussion on the origin of the variation of acidities in ILs compared with those in traditional molecular solvent is presented.



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## METHODOLOGY

**p$K_a$ Calculation and Thermodynamic Cycle.** The p$K_a$ of a given acid A−H represents the standard Gibbs free energy change of heterolytic cleavage of the A−H bond (eq 1, Figure 1), which can be derived using the relationship shown in eq 2. In eq 2, $\Delta G^*_{(IL)}$ is the standard Gibbs free energy change of acidic dissociation, where superscript "∗" denotes the standard states referring to 1 mol $L^{-1}$. Based on the thermodynamic cycle (Figure 1), $\Delta G^*_{(IL)}$ can be evaluated from eq 3, where $\Delta G^*_{(gas)}$ is the gas-phase acidity of A−H defined by eqs 4 and 5, $\Delta G^*_{solv}(HA)$ and $\Delta G^*_{solv}(A^-)$ are the solvation free energies of A−H and its conjugate base $A^-$, $\Delta G^*_{solv}(H^+)$ is the solvation free energy of the proton in the IL. As mentioned previously, the primary challenge for absolute p$K_a$ calculation lies on accurate estimation of the solvation free energies of ionic species, especially for the proton. We give a brief description of using the above-mentioned IB-CCM to handle this challenge in the following section.

**Ion-Biased Cluster-Continuum Model.** The original cluster-continuum model was pioneered by Pliego and Riveros for the calculation of the solvation free energy of ions in aqueous solution.[14a] It is based on the premise that a few solvent molecules (S) are strongly bound to the central ion (X) and that the solvation process can be seen as a chemical reaction, as shown in eq 6 (Figure 2). On this basis, the solvation free energy of the bare ion (X) in IL can be calculated by eq 7,[14a] where $\Delta G^*_{clust}[X(S)_n]$ is the free energy for the cluster formation in the gas phase, $\Delta G^*_{solv}[X(S)_n]$ is the solvation free energy of the cluster, $\Delta G^*_{solv}(S)$ is the solvation free energy of the solvent molecule, and the last term is related to the density number of the solvent (for [Bmim][$NTf_2$], [S] = 3.41 mol $L^{-1}$).

Differing from the conventional molecular solvents, ILs are composed entirely of ions. It is thus reasonable to expect that the proton is solvated mainly by the IL anion(s), while the conjugate anionic base is solvated by the IL cation(s) rather than by strongly associated ion pairs upon acidic dissociation. This is because, as mentioned above, the IL cation [$Bmim^+$] and its counteranion [$NTf_2^-$] used in the experimental measurement[17,18] do not strongly associate with each other to form long-lived ion pairs. Accordingly, certain numbers of the "explicit" cation or anion of ILs were employed to describe the specific solute−solvent interactions of the conjugate anion of the acid and the generated proton in the first solvation shell with the IL cation and anion, respectively. The number ($n$) of the attached IL cations or anions in the inner shell was chosen to minimize the total free energy change of the solution-phase reaction depicted in eq 7.[14a] We refer to this approach as the ion-biased cluster-continuum model.

## RESULTS AND DISCUSSION

The p$K_a$ values of benzoic acids[17] and benzenethiols[18] in [Bmim][$NTf_2$] have been precisely determined by this group. Some intriguing medium effects of ILs on the acidities were observed. For instance, the p$K_a$ values of benzoic acid (**1a**) and benzenethiol (**2a**) in [Bmim][$NTf_2$] were determined to be 15.2[17] and 17.2,[18] respectively, which are greater than their corresponding p$K_a$ values of 11.0[19] and 10.3[20] in DMSO. This may be contrary to one's intuition. Compared with the situation in a neutral molecular solvent like DMSO, IL is composed of charged ions and hence its strong solvation toward proton and the conjugate anionic base of an acid should have been able to facilitate acidic dissociation of a given substrate. The underlying reason for this counterintuitive observation in IL is unclear. In addition, a closer scrutiny on the relative acidities of benzoic acid versus benzenethiol in [Bmim][$NTf_2$] and DMSO revealed that benzoic acid is a stronger acid than benzenethiol by 2.0 p$K_a$ units in [Bmim][$NTf_2$], whereas in DMSO, it is a weaker acid instead. The reason for the inversion of their acidity order on going from DMSO to [Bmim][$NTf_2$] also remains elusive. Nonetheless, these precisely measured experimental p$K_a$ values in IL provide an excellent opportunity for a computational approach, as well as its potential for analyzing complicated chemical problems. In the following, we demonstrate that the new computation strategy with the IB-CCM can nicely reproduce the absolute p$K_a$ values measured experimentally in [Bmim][$NTf_2$] and can also provide informative insights into the intriguing solvation effect of IL.

**Solvation Free Energy of the Proton in [Bmim][$NTf_2$].** In order to calculate the absolute p$K_a$ values, we first calculated the solvation free energy of the proton in [Bmim][$NTf_2$] by using the IB-CCM. Previous studies have shown that the proton may be associated with IL anions to form a cluster such as the dianion $H[X]_2^-$ species in ILs.[21] Accordingly, we considered the attachment of one IL anion, one ion pair, two IL anions, and two ion pairs to the proton in the first solvent shell (Figure 3). The attachment of more IL anions to the proton was not considered because the proton appears to be completely surrounded by two IL anions because the size of the IL anion [$NTf_2$] is several times larger than that of the proton. This can be clearly seen for the optimized structure of dianion $H[NTf_2]_2^-$ from Figure 3. It was found that the calculated solvation free energy of the proton reaches the minimum $\Delta G^*_{solv}(H^+)$ = −258.0 kcal $mol^{-1}$ when two IL anions were attached to the proton. This implies that the proton is most likely solvated by two IL anions in the first solvation shell. In fact, this is in agreement with Trulove and co-worker's spectroscopic findings.[22]

