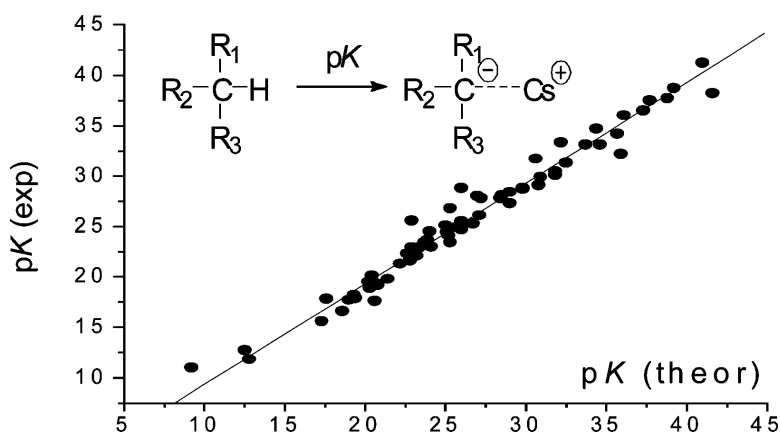


## First-Principle Calculation of Equilibrium Cesium Ion-Pair Acidities in Tetrahydrofuran

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## First-Principle Calculation of Equilibrium Cesium Ion-Pair Acidities in Tetrahydrofuran

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**Abstract:** The ion-pair acidities of organic acids in THF are fundamental to synthetic organic chemistry. Although the ion-pair acidities of a number of carbon acids have been experimentally measured by Streitwieser and co-workers, it is important to develop a theoretical method that can accurately predict these quantities because not all the organic acids (e.g., very weak acids or complex synthetic intermediates with multiple acidic positions) are amenable to experimental characterization. In the present study is reported the first theoretical protocol for predicting the cesium ion-pair acidities in THF whose reliability has been tested against almost all the available experimental data. It is found that the root-mean-square error of the current theoretical model equals 1.2 pK units. With the newly developed theoretical method in hand, the structures of cesium ion pairs of different types of carbon acids are then studied. The cesium ion-pair acidities in THF and absolute ionic acidities in DMSO are also systematically compared, which confirms Streitwieser's previous finding that the two scales of acidities have only minor difference. Significantly, from detailed energy analysis the mechanism for the "fortunate" match of the two scales of acidities is found. That is, the combined process of the Cs binding ("micro"-solvation) and the solvation of the ion pair resembles the one-step solvation of a carbanion in DMSO. Finally, it is found that the cesium ion-pair acidities of nitrogen acids in THF have only minor difference from the absolute ionic acidities in DMSO. Consequently, one can easily estimate the cesium ion-pair acidities of almost all types of organic nitrogen acids in THF on the basis of Bordwell's data.

### 1. Introduction

The use of carbanion intermediates for the formation of carbon-carbon bonds is an important method in synthetic organic chemistry.<sup>1</sup> These carbanions are usually generated through the abstraction of a proton from weak carbon acids by appropriate bases. For the deprotonation to proceed successfully, a fundamental requirement is that the thermodynamic acidity of the carbon acid should be higher than the acidity of the base-H bond. Thus, in order to facilitate the synthetic studies involving the use of carbanions, there is a need to know the equilibrium acidities of the C-H bonds in various types of weak carbon acids in the organic solvents.

Thanks to the systematic studies by a number of eminent researchers over the past few decades, we currently have several quantitative equilibrium acidity scales available for weak carbon acids. One of the scales was mainly developed by Bordwell and co-workers for the acidities in DMSO, where it was believed that the deprotonated carbanions should exist as monomeric anions due to the high ionizing power of DMSO.<sup>2</sup> Another famous scale was developed by Streitwieser and co-workers for the acidities in THF, which is probably more useful for the

synthetic chemists because of the widespread use of THF as a solvent in carbanion reactions.<sup>3</sup>

Noteworthy, THF has a relatively low dielectric constant, and therefore, the carbanion intermediate must exist as an ion pair in THF. To address this ion-pair problem, Streitwieser and co-workers proposed to measure the equilibrium ion-pair acidity where the relative acidities of carbon acid pairs were evaluated by spectroscopic determination of the equilibrium constant for the reaction 1



Eventually the relative carbon acidities were placed on an absolute basis by assigning a pK to fluorene of 22.9. With the use of this approach a scale of hydrocarbon acidities in THF has been successfully developed which spanned a range of about 40 pK units.

The validity of the above cesium ion-pair acidities was based on the assumption that the cesium salts of carbanions should exist in the form of monomeric contact ion pairs at low concentrations. This assumption has been carefully examined by Streitwieser and co-workers through their elegant studies on

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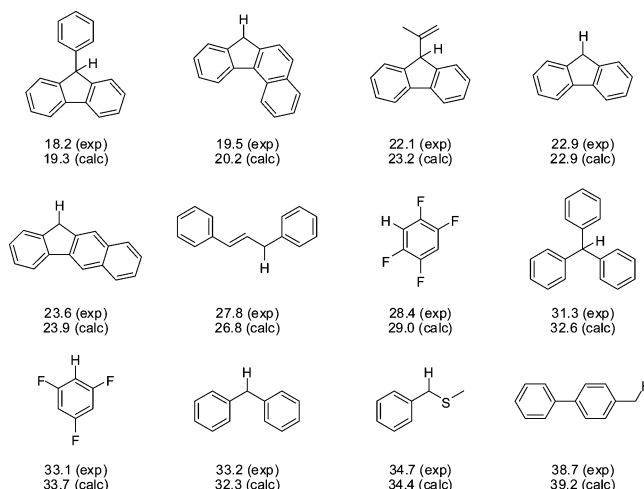
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ion-pair aggregations in THF.<sup>4</sup> Nonetheless, it must be pointed out that up to now little detail has been obtained about the structures and properties of such cesium–carbon ion pairs by direct experimental or theoretical approaches. Furthermore, there have been few theoretical methods developed to quantitatively interpret or predict the cesium ion-pair acidities.<sup>5</sup>