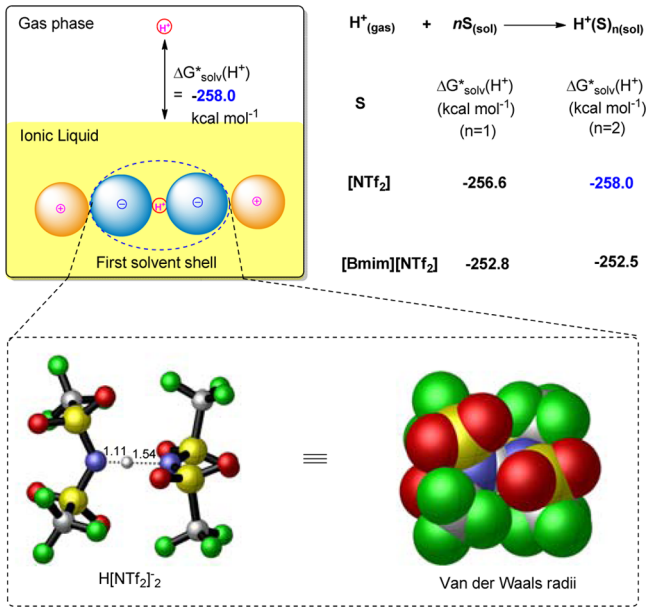


**Figure 3.** Optimized geometry of $H[NTf_2]_2^-$ with the M06-2X/6-31+G(d,p) method and calculated solvation free energy of the proton (in kcal $mol^{-1}$) in [Bmim][$NTf_2$] by the IB-CCM.



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Table 1. Calculated Solvation Free Energy $\Delta G^*_{solv}(X)$ of Substituted Benzoic Acids and Benzenethiols and Their Conjugate Bases by the IB-CCM[a]

| X[$NTf_2$]$_n$ | $\Delta G^*_{solv}(X)$ | X[Bmim]$_n$ | $\Delta G^*_{solv}(X)$ | X[$NTf_2$]$_n$ | $\Delta G^*_{solv}(X)$ | X[Bmim]$_n$ | $\Delta G^*_{solv}(X)$ |
|---|---|---|---|---|---|---|---|
| $PhCO_2H$ (**1a**) | **−7.8** | $PhCO_2^-$ (**1a**$^-$) | −57.7 | PhSH (**2a**) | **−6.1** | $PhS^-$ (**2a**$^-$) | −52.8 |
| $PhCO_2H[NTf_2]$ | −4.8 | $PhCO_2^-$[Bmim] | −59.8 | $PhSH[NTf_2]$ | −3.2 | $PhS^-$[Bmim] | **−56.0** |
| | | $PhCO_2^-$[Bmim]$_2$ | **−61.1** | | | $PhS^-$[Bmim]$_2$ | −55.8 |
| *p*-$FPhCO_2H$ (**1b**) | **−7.5** | *p*-$FPhCO_2^-$ (**1b**$^-$) | −55.0 | *p*-MePhSH (**2b**) | **−6.1** | *p*-$MePhS^-$ (**2b**$^-$) | −53.3 |
| *p*-$FPhCO_2H[NTf_2]$ | −5.1 | *p*-$FPhCO_2^-$[Bmim] | **−57.7** | *p*-$MePhSH[NTf_2]$ | −2.7 | *p*-$MePhS^-$[Bmim] | −53.1 |
| | | *p*-$FPhCO_2^-$[Bmim]$_2$ | −57.4 | | | *p*-$MePhS^-$[Bmim]$_2$ | **−56.0** |
| *p*-$MePhCO_2H$ (**1c**) | **−8.1** | *p*-$MePhCO_2^-$ (**1c**$^-$) | −58.5 | *p*-*t*BuPhSH (**2c**) | **−6.6** | *p*-*t*$BuPhS^-$ (**2c**$^-$) | −52.8 |
| *p*-$MePhCO_2H[NTf_2]$ | −6.6 | *p*-$MePhCO_2^-$[Bmim] | −60.6 | *p*-*t*$BuPhSH[NTf_2]$ | −4.0 | *p*-*t*$BuPhS^-$[Bmim] | −53.3 |
| | | *p*-$MePhCO_2^-$[Bmim]$_2$ | **−61.8** | | | *p*-*t*$BuPhS^-$[Bmim]$_2$ | **−55.9** |
| *p*-$MeOPhCO_2H$ (**1d**) | **−8.6** | *p*-$MeOPhCO_2^-$ (**1d**$^-$) | −57.5 | *p*-MeOPhSH (**2d**) | **−7.4** | *p*-$MeOPhS^-$ (**2d**$^-$) | −53.9 |
| *p*-$MeOPhCO_2H[NTf_2]$ | −5.2 | *p*-$MeOPhCO_2^-$[Bmim] | −62.9 | *p*-$MeOPhSH[NTf_2]$ | −3.5 | *p*-$MeOPhS^-$[Bmim] | −55.0 |
| | | *p*-$MeOPhCO_2^-$[Bmim]$_2$ | **−63.0** | | | *p*-$MeOPhS^-$[Bmim]$_2$ | **−57.7** |
| *p*-$ClPhCO_2H$ (**1e**) | **−8.2** | *p*-$ClPhCO_2^-$ (**1e**$^-$) | −54.6 | *p*-FPhSH (**2e**) | **−5.6** | *p*-$FPhS^-$ (**2e**$^-$) | −50.5 |
| *p*-$ClPhCO_2H[NTf_2]$ | −6.0 | *p*-$ClPhCO_2^-$[Bmim] | **−57.2** | *p*-$FPhSH[NTf_2]$ | −3.2 | *p*-$FPhS^-$[Bmim] | −52.0 |
| | | *p*-$ClPhCO_2^-$[Bmim]$_2$ | −56.9 | | | *p*-$FPhS^-$[Bmim]$_2$ | **−52.8** |
| *p*-$BrPhCO_2H$ (**1f**) | **−8.6** | *p*-$BrPhCO_2^-$ (**1f**$^-$) | −54.6 | *p*-ClPhSH (**2f**) | **−6.5** | *p*-$ClPhS^-$ (**2f**$^-$) | −49.6 |
| *p*-$BrPhCO_2H[NTf_2]$ | −6.5 | *p*-$BrPhCO_2^-$[Bmim] | **−57.6** | *p*-$ClPhSH[NTf_2]$ | −4.6 | *p*-$ClPhS^-$[Bmim] | −50.7 |
| | | *p*-$BrPhCO_2^-$[Bmim]$_2$ | −57.4 | | | *p*-$ClPhS^-$[Bmim]$_2$ | **−51.4** |
| *p*-$CF_3PhCO_2H$ (**1g**) | **−7.4** | *p*-$CF_3PhCO_2^-$ (**1g**$^-$) | −51.5 | *p*-BrPhSH (**2g**) | **−6.9** | *p*-$BrPhS^-$ (**2g**$^-$) | −49.3 |
| *p*-$CF_3PhCO_2H[NTf_2]$ | −5.1 | *p*-$CF_3PhCO_2^-$[Bmim] | **−53.8** | *p*-$BrPhSH[NTf_2]$ | −4.8 | *p*-$BrPhS^-$[Bmim] | **−51.9** |
| | | *p*-$CF_3PhCO_2^-$[Bmim]$_2$ | −53.2 | | | *p*-$BrPhS^-$[Bmim]$_2$ | −48.9 |
| *p*-$CNPhCO_2H$ (**1h**) | **−9.4** | *p*-$CNPhCO_2^-$ (**1h**$^-$) | −51.5 | *p*-$CF_3$−PhSH (**2h**) | **−6.5** | *p*-$CF_3$−$PhS^-$ (**2h**$^-$) | −45.7 |
| *p*-$CNPhCO_2H[NTf_2]$ | −7.1 | *p*-$CNPhCO_2^-$[Bmim] | **−53.5** | *p*-$CF_3$−$PhSH[NTf_2]$ | −2.2 | *p*-$CF_3$−$PhS^-$[Bmim] | **−48.5** |
| | | *p*-$CNPhCO_2^-$[Bmim]$_2$ | −52.7 | | | *p*-$CF_3$−$PhS^-$[Bmim]$_2$ | −47.8 |
| *p*- $NO_2PhCO_2H$ (**1i**) | **−8.5** | *p*- $NO_2PhCO_2^-$ (**1i**$^-$) | −49.7 | *m*-FPhSH (**2i**) | **−6.1** | *m*-$FPhS^-$ (**2i**$^-$) | −49.9 |
| *p*-$NO_2PhCO_2H[NTf_2]$ | −6.5 | *p*-$NO_2PhCO_2^-$[Bmim] | **−52.8** | *m*-$FPhSH[NTf_2]$ | −2.0 | *m*-$FPhS^-$[Bmim] | −52.0 |
| | | *p*-$NO_2PhCO_2^-$[Bmim]$_2$ | −50.7 | | | *m*-$FPhS^-$[Bmim]$_2$ | **−52.5** |
| *m*-$MeOPhCO_2H$ (**1j**) | **−8.2** | *m*-$MeOPhCO_2^-$ (**1j**$^-$) | **−57.4** | *m*-BrPhSH (**2j**) | **−6.9** | *m*-$BrPhS^-$ (**2j**$^-$) | −49.4 |
| *m*-$MeOPhCO_2H[NTf_2]$ | **−4.7** | *m*-$MeOPhCO_2^-$[Bmim] | −59.8 | *m*-$BrPhSH[NTf_2]$ | −4.8 | *m*-$BrPhS^-$[Bmim] | **−51.4** |
| | | *m*-$MeOPhCO_2^-$[Bmim]$_2$ | **−60.2** | | | *m*-$BrPhS^-$[Bmim]$_2$ | −50.9 |
| *m*-$MePhCO_2H$ (**1k**) | **−8.0** | *m*-$MePhCO_2^-$ (**1k**$^-$) | −58.3 | *m*-$CF_3$−PhSH (**2k**) | **−6.2** | *m*-$CF_3$−$PhS^-$ (**2k**$^-$) | −46.7 |
| *m*-$MePhCO_2H[NTf_2]$ | −5.8 | *m*-$MePhCO_2^-$[Bmim] | **−60.9** | *m*-$CF_3$−$PhSH[NTf_2]$ | −2.1 | *m*-$CF_3$−$PhS^-$[Bmim] | **−49.0** |
| | | *m*-$MePhCO_2^-$[Bmim]$_2$ | −60.8 | | | *m*-$CF_3$−$PhS^-$[Bmim]$_2$ | −48.5 |
| *m*-$ClPhCO_2H[NTf_2]$ (**1l**) | **−8.2** | *m*-$ClPhCO_2^-$ (**1l**$^-$) | −54.7 | $PhCH_2CO_2H$ (**1n**) | **−9.8** | $PhCH_2CO_2^-$ (**1n**$^-$) | −58.5 |
| *m*-$ClPhCO_2H[NTf_2]$ | −5.2 | *m*-$ClPhCO_2^-$[Bmim] | **−57.6** | $PhCH_2CO_2H[NTf_2]$ | −6.0 | $PhCH_2CO_2^-$ [Bmim] | **−62.6** |
| | | *m*-$ClPhCO_2^-$[Bmim]$_2$ | −57.3 | | | $PhCH_2CO_2^-$[Bmim]$_2$ | −61.9 |
| *m*-$NO_2PhCO_2H$ (**1m**) | **−8.9** | *m*-$NO_2PhCO_2^-$ (**1m**$^-$) | −51.0 | 1-adamantane-$CO_2H$ (**1o**) | **−8.4** | 1-adamantane-$CO_2^-$ (**1o**$^-$) | −57.4 |
| *m*-$NO_2PhCO_2H[NTf_2]$ | −5.5 | *m*-$NO_2PhCO_2^-$[Bmim] | −53.4 | 1-adamantane-$CO_2H[NTf_2]$ | −3.6 | 1-adamantane-$CO_2^-$[Bmim] | **−60.0** |
| | | *m*-$NO_2PhCO_2^-$[Bmim]$_2$ | **−53.8** | | | 1-adamantane-$CO_2^-$[Bmim]$_2$ | −58.2 |

[a]Units are in kcal mol$^{-1}$, $T$ = 298.15 K; minimum $\Delta G^*_{solv}(X)$ is labeled in bold.