In the present study we attempted to bridge the gap by developing the first theoretical method to accurately calculate the cesium ion-pair acidities of various carbon acids. This study was encouraged by our recent successes in developing ab initio theoretical protocols to calculate the absolute ionic acidities of various organic acids in DMSO and MeCN.<sup>6</sup> In comparison to the previous work, an important challenge encountered in the present study was the involvement of an inorganic cesium cation. This cost us a considerable amount of modeling time through trials and errors because very few theoretical studies had been reported about organocesiums before this work.<sup>7</sup>

## 2. Method Development

Because of the large size of the cesium atom, it is not feasible to use any complete electron basis set to model organocesiums. This forces us to examine the utilization of an effective core potential (ECP) for cesium,<sup>8</sup> which not only reduces the number of electrons to be treated explicitly in the calculation, but also accounts for the relativistic effects essential in treating the core electrons of heavy elements. Noteworthy, Streitwieser and co-workers recently reported the use of the Hay–Wadt ECP and the Ross ECP for cesium.<sup>5</sup> In our own work, we decide to examine the performances of the Hay–Wadt ECP (in the form of Lanl2dz ECP) and its augmented version, Lanl2dz+p.<sup>9</sup> We

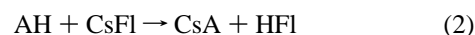


**Figure 1.** Twelve representative carbon acids tested for the method development.

also decide to examine the more recent Stuttgart–Dresden SDD ECP, which was previously claimed to be slightly superior to Lanl2dz.<sup>10</sup> Furthermore, we employ the commonly used basis sets such as 6-31G\* and 6-311+G(2df,2p) to describe the C, N, O, and S atoms.

As to the selection of computational methods, we focus on the density functional theory (DFT) methods. One reason for this particular choice is that the DFT methods include electron correlation per definition. Furthermore, because we hope to develop a theoretical protocol that can handle organic acids containing 10–20 non-hydrogen atoms, it appears obligatory to use the DFT methods which can dramatically decrease the CPU time versus ab initio methods of similar accuracy. As to the density functionals, we decide to compare the commonly used B3LYP, B3P86, B3PW91, and PBEPBE functionals.<sup>11</sup> Finally, on the basis of our previous studies we decide to use the IEF-PCM (integral equation formalism of polarizable continuum model) method to calculate the solvation energies, where the performances of two types of atomic radii (i.e., united atom topological model, UA0 radii and Bondi radii) are compared for the construction of a solvent-inaccessible cavity in which the solute molecule resides.<sup>12</sup>

Having selected a number of theoretical methods, we next need to derive the equations to calculate the cesium ion-pair acidities. To this end we consider the following proton-exchange reaction between the cesium salt of fluorene (CsFl) and an organic acid (AH),



If the free energy change of the above reaction in the THF solution is defined as  $\Delta G_{\text{exchange}}$ , the cesium ion-pair acidity (pK) of the acid can be readily calculated by eq 3.

$$\text{pK}(\text{AH}) = 22.9 + \frac{\Delta G_{\text{exchange}}}{2.303RT} \quad (3)$$

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**Table 1.** Performances of Different Methods for the 12 Representative Carbons Acids

entry	DFT	basis set for geometry optimization	basis set for energy calculation	solvation model	rms error	maximum error
1	B3LYP	Lan12dz	Lan12dz+p/6-311G**	IEFPCM/UA0	1.0	2.2
2	B3LYP	Lan12dz	Lan12dz+p/6-311G**	IEFPCM/Bondi	1.2	2.7
3	B3LYP	Lan12dz+p/6-31G*	Lan12dz+p/6-311+G(2df,2p)	IEFPCM/UA0	1.2	1.9
4	B3LYP	Lan12dz+p/6-31G*	Lan12dz+p/6-311+G(2df,2p)	IEFPCM/Bondi	1.2	2.4
5	B3LYP	SDD/6-31G*	SDD/6-311+G(2df,2p)	IEFPCM/UA0	1.2	1.6
6	B3LYP	SDD/6-31G*	SDD/6-311+G(2df,2p)	IEFPCM/Bondi	1.2	1.8
7	B3P86	Lan12dz+p/6-31G*	Lan12dz+p/6-311+G(2df,2p)	IEFPCM/UA0	0.9	1.6
8	B3P86	Lan12dz+p/6-31G*	Lan12dz+p/6-311+G(2df,2p)	IEFPCM/Bondi	0.9	1.7
9	B3P86	SDD/6-31G*	SDD/6-311+G(2df,2p)	IEFPCM/UA0	1.0	1.6
10	B3P86	SDD/6-31G*	SDD/6-311+G(2df,2p)	IEFPCM/Bondi	1.1	1.8
<b>11</b>	<b>B3PW91</b>	<b>Lan12dz+p/6-31G*</b>	<b>Lan12dz+p/6-311+G(2df,2p)</b>	<b>IEFPCM/UA0</b>	<b>0.8</b>	<b>1.3</b>
12	B3PW91	Lan12dz+p/6-31G*	Lan12dz+p/6-311+G(2df,2p)	IEFPCM/Bondi	1.0	1.9
13	B3PW91	SDD/6-31G*	SDD/6-311+G(2df,2p)	IEFPCM/UA0	0.9	1.4
14	B3PW91	SDD/6-31G*	SDD/6-311+G(2df,2p)	IEFPCM/Bondi	1.0	1.8
15	PBEPBE	Lan12dz+p/6-31G*	Lan12dz+p/6-311+G(2df,2p)	IEFPCM/UA0	1.3	2.4
16	PBEPBE	Lan12dz+p/6-31G*	Lan12dz+p/6-311+G(2df,2p)	IEFPCM/Bondi	1.6	2.9
17	PBEPBE	SDD/6-31G*	SDD/6-311+G(2df,2p)	IEFPCM/UA0	1.3	2.4
18	PBEPBE	SDD/6-31G*	SDD/6-311+G(2df,2p)	IEFPCM/Bondi	1.6	2.9

Using eq 3 and 12 representative carbon acids (Figure 1), we then systematically test the performances of all the possible combinations of theoretical methods aforementioned. The results of these tests are shown in Table 1.