**Solvation Free Energies of Benzoic Acids, Benzenethiols, and Their Conjugate Bases in [Bmim][$NTf_2$].** The solvation free energies of benzoic acids, benzenethiols, and their conjugate bases in [Bmim][$NTf_2$] calculated by the IB-CCM are presented in Table 1. For neutral benzoic acid (**1a**), the standard SMD calculation leads to $\Delta G^*_{solv}(PhCO_2H)$ = −7.9 kcal mol$^{-1}$, while the IB-CCM, attaching one IL anion [$NTf_2$] to benzoic acid through hydrogen-bonding interaction (see Figure S1), results in $\Delta G^*_{solv}(PhCO_2H)$ = −4.8 kcal mol$^{-1}$. Similar results were obtained for electron-donating and electron-withdrawing group substituted benzoic acids and benzenethiols (Table 1). Thus, the standard SMD approach was used for neutral species.

For the conjugate base of benzoic acid $PhCO_2^-$ (**1a**$^-$), it should be solvated by the IL cations. Given the fact that the volume of the [Bmim] cation is quite large and both sides of $PhCO_2^-$ should already be shielded well by two [Bmim] cations (see Figure S1), at most, two [Bmim] cations were considered in the first solvent shell. For the conjugate base of parent benzoic acid (**1a**$^-$), the adequate number of the IL cations in the cluster was calculated to be $n$ = 2, resulting in a solvation free energy of −61.1 kcal mol$^{-1}$. For the conjugate bases of electron-donating group substituted benzoic acids, such as *p*-$MePhCO_2^-$ (**1c**$^-$) and *p*-$MeOPhCO_2^-$ (**1d**$^-$), the adequate number of the IL cations in the cluster was calculated to be $n$ = 2, as well. On the other hand, for the conjugate bases of strong electron-withdrawing group substituted benzoic acids, such as *p*-$CNPhCO_2^-$ (**1h**$^-$) and *p*-$NO_2PhCO_2^-$ (**1i**$^-$), the adequate number of the IL cations in the cluster was calculated to be $n$ = 1. This suggested that anionic charge on the



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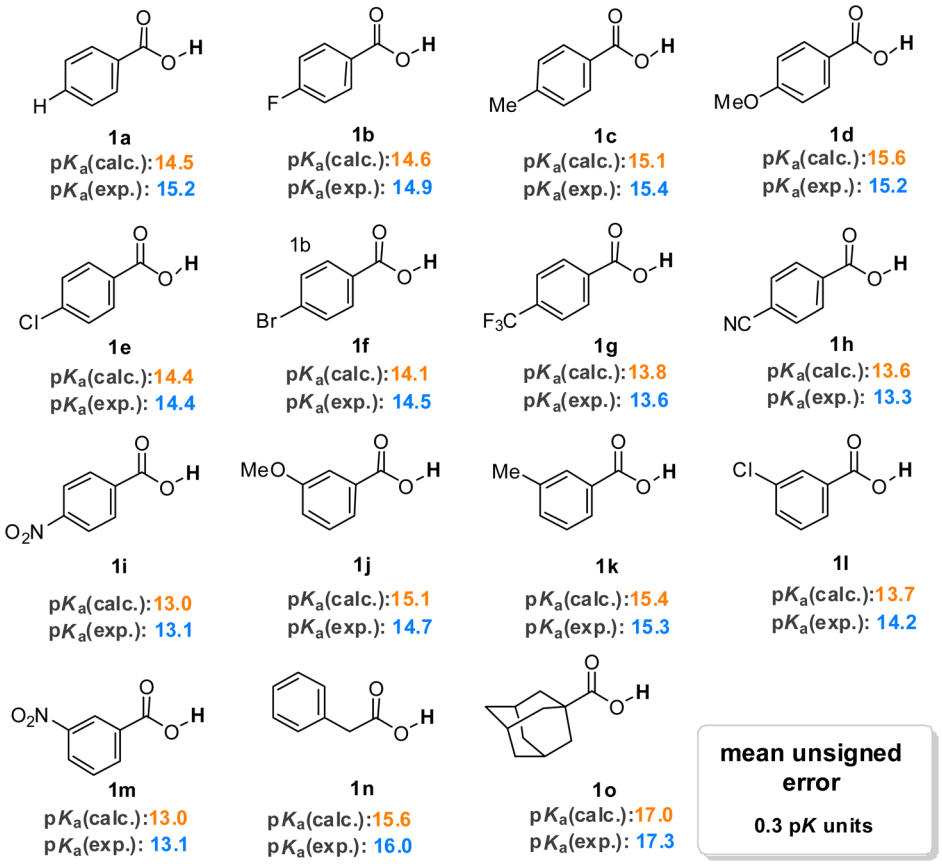


**Figure 4.** Experimental and computational p$K_a$ values of carboxylic acids in [Bmim][$NTf_2$].

carboxylate anion plays an important role in dictating the number of the IL cations in the first solvent shell. Overall, the specific solute−solvent interactions are important and should be considered explicitly for the calculation of solvation free energy of these anion species. Similar observation was made for the calculation of solvation free energy of the conjugate base of benzenethiols. Notably, the adequate number of the IL cations in the cluster was calculated to be $n$ = 1 for the conjugate anionic base of parent benzenethiol (**2a**$^-$).