From the results in Table 1 we find that the performances of the B3LYP, B3P86, and B3PW91 methods are close to each other, whereas the PBEPBE method provides noticeably worse results. Increasing the flexibility of the basis set does not significantly improve the rms (root of mean square) errors, but it definitely reduces the maximum errors. For most of the methods the SDD ECP provides similar results as compared to the Lan12dz ECP. Finally, use of the UA0 radii tends to provide better results than the use of Bondi radii. On the basis of these findings, we conclude that the optimal method should be a combination of B3PW91/Lan12dz/6-31G\* for geometry optimization, B3PW91/Lan12dz+p/6-311+G(2df,2p) for energy calculation, and IEF/PCM/UA0 for solvation energy calculation. The rms error for this method is 0.8 pK unit for the 12 carbon acids, and the corresponding maximum error is only 1.3 pK units.

### 3. An Extensive Theoretical Scale of Cesium Ion-Pair Acidities

Having optimized a theoretical protocol that can handle 12 carbon acids, we next examine whether the same method can be applied to all the other carbon acids that have been experimentally studied. To this end we have systematically calculated the cesium ion-pair acidities for 65 structurally unrelated carbon acids, using the same theoretical protocol as described in the previous section.

Our calculation results are listed in Table 2. It is found that the newly developed theoretical protocol can successfully predict the cesium ion-pair acidities for all the 65 carbon acids whose pK values range from about 10 to 45 (Figure 2). The correlation coefficient between the experimental and theoretical pK values is as high as 0.9854, and the rms error is only 1.2 pK units. On the basis of these data, we conclude that the theoretical method developed here can be used to predict the cesium ion-pair acidity of structurally unrelated weak carbon acids with an error bar of 1.2 pK units. Although such a magnitude of error bar is larger

than the experimental errors ( $\pm 0.2$  to  $\sim 0.5$  pK units), the current theoretical method may be very helpful in the study of chemical species (e.g., reaction intermediates and weak acids) that are not readily amenable to experimental characterization. Noteworthy, some very weak ( $pK \sim 40$ ) and very strong ( $pK \sim 10$ ) acids appear not to correlate well in Figure 2. As to the weak acids there may exist the aggregation problem, whereas for the strong acids the hydrogen-bonding interaction between the acid and the solvent may be too strong to be accurately handled by the continuum solvation model.

## 4. Discussion

**4.1. Structures of Organocesiums.** As mentioned above, little has been known in the past about the structures of organocesiums. To make the situation worse, most existing crystal structures of cesium compounds often show extended networks not suitable for modeling with computations of isolated single molecules. Therefore, we have to create and then optimize the structure of each cesium ion pair from scratch, where all the possible conformers need to be calculated and compared. Fortunately it is found that different density functionals and basis sets always provide very similar optimized structures. The good agreement between different methods gives us confidence about the modeling results.

**4.1.1. Cesium- $\pi$  Systems.** For the cesium salts of cyclopentadiene derivatives (e.g., fluorene) or carbon acids carrying a neighboring phenyl group (e.g., triphenylmethane), the optimal structure can be described as a cation- $\pi$  complex. In the complex the cesium cation is seated above the  $\pi$  plane by about 3 Å, whereas the  $\pi$  plane is curved slightly toward the cesium cation (Figure 3a).

**4.1.2.  $\sigma$ -Carbanion Systems.** For the cesium salts of arenes (e.g., 1,2,4,5-tetrafluorobenzene) and 1,3-dithianes, the negative charge is centered at a single carbon atom leading to a  $\sigma$ -carbanion structure (Figure 3b). However, due to the possible chelation effect the cesium cation tends to be tilted to the neighboring heteroatoms.

**4.1.3. Enolates.** For the cesium salts of carbonyl compounds, the cesium cation is located closer to the carbonyl oxygen as compared to the  $\alpha$ -carbon consistent with the classical enolate structure (Figure 3c). In the cases where the enolate carries a

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




**Table 2.** Cesium Ion-Pair Acidities in THF vs Absolute Ionic Acidities in DMSO

Entry	Structure	Cesium ion-pair acidity in THF		Absolute ionic acidity in DMSO		Cesium affinity (kcal/mol)
		Exp <sup>a</sup>	Theor	Exp <sup>b</sup>	Theor	
1		11.0	9.2		5.3	-96.2
2		11.8	12.8	11.5	10.6	-80.3
3		12.7	12.5		11.6	-79.4
4		15.6	17.3		15.0	-77.6
5		16.6	18.6		18.1	-83.4
6		17.6	20.6	18.8	17.4	-80.7
7		17.7	19.0		17.0	-76.9
8		17.8	17.6		15.4	-84.1
9		17.9	19.4		17.4	-77.9
10		18.2	19.3	17.9	18.0	-79.4
11		18.9	20.3		18.5	-76.2
12		19.2	20.8		18.7	-81.1
13		19.3	20.7		18.7	-84.2
14		19.5	20.2		19.1	-81.1
15		19.8	21.4		20.1	-87.5
16		20.1	20.4		19.3	-80.7
17		21.3	22.2		21.4	-82.3
18		21.6	22.8	21.5	22.8	-80.8
19		22.1	23.2		22.8	-81.8
20		22.3	22.6	22.3	22.6	-82.9
21		22.9	22.9	22.9	22.9	-83.5
22		22.9	23.4		22.7	-82.7
23		23.0	24.1		23.4	-84.0
24 <sup>c</sup>		23.4	23.7	24.7	23.8	-88.7