**p$K_a$ of Substituted Benzoic Acids in [Bmim][$NTf_2$].** With the calculated solvation free energies in hand, the p$K_a$ values of benzoic acids (**1a**−**1o**) were calculated by using the thermodynamic cycle, as shown in Figure 1, and the results are presented in Figure 4. As can be seen, the theoretical p$K_a$ of benzoic acid (**1a**) in [Bmim][$NTf_2$] is 14.5, which is in excellent agreement with the experimental value of 15.2.[17] For substituted benzoic acids with both electron-donating and electron-withdrawing groups, their p$K_a$ values in [Bmim]-[$NTf_2$] are also accurately reproduced. The MUE was found to be only 0.3 p$K_a$ units, which is even better than the accuracy generally reported for the calculations of p$K_a$ in molecular solvents.[7,8] Moreover, the present calculation for some aliphatic carboxylic acids, such as phenylacetic acid (**1n**) and 1-adamantane carboxylic acid (**1o**), also showed excellent agreement with the corresponding experimental values (Figure 4). The plot of the calculated p$K_a$ values against the experimental data of these carboxylic acids yielded a regression equation with a slope of 1.00, an intercept of 0.06, and a correlation coefficient of 0.96 (Figure 5). Thus, we can conclude that the protocol developed herein is successful in predicting the p$K_a$ of carboxylic acids in [Bmim][$NTf_2$].

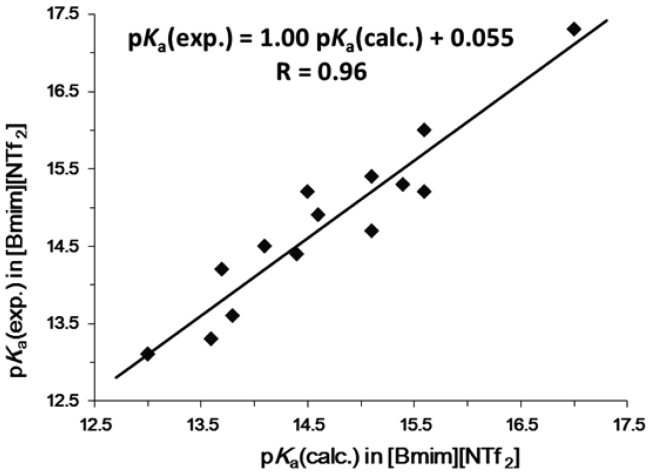


**Figure 5.** Correlation between experimental and calculated p$K_a$ values of carboxylic acids in [Bmim][$NTf_2$].

**p$K_a$ of Substituted Benzenethiols in [Bmim][$NTf_2$].** As shown above, the IB-CCM presented a high accuracy for predicting the p$K_a$ values of aromatic and aliphatic carboxylic acids in IL. To further examine its general performance, p$K_a$ values of benzenethiols (**2a**−**2k**) in [Bmim][$NTf_2$] were calculated. The resulting p$K_a$ values of benzenethiols together with their corresponding experimental values are shown in Figure 6. The theoretically predicted p$K_a$ value of benzenethiol (**2a**) is 17.4, which is in excellent agreement with the experimental value of 17.2.[18] The p$K_a$ values of the substituted benzenethiols are also well reproduced with an MUE of 0.5 p$K_a$



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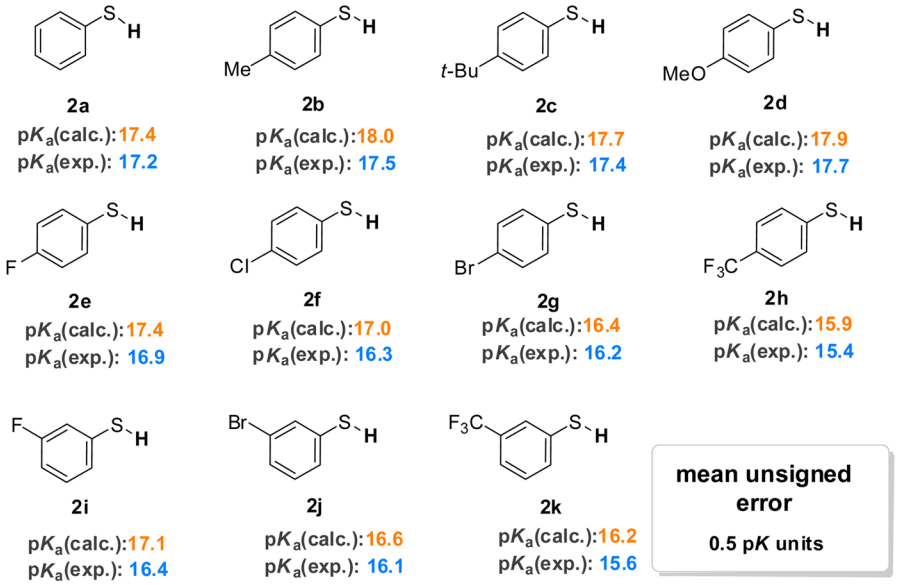


**Figure 6.** Experimental and computational p$K_a$ values of benzenethiols in [Bmim][$NTf_2$].

units. Notably, however, the MUE of calculated p$K_a$ values of benzenethiols is 0.2 p$K_a$ units larger than that of carboxylic acids, meaning a somewhat lower accuracy of the p$K_a$ calculation of benzenethiols as compared to that of carboxylic acids. Moreover, the plot of linear regression of the calculated p$K_a$ values against experimental values of benzenethiols gives a regression equation with a slope of 1.07 and an intercept of −1.74 (Figure 7), whereas the slope is 1.00 and intercept is very

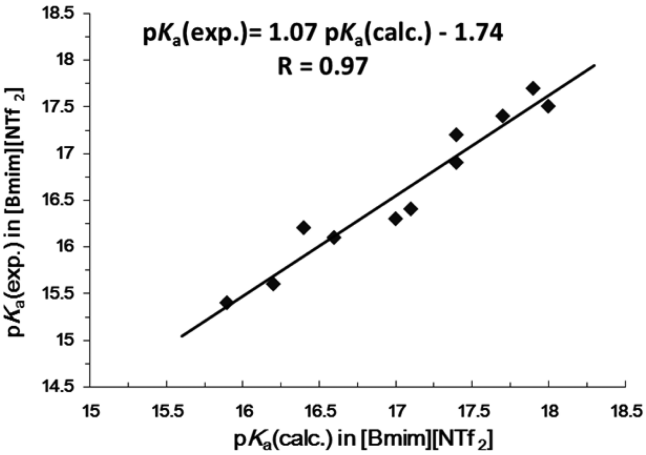


**Figure 7.** Correlation between experimental and calculated p$K_a$ values of benzenethiols in [Bmim][$NTf_2$].

close to 0 (0.055) in the case of carboxylic acids (Figure 5). Again, this indicated that the accuracy of the calculated p$K_a$ values of benzenethiols is not as good as that of carboxylic acids. The reason could be that the calculated p$K_a$ values for benzenethiols are systematically larger than their corresponding experimental values. At the present stage, it is still unclear why the p$K_a$ calculation of carboxylic acids exhibits a slightly higher accuracy than that of benzenethiols. Overall, the above outcome suggests that the IB-CCM may be generally applicable for studying thermodynamics in ILs at least for the heterolytic process, providing a possible tool to sort out the maze observed in IL chemistry.

**Origin of the Inversion of Acidity Order.** Having established a protocol that can accurately reproduce the experimental p$K_a$ values of benzoic acids and benzenethiols (26 compounds in total), we next sought to find out whether the inversed acidity order of benzoic acid (**1a**) and benzenethiol (**2a**) on going from molecular solvent DMSO to ionic liquid [Bmim][$NTf_2$] can be verified and rationalized by the computation. As shown in Table 2, the inversion of

**Table 2. Experimental and Calculated p$K_a$ in [Bmim][$NTf_2$], DMSO, and Water**

| | p$K_a$ in BmimNTf$_2$ | | p$K_a$ in DMSO | | p$K_a$ in $H_2O$ |
|---|---|---|---|---|---|
| compounds | exptl | calcd | exptl | calcd | exptl |
| $PhCO_2H$ (**1a**) | 15.2[a] | 14.5[c] | 11.0[d] | 10.0[f] | 4.2[g] |
| PhSH (**2a**) | 17.2[b] | 17.4[c] | 10.3[e] | 9.4[f] | 6.5[h] |

[a]Taken from ref 17. [b]Taken from ref 18. [c]Calculated with the ion-biased cluster-continuum model. [d]Taken from ref 19. [e]Taken from ref 20. [f]Calculated with the SMD model. [g]Taken from ref 23. [h]Taken from ref 2a.

acidity order is indeed well reproduced, as seen from the calculation outcomes. In DMSO, benzenethiol (**2a**) is computed to be a stronger acid than benzoic acid (**1a**) by 0.6 p$K_a$ units, which agrees very well with the experimental value of 0.7 p$K_a$. On the other hand, benzenethiol (**2a**) is computed to be a weaker acid than benzoic acid (**1a**) by 2.9 p$K_a$ units in [Bmim][$NTf_2$], which is also quite close to the experimental value of 2.0 p$K_a$.

Figure 8 shows that the changes in the solvation free energies of both benzoic acid (**1a**) and benzenethiol (**2a**) from DMSO to [Bmim][$NTf_2$] are negligible. The same is true for the benzenethiolate anion $PhS^-$ ($\mathbf{2a}^-$). In contrast, the solvation free energy of the benzoate anion $PhCO_2^-$ ($\mathbf{1a}^-$) in [Bmim][$NTf_2$] is 4.3 kcal $mol^{-1}$ greater than that in DMSO, which can be rationalized by considering the relatively strong Coulombic and hydrogen-bonding interactions between $PhCO_2^-$ ($\mathbf{1a}^-$) and [$Bmim^+$] compared to those in the neutral aprotic solvent DMSO. This factor appears to be the determinant for the inversion of the acidity order. On the


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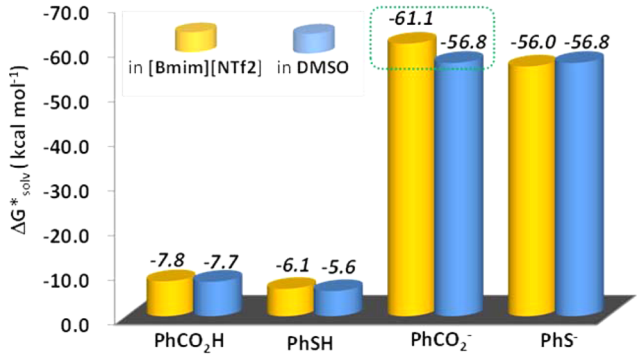


**Figure 8.** Estimated solvation free energies (in kcal $mol^{-1}$) of benzoic acid (**1a**) and benzenethiol (**2a**) and their corresponding conjugate bases in [Bmim][$NTf_2$] and DMSO.

other hand, compared to the solvation stabilization of $PhCO_2^-$ ($\mathbf{1a}^-$) in [Bmim][$NTf_2$], the solvation of $PhS^-$ ($\mathbf{2a}^-$) is not as strong, due mainly to a weaker C–H···$S^-$ hydrogen-bonding interaction between $PhS^-$ and [$Bmim^+$] as compared to the C–H···$O^-$ interaction between $PhCO_2^-$ ($\mathbf{1a}^-$) and the [$Bmim^+$] cation.[24] This can be seen from the noncovalent interaction (NCI) analysis,[25,26] which is based on analyzing the electron densities and their reduced density gradient (RDG) isosurface, for the interaction between the conjugate anionic bases and the [$Bmim^+$] cation shown in Figure 9. Clearly, the hydrogen-