Table 2 (Continued)

Entry	Structure	Cesium ion-pair acidity in THF		Absolute ionic acidity in DMSO		Cesium affinity (kcal/mol)
		Exp <sup>a</sup>	Theor	Exp <sup>b</sup>	Theor	
25		23.4	25.3		21.7	-86.3
26		23.6	23.9		23.0	-79.4
27 <sup>c</sup>		24.1	25.2		24.4	-93.7
28		24.4	25.1		25.2	-81.9
29 <sup>c</sup>		24.5	24.0		22.9	-89.7
30 <sup>c</sup>		24.7	26.0	26.3	25.7	-87.0
31		24.9	25.7		24.1	-84.7
32		25.1	25.0		22.5	-86.6
33		25.3	26.7		24.6	-84.0
34		25.5	26.0		26.9	-87.5
35		25.6	22.9		21.9	-72.0
36		26.1	27.1		28.6	-87.2
37		26.8	25.3		23.0	-75.2
38		27.3	29.0	29.5	28.0	-91.4
39		27.8	28.4		28.0	-78.4
40		27.8	27.2		25.5	-75.9
41		28.0	27.0		26.6	-83.8
42		28.1	28.5		28.6	-80.8
43		28.4	29.0		27.9	-84.1
44		28.7	29.8		28.1	-76.1
45	$\text{NCCH}_2\text{Si}(\text{CH}_3)_3$	28.8	26.0		26.0	-84.7
46	$\text{CH}_3\text{SO}_2\text{CH}_2\text{-H}$	28.8	29.8		30.5	-96.0
47		29.1	30.8	29	29.2	-75.2
48		29.9	30.9		29.6	-84.7
49		30.1	31.8		29.2	-72.7
50		30.5	31.8	30.7	31.2	-79.6
51	$\text{Ph}_3\text{CH}$	31.3	32.5		31.1	-76.2
52		31.7	30.6		29.5	-77.1
53		32.2	35.9		35.3	-84.8
54	$(p\text{-MePh})_3\text{CH}$	33.1	34.6		32.7	-77.4

Table 2 (Continued)

Entry	Structure	Cesium ion-pair acidity in THF		Absolute ionic acidity in DMSO		Cesium affinity (kcal/mol)
		Exp <sup>a</sup>	Theor	Exp <sup>b</sup>	Theor	
55		33.1	33.7		31.5	-87.6
56	Ph <sub>2</sub> CH <sub>2</sub>	33.3	32.2		32.5	-82.1
57	( <i>o</i> -MePh) <sub>2</sub> CH <sub>2</sub>	34.2	35.7		35.9	-80.4
58	PhCH <sub>2</sub> SCH <sub>3</sub>	34.7	34.4		35.0	-81.8
59	( <i>o,p</i> -biMePh) <sub>2</sub> CH <sub>2</sub>	36.0	36.1		34.0	-81.7
60		36.5	37.3	39.3	42.0	-97.7
61	PhCH <sub>2</sub> Si(CH <sub>3</sub> ) <sub>3</sub>	37.5	37.7		38.8	-83.0
62		37.7	38.8		37.4	-79.7
63		38.2	41.6		44.8	-95.5
64		38.7	39.2		39.4	-81.2
65	PhCH <sub>3</sub>	41.2	41.0	43.5	42.8	-88.8

<sup>a</sup> Experimental data collected from ref 3. They are converted to acidities per hydrogen. <sup>b</sup> Experimental data collected from ref 2. They are converted to acidities per hydrogen. <sup>c</sup> These Cs enolates are known to be aggregated in THF solution, and their p*K*'s vary with concentration.

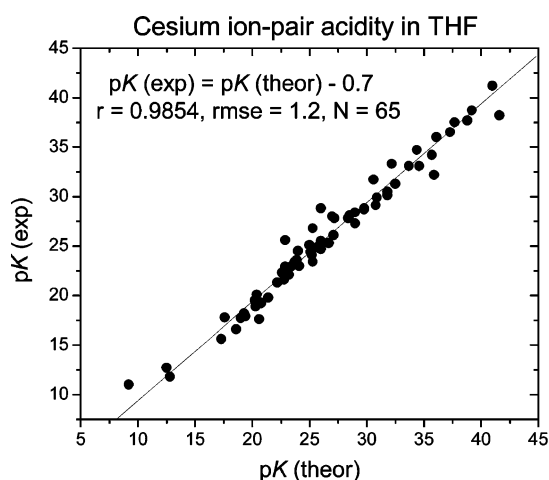


Figure 2. Correlation between the experimental and theoretical cesium ion-pair acidities.

neighboring phenyl group, the cesium cation is also tilted to the  $\pi$  electrons of the aromatic ring.

Noteworthy, cesium ion pairs of ketones may exist as aggregates in solution rather than monomers,<sup>3c,f,i,j</sup> but we only consider the monomer ion pairs in the present study. The calculated p*K*'s for ketones are found to agree with the experimental values, either fortuitously, or because the aggregates have p*K*'s close to the monomeric ion pairs.

**4.2. Cesium Ion-Pair Acidities in THF versus Absolute Ionic Acidities in DMSO.** Streitwieser et al. previously reported that a comparison between cesium relative ion-pair acidities in THF and absolute ionic acidities measured in DMSO revealed only minor differences.<sup>13</sup> This conclusion was made on the basis of a limited number of available experimental data (specifically, for the 65 cesium ion-pair acidities reported by Streitwieser et al., only 13 of them have the corresponding p*K*<sub>a</sub> values measured in DMSO). Here we decide to obtain a full list of the cesium ion-pair acidities in THF and absolute ionic acidities in DMSO for all the 65 compounds. This will allow us to reexamine the relationship between the two scales of acidities more confidently.