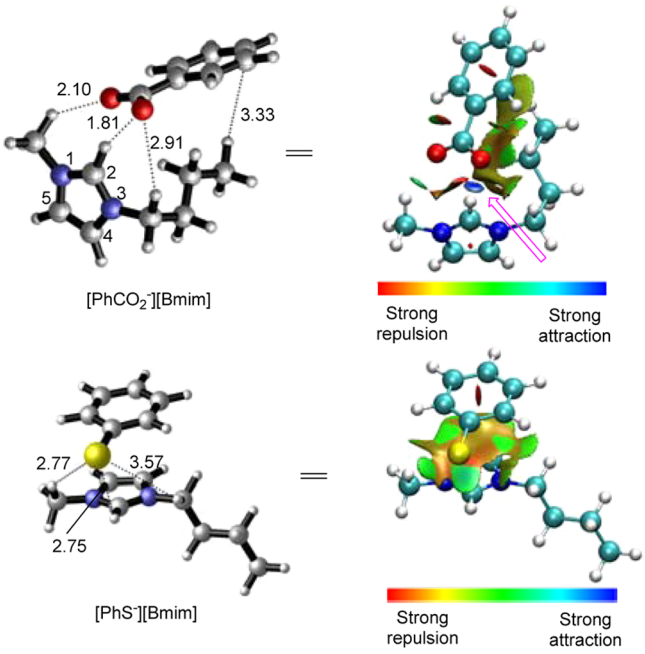


**Figure 9.** Noncovalent interaction analysis (blue, strong attraction; green, weak interaction; and red, strong repulsion) for the interaction between the conjugate anionic bases and the ionic liquid cation calculated with M06-2X/6-31+G(d,p).

bonding interaction between the hydrogen atom at the [$Bmim^+$] ring ($C_2$–H) and the oxygen atom of the $PhCO_2^-$ ($\mathbf{1a}^-$) is much stronger than the interaction between the same hydrogen atom and the sulfur atom of the $PhS^-$ (the strong attraction related to the C–H···$O^-$ hydrogen bond is displayed in blue, and weak interactions are displayed in light green). It is worth emphasizing that, as a result of a stronger interaction between [$Bmim^+$] and $PhCO_2^-$ ($\mathbf{1a}^-$) than that for [$Bmim^+$] and $PhS^-$, the adequate number of the [$Bmim^+$] cation in the inner solvation shell was calculated to be $n$ = 2 for $PhCO_2^-$ ($\mathbf{1a}^-$) but $n$ = 1 for $PhS^-$ (see Table 3). In other words, $PhCO_2^-$ ($\mathbf{1a}^-$) is solvation stabilized by two [$Bmim^+$] cations, while $PhS^-$ ($\mathbf{2a}^-$) is mainly stabilized by one [$Bmim^+$] in [Bmim][$NTf_2$]. Therefore, it is the better solvation stabilization of $PhCO_2^-$ ($\mathbf{1a}^-$) than $PhS^-$ ($\mathbf{2a}^-$) by the IL cation [$Bmim^+$] that induces the observed stronger acidity of benzoic acid than benzenethiol in [Bmim][$NTf_2$].

**Origin of Weak Acidity in Ionic Medium.** To find out why benzoic acid (**1a**) and benzenethiol (**2a**) are less acidic in ionic medium [Bmim][$NTf_2$] than in the molecular solvent DMSO, we analyzed the solvation free energies of benzoic acid and benzenethiol, their conjugate bases, and the proton in [Bmim][$NTf_2$] and DMSO. As mentioned above, the changes of the solvation free energies of benzoic acid and benzenethiol from DMSO to [Bmim][$NTf_2$] are negligible (Figure 8), and as such, it should not induce a pronounced decrease in acidity. Although the solvation free energy of the benzenethiolate anion in DMSO was predicted to be slightly greater than that in [Bmim][$NTf_2$], the small difference of only 0.8 kcal $mol^{-1}$ (or ~0.6 p$K_a$; see Figure 8) also could not justify the observed acidity decrease of nearly 7 p$K_a$ units for benzenethiol in changing from DMSO to [Bmim][$NTf_2$]. Besides, as seen from Figure 8, the benzoate anion is even 4.3 kcal $mol^{-1}$ better solvation stabilized in [Bmim][$NTf_2$] than in DMSO, which corresponds to an acidity *increase* for the parent compound in IL by about 3.1 p$K_a$ compared to that in DMSO. However, when one's attention is switched to the other side on the solvation of the proton, it is immediately noted that the reported experimental and theoretical values for the solvation free energy of the proton in DMSO are actually quite large, ranging from −273.3,[27] −270.5,[28] −268.4,[29] and −267.0[8b] kcal $mol^{-1}$, which are 9.0–15.3 kcal $mol^{-1}$ (or 6.6–11.2 p$K_a$ units) greater than the currently estimated solvation free energy of proton in [Bmim][$NTf_2$] (258.0 kcal $mol^{-1}$; see Figure 3). Therefore, it is safe to conclude that a lower degree of acidic dissociations in [Bmim][$NTf_2$] than in DMSO is mainly due to a significantly poorer solvation stabilization of the proton in the former medium. This may account also for the observed lower acidities of other acids in [Bmim][$NTf_2$] than in DMSO and water.[30]