To calculate the p*K*<sub>a</sub> values in DMSO, we use the following isodesmic equation

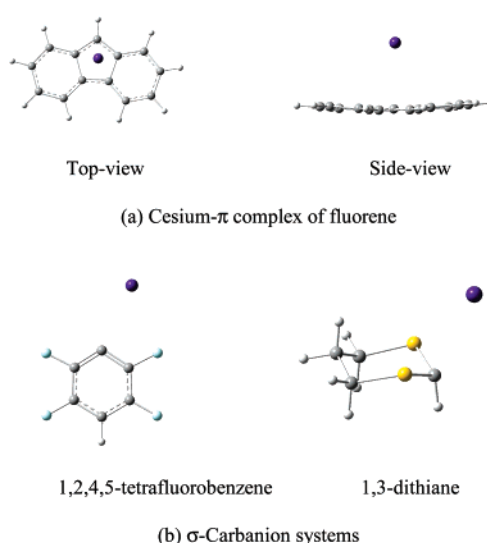
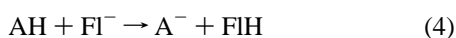


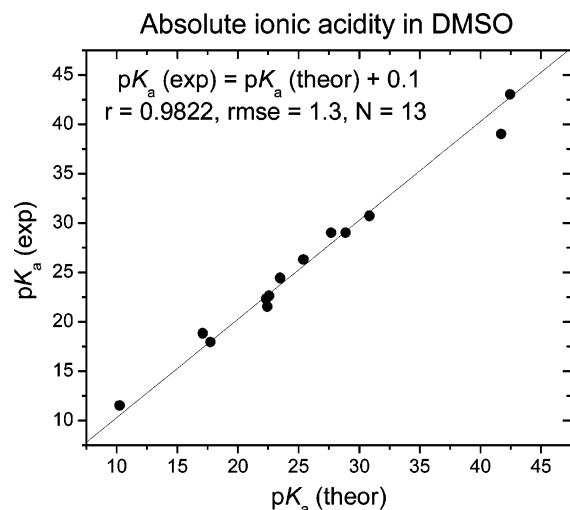
Figure 3. Three-dimensional structures for representative cesium ion pairs.

where FI is fluorene that has a p*K*<sub>a</sub> value of 22.6 in DMSO. If the free energy change of the above reaction in DMSO is calculated to be  $\Delta G_{\text{exchange}}$ , the p*K*<sub>a</sub> value of AH can be readily calculated by eq 5.

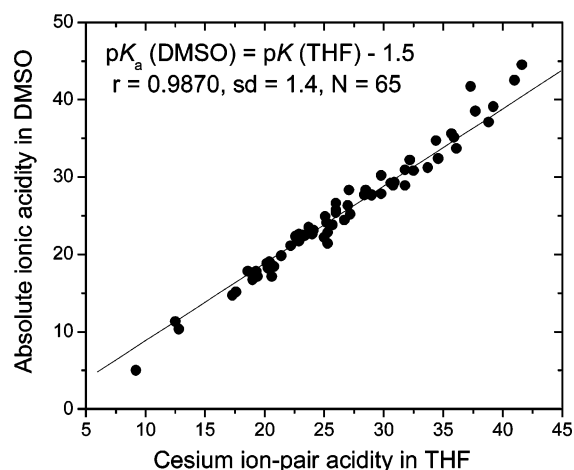
$$\text{p}K_{\text{a}}(\text{AH}) = 22.6 + \frac{\Delta G_{\text{exchange}}}{2.303RT} \quad (5)$$

Using eq 5 we have calculated the absolute ionic p*K*<sub>a</sub> values for all the 65 compounds listed in Table 2. Comparing the calculated values with available experimental data (Figure 4),

(13) Streitwieser, A., Jr.; Bors, D. A.; Kaufman, M. J. *Chem. Commun.* **1983**, 1394.



**Figure 4.** Correlation between the experimental and theoretical  $pK_a$ 's in DMSO.

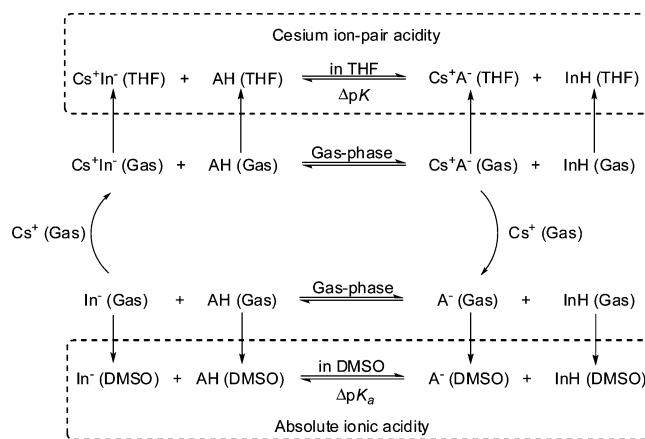


**Figure 5.** Correlation between the cesium ion-pair acidities in THF and the absolute ionic acidities in DMSO. The slope of this linear correlation is set to 1.00.

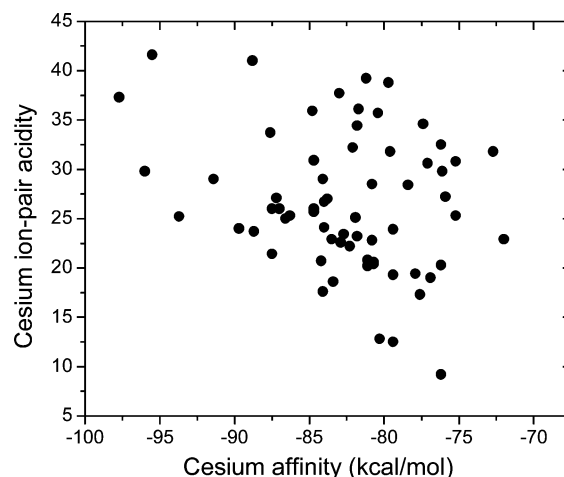
we find that the theoretical  $pK_a$ 's match the experimental values excellently over a large  $pK_a$  range (from about 10 to 45). The mean error of the calculation is  $+0.1 pK_a$  unit, while the rms error equals  $1.3 pK_a$  units.

Figure 4 indicates that the theoretical  $pK_a$  values in DMSO are trustworthy. Comparing the cesium ion-pair acidities in THF and the absolute ionic acidities in DMSO for all the 65 carbon acids (Figure 5), we find that the two scales of acidities are linearly correlated to each other with a systematic deviation of  $1.5 pK$  units. Thus, our conclusion drawn from a more extensive comparison is in good agreement with Streitwieser's previous conclusion made on the basis of a limited number of experimental data. That is, for the same carbon acid the cesium relative ion-pair acidity in THF and absolute ionic acidity in DMSO have only a minor difference.

**4.3. Why Do the Acidities of Hydrocarbon Acids Appear to be Insensitive to External Solvent Effects?** Considering the minor difference between the cesium ion-pair acidities in THF with the absolute ionic acidities in DMSO, one may conclude that the acidity of the hydrocarbon acids is insensitive to solvent effects. In view of the marked difference in solvent properties, the match of  $pK_a$  values in different solvents is remarkable but fortunate. Here we attempt to understand why



**Figure 6.** Individual contributions of every ionization and solvation process to the  $pK$  and  $pK_a$  calculations.



**Figure 7.** Lack of correlation between the cesium ion-pair acidities of carbon acids (theoretical) and the cesium affinities of the corresponding carbanions (theoretical).

the acidities of hydrocarbon acids are insensitive to the solvent effects by looking into the individual contributions of different solvation processes.

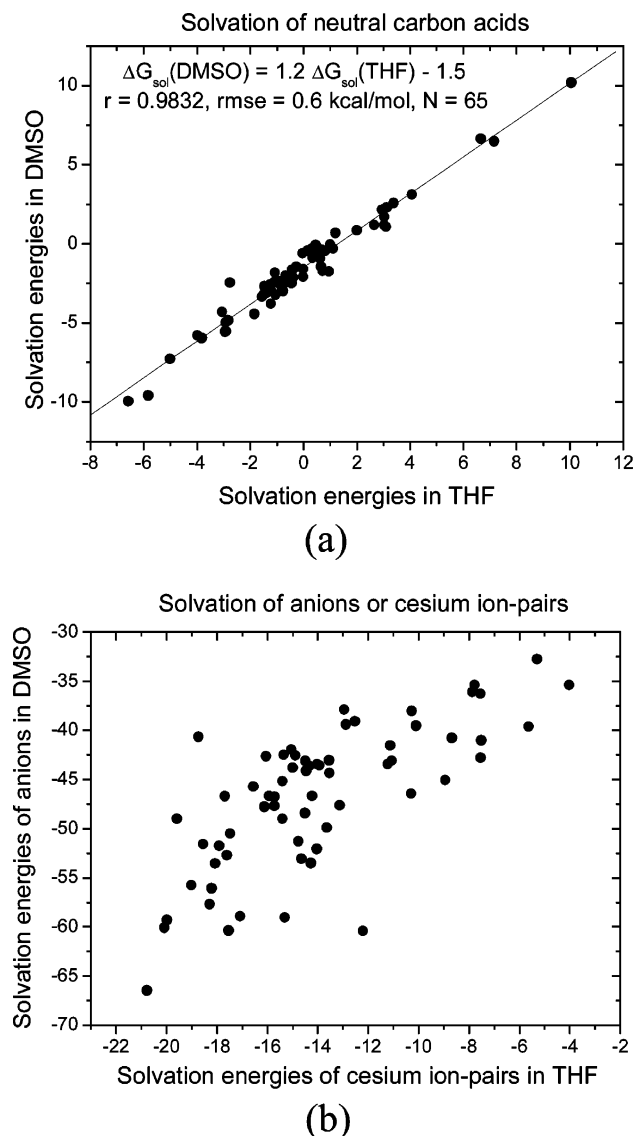
As shown in Figure 6, the difference between the cesium ion-pair acidity calculation (i.e., the calculation of  $\Delta pK$ ) and the absolute ionic acidity calculation (i.e., the calculation of  $\Delta pK_a$ ) for the same carbon acid AH can be attributed to the following terms: (i) the gas-phase binding of  $Cs^+$  with the carbanion  $A^-$  (note: both processes involve an identical deprotonation step), (ii) the solvation of AH (or InH) in THF versus the solvation of AH (or InH) in DMSO, and (iii) the solvation of  $A^-Cs^+$  (or  $In^-Cs^+$ ) in THF versus the solvation of  $A^-$  (or  $In^-$ ) in DMSO.