## ■ CONCLUSIONS

In summary, we reported an accurate and effective computational methodology for the calculation of fundamental bond energetic properties in neat ionic media. With the IB-CCM protocol developed here, the absolute p$K_a$ values of two representative acid series, carboxylic acids and benzenethiols, in [Bmim][$NTf_2$] were calculated with MUE of ≤0.5 p$K_a$ units, which is at least as good as or even significantly better than the typical calculations of the p$K_a$ in the conventional molecular solvents.[7,8] Besides, the once intriguing acidity inversion found between the molecular (DMSO) and ionic ([Bmim][$NTf_2$]) phase p$K_a$ values and the counterintuitive weaker acidity in IL than in DMSO were rationalized with the assistance of computation. Considering the importance of bond energetics in promoting chemistry becoming a rational science, as well as the potential of ILs becoming a mainstream solvent category for exploring new chemistry,[9] it is believed that development of computation methodologies on the basis of the experimental facts of IL, such as the IB-CCM in the present study, will be


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Table 3. Calculated Gas-Phase Clustering Free Energies $\Delta G^*_{clust}$, Solvation Free Energy of Clusters $\Delta G^*_{solv}$, Solvation Free Energy $\Delta G^*_{solv}(X)$ of Benzoic Acid, Benzenethiol, and Their Conjugate Bases (kcal mol$^{-1}$; minimum $\Delta G^*_{solv}(X)$ in Bold), and the p$K_a$ Values in [Bmim][$NTf_2$] and DMSO

| species | $\Delta G^*_{clust}$ | $\Delta G^*_{solv}$ in [Bmim][$NTf_2$] | $\Delta G^*_{solv}(X)$ in [Bmim][$NTf_2$] | $\Delta G^*_{solv}(X)$ in DMSO | p$K_a$ (calcd) in [Bmim][$NTf_2$] | p$K_a$ (calcd) in DMSO |
|---|---|---|---|---|---|---|
| $PhCO_2H$ (**1a**) | | −7.8 | **−7.8** | **−7.7** | 14.5 | 10.0 |
| PhSH (**2a**) | | −6.1 | **−6.1** | **−5.6** | 17.4 | 9.4 |
| $PhCO_2^-$ ($\mathbf{1a}^-$) | | −57.7 | −57.7 | **−56.8** | | |
| $PhCO_2^-$[Bmim] | −88.0 | −22.5 | −59.8 | | | |
| $PhCO_2^-[Bmim]_2$ | −110.7 | −52.4 | **−61.1** | | | |
| $PhS^-$ ($\mathbf{2a}^-$) | | −52.8 | −52.8 | **−56.8** | | |
| $PhS^-$[Bmim] | −81.6 | −25.1 | **−56.0** | | | |
| $PhS^-[Bmim]_2$ | −102.8 | −54.4 | −55.8 | | | |

much in demand for eventually realizing the rational design and selection for the desired applications in ILs.

## COMPUTATIONAL DETAILS

Truhlar and co-worker's M06-2X density functional has been shown to provide accurate predictions for main group thermochemistry, kinetics, and noncovalent interactions.[31] Accordingly, geometry optimizations were conducted with the M06-2X functional combined with the 6-31+G(d,p) basis set. The nature of the stationary points was confirmed by frequency calculations at the same level of theory. To obtain reliable gas-phase acidities, single-point electronic energies were calculated at the MP2/6-311++G(2d,p) level (Table S1). For the calculation of solvation free energies using the IB-CCM, the gas-phase clustering free energy $\Delta G^*_{(clust)}[X(S)_n]$ was obtained at the M06-2X/cc-PVTZ//M06-2X/6-31+G(d,p) level of theory. For clusters that have more than one possible conformation, possible conformers were manually constructed and optimized. The conformation with the lowest free energy was singled out and used in the ensuing calculations (for details, see Figures S2−S5). The solvation free energy of the cluster was calculated by using the SMD/M06-2X/6-31+G(d,p) method with the M06-2X/6-31+G(d,p) optimized geometries. The SMD model[32] was used because it has been demonstrated to provide good accuracy for the calculation of solvation free energies for neutral solutes in ILs.[33] Solvent descriptors for [Bmim][$NTf_2$] in the SMD calculation include dielectric constant ($\varepsilon$ = 11.25), refractive index ($n$ = 1.4225), macroscopic surface tension ($\gamma$ = 56.13), Abraham's hydrogen bond acidity ($\sum\alpha_2^H$ = 0.259) and basicity ($\sum\beta_2^H$ = 0.238), the fraction of non-hydrogen atoms that are aromatic carbon atoms ($\varnothing$ = 0.1304), and the fraction of non-hydrogen atoms that are electronegative halogen atoms ($\psi$ = 0.2609).[33] Since some solvent descriptors for other ILs are still not avaliable,[33] we focused our attention on the calculation of the experimental p$K_a$ values in [Bmim][$NTf_2$] in the present study. For each species, the final Gibbs free energy $G^*_{sol}(X)$ in [Bmim][$NTf_2$] can be calculated by using the following formula:

$$G^*_{sol}(X) = E(X)_{gas} + G^\circ_{therm}(X) + \Delta G^*_{solv}(X) \quad (8)$$

In eq 8, $E(X)_{gas}$ is the electronic energy (including nuclear repulsion) obtained at the MP2/6-311++G(2d,p)//M06-2X/6-31+G(d,p) level of theory, $G^\circ_{therm}(X)$ is the thermal contribution to Gibbs free energy in the gas phase obtained at the M06-2X/6-31+G(d,p) level of theory. The last term $\Delta G^*_{solv}(X)$ in eq 8 is solvation free energy obtained by using the eq 7 in Figure 2. All energetics reported throughout the text are in kcal mol$^{-1}$, and the bond lengths are in angstroms (Å). Structures were generated using CYLview[34] and VMD.[35] All calculations were performed with Gaussian 09.[36]

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00693.

Figures S1−S5, complete citation for ref 36, and optimized geometries and energies of all computed species (PDF)

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### Notes

The authors declare no competing financial interest.

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