As to the gas-phase binding of  $Cs^+$  with the carbanion  $A^-$ , we have calculated the cesium affinities for all the 65 carbon acids shown in Table 2. Here the cesium affinity is defined as the free energy change of the following equation in the gas phase



We are surprised to find that the cesium ion-pair acidities exhibit a very poor correlation with the cesium affinities (Figure 7). Noteworthy, the cesium affinities for the 65 carbanions vary widely from about  $-100$  to  $-70$  kcal/mol. The absence of a good correlation between the cesium affinities and the cesium



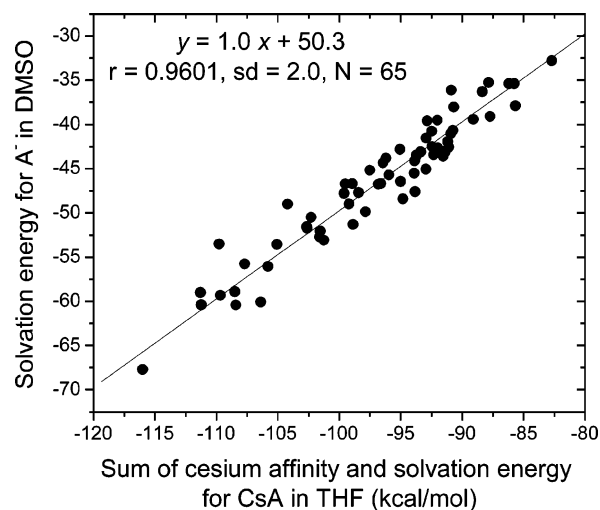


**Figure 8.** Correlation between the solvation energies of AH in THF and the solvation energies of AH in DMSO (a) and correlation between the solvation energies of the cesium ion pairs in THF and the solvation energies of the carbanions in DMSO (b).

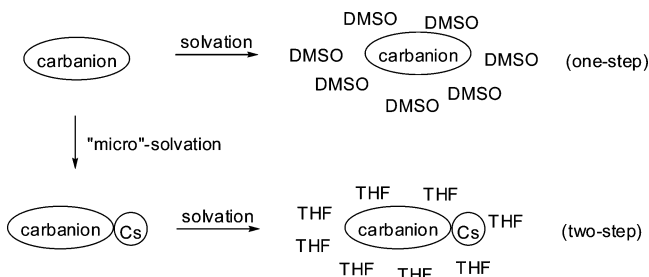
ion-pair acidities means that there must be a certain term in the  $pK_a$  calculation to counterbalance the irregular variation of cesium affinities.

As to the solvation of AH in THF versus the solvation of AH in DMSO, we find that the two solvation energies correlate with each other very nicely (Figure 8a). The slope (i.e., 1.2) of the correlation is close to unity, while the intercept ( $-1.5$  kcal/mol) is close to zero. On the other hand, as to the solvation of  $A^-Cs^+$  in THF versus the solvation of  $A^-$  in DMSO, we find that these two solvation energies do not have a good correlation with each other (Figure 8b). This means that the solvation of the neutral acids in different solvents will not cause a change of  $pK_a$  values in different solvents, whereas the solvation of carbanions versus the solvation of cesium ion pairs appears not consistent with the match of  $pK_a$  values in different solvents.

Given the fact that the cesium affinities have a very poor correlation with the cesium ion-pair acidities, we hypothesize that the binding between a carbanion and a cesium cation in



**Figure 9.** Correlation between the solvation energy for carbanions in DMSO and the sum of the cesium affinity and the solvation energy of cesium ion pair in THF.



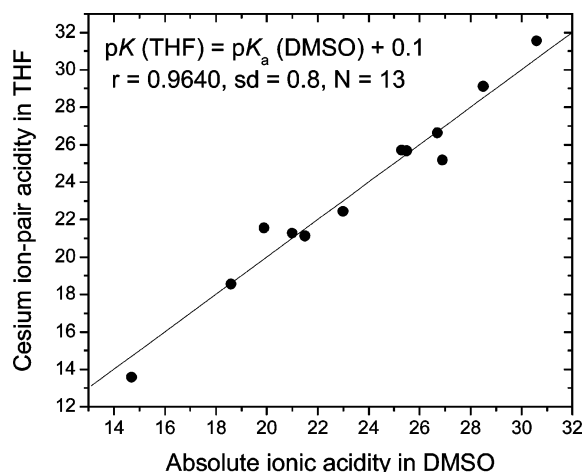
**Figure 10.** One-step solvation in DMSO vs two-step solvation in THF.

THF more or less resembles a “micro”-solvation process (which means that the solvated molecule interacts with its neighboring species). If this hypothesis is correct, then the two-step process (i.e., formation of a cesium ion pair and subsequent solvation of this ion pair in THF) should resemble the one-step solvation of a carbanion in DMSO. To test this hypothesis, we calculate the sum of the cesium affinity and the solvation energy of cesium ion pair in THF. We then plot this quantity against the solvation energy for the corresponding carbanions in DMSO (Figure 9).

Much to our pleasure we find that the two quantities indeed correlate very well with each other. The slope of the correlation equals unity, whereas the correlation coefficient is 0.9601. This confirms our theoretical model where the overall process of the Cs binding (“micro”-solvation) and the solvation of the ion pair resembles the one-step solvation of a carbanion in DMSO (Figure 10). Noteworthy, the cesium affinity of fluorene (the indicator) is  $-47.8$  kcal/mol, whose absolute value is very close to the intercept of the above correlation (i.e.,  $+50.3$ ). Because the cesium ion-pair acidity is measured as a relative value compared to fluorene, it is now easy to understand why the cesium ion-pairs’ acidities in THF are so close to the absolute ionic acidities in DMSO.

#### 4.4. Cesium Ion-Pair Acidities of Organic Nitrogen Acids.

In addition to carbanions, nitrogen-centered anions are also common reagents in synthetic organic chemistry ranging from amidation reactions to nitrogen heterocycle transformations. THF is often used as an inert and, therefore, ideal solvent for the reactions involving nitrogen anions. Due to the relatively low dielectric constant of THF, we expect that nitrogen anion



**Figure 11.** Correlation between the cesium ion-pair acidities in THF and the absolute ionic acidities in DMSO for organic nitrogen acids.

**Table 3.** Cesium Ion-Pair Acidities in THF vs Absolute Ionic Acidities in DMSO for Organic Nitrogen Acids

Entry	Structure	Cesium ion-pair acidity in THF (Theor)	Absolute ionic acidity in DMSO (Exp <sup>a</sup> )
1		13.6	14.7
2		18.6	18.6
3		21.5 (exp: 19.2)	19.9
4		21.3	21.0
5		21.1	21.5
6		22.4	23.0
7		25.7	25.3
8		25.9 (exp: 24.2)	25.0
9		25.7	25.5
10		26.6	26.7
11		25.2	26.9
12		29.1	28.5
13		31.5	30.6

<sup>a</sup> Experimental data collected from ref 2.

intermediates must exist as ion pairs in THF. Therefore, it is meaningful to study the ion-pair acidities of organic nitrogen acids in THF. Noteworthily, Streitwieser and co-workers have not systematically studied the ion-pair acidities of nitrogen acids in THF (they did report the Cs ion-pair acidities of two amines in THF/diphenylamine (24.2) and carbazole (19.2)<sup>3</sup>), although Bordwell et al. have systematically measured the absolute ionic acidities of many nitrogen acids in DMSO.<sup>2</sup>

Here we ask whether or not the cesium relative ion-pair acidities of nitrogen acids in THF have any major difference from the absolute ionic acidities measured by Bordwell et al. in DMSO. If the answer is negative, then one can easily estimate the cesium ion-pair acidities of almost all types of organic nitrogen acids in THF on the basis of Bordwell's data. It is important to point out that the solvation of a nitrogen-centered anion may be significantly different from the solvation of a carbanion (as we previously reported in the study of bond

dissociation enthalpies in the solutions<sup>14</sup>). Thus, some systematic calculations (or more rigorously, experiments) must be done to answer the above question.

In Table 3 are shown our calculation results for 12 representative nitrogen acids whose absolute ionic  $pK_a$ 's range considerably from 15 to 30. It is immediately clear that the cesium ion-pair acidities in THF and the absolute ionic acidities in DMSO are very close to each other for almost all types of organic nitrogen acids. As shown in Figure 11, the correlation coefficient between the two scales of acidities is as high as 0.9640, whereas the intercept of the correlation is found to be 0.1 pK unit. Thus, the cesium ion-pair acidities of nitrogen acids in THF have only minor difference from the absolute ionic acidities measured by Bordwell et al. in DMSO. Consequently, one can easily estimate the cesium ion-pair acidities of almost all types of organic nitrogen acids in THF on the basis of Bordwell's data.

## 5. Summary

The ion-pair acidities of organic acids in THF are fundamental to synthetic organic chemistry. Although the ion-pair acidities of a number of carbon acids have been experimentally measured by Streitwieser and co-workers, it is important to develop a first-principle method that can accurately predict these quantities because not all the organic acids (e.g., very weak acids or complex synthetic intermediates with multiple acidic positions) are amenable to experimental characterization. Here we report the first theoretical protocol for predicting the cesium ion-pair acidities in THF whose reliability has been tested against almost all the available experimental data.<sup>5</sup> It is found that the rms error of the current theoretical model equals 1.2 pK units.

With the newly developed theoretical method in hand, we next investigate the structures of cesium ion pairs of different types of carbon acids. We also systematically compare the cesium ion-pair acidities in THF and absolute ionic acidities in DMSO and confirm Streitwieser's previous finding that the two scales of acidities have only minor difference. Significantly, using detailed energy analysis we find the mechanism for the "fortunate" match of the two scales of acidities. That is, the combined process of the Cs binding ("micro"-solvation) and the solvation of the ion pair resembles the one-step solvation of a carbanion in DMSO. Finally, we find that the cesium ion-pair acidities of nitrogen acids in THF have only minor difference from the absolute ionic acidities in DMSO. Consequently, one can easily estimate the cesium ion-pair acidities of almost all types of organic nitrogen acids in THF on the basis of Bordwell's data.

## 6. Computational Methodologies

All the calculations were performed with the Gaussian03 programs<sup>11</sup> using our HP Superdome server (32 × 1.5 GHz Itanium 2 Madison CPU). Geometry optimizations were conducted using several DFT methods (B3LYP, B3PW91, B3P86, or PBEPBE, with the LanL2dz basis set for cesium and 6-31G\* basis set for the other atoms). Each optimized structure was confirmed by the frequency calculation at the same level to be the real minimum without any imaginary vibration frequency. For compounds that had multiple conformations, efforts were made to find the lowest-energy conformation by comparing the structures optimized from different starting geometries.

(14) Fu, Y.; Liu, L.; Wang, Y.-M.; Li, J.-N.; Yu, T.-Q.; Guo, Q.-X. *J. Phys. Chem. A* **2006**, *110*, 5874.

Harmonic vibrational frequencies were calculated using the DFT/Lanl2dz/6-31G\* method from the optimized geometries. Zero-point vibrational energy (ZPE) corrections were obtained using unscaled frequencies. Single-point electronic energies were then calculated at the DFT/Lanl2dz+p/6-311+G(2df,2p) methods. Gas-phase acidity was calculated as the free energy change of the deprotonation reaction described in eq 1 in the gas phase. This free energy change was corrected with ZPE, thermal corrections (0 → 298 K), and the entropy terms. It is worth noting that all the calculated gas-phase free energies correspond to the reference state of 1 atm, 298 K.

To calculate solvation energies, we used the PCM model at the DFT/6-311+G(2df,2p) level (solution method = matrix inversion, polarization charges = total charges, cavity = GePol (RMin = 0.200, OFac = 0.890), The default sphere list was used, where NSphG = 18, radii = UA0 (simple united atom topological model). The gas-phase geometry was used for all of the solution-phase calculations, as it has been demonstrated that the change of geometry by the solvation effect is

usually not significant. All the solution-phase free energies reported in the paper correspond to the reference state of 1 mol/L, 298 K.

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**Supporting Information Available:** Cartesian coordinates of optimized structures, detailed thermodynamic data, complete ref 11. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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