A Comparison of Density-Functional Theory and *Hartree–Fock* Modeling of Organolithium Equilibria

by **Andrew Streitwieser*** and **Yew Hung Leong**

Department of Chemistry, University of California, Berkeley, Berkeley, CA 94720-1460, USA

Dedicated to Professor *Dieter Seebach* on the occasion of his 75th birthday

Experimental values for a number of organolithium equilibria in THF solution expressed as pK values are compared with computational results at several theory levels. Solvation effects are considered only by coordination of lithium with two THF molecules. Best results are obtained with the hybrid density-functional method mPW1PW91, which gives satisfactory results over a range of almost 40 pK units, but explicit thermal corrections to 25° are required.

Introduction. – For the last several decades, organolithium compounds have been among the most important reagents in synthetic organic chemistry [1][2]. Since many are used in transmetallation reactions, their effective basicity is an important physical property that can be measured experimentally. We have preferred to refer to the conjugate property, the relative acidity as defined by *Eqn. 1* in which K_{ip} is an ion pair equilibrium constant [3].

$$RH + R'^{-}Li^{+} \overset{K_{ip}}{\rightleftharpoons} R^{-}Li^{+} + R'H \qquad (1)$$

The logarithm of K_{ip} is equivalent to the pK difference between RH and R′H. We have discussed previously that absolute acidities are not known for organolithium compounds, and that only relative acidities can be assigned at present. Accordingly, in order to have the convenience of dealing with absolute numbers we have arbitrarily assigned to the solvent-separated ion pair acidity in THF solution of fluorene its known ionic pK in DMSO, 23.9 (per hydrogen) [4]. Over the years, we have determined a number of these pK values that we refer to as pK(Li) to emphasize that these are relative pK values of Li derivatives.

In our previous computational studies [3] of RLi compounds in THF solution, we found that polarized continuum-type models (PCM) do not work well for non-polar ether solutions. Consequently, only direct coordination of solvent with Li was considered explicitly. We had used Me_2O as a model for THF because it is computationally smaller, but this restriction has become less important with our present access to a larger computer. Although Me_2O is not a bad model for THF (for a contrary opinion, see [5]), it does have smaller steric requirements and it is undoubtedly better to use THF where possible. We have now done this in a revised version of the isodesmic type *Eqn. 2*.

$$RH + PhLi \cdot 2\,THF \rightleftharpoons RLi \cdot 2\,THF + PhH \qquad (2)$$

In applying this equation to more than two dozen experimental values, we have studied various energy functions, and in this paper we compare a density-functional (DFT) method with *Hartree–Fock* (HF).

Method. – Computations were run with GAUSSIAN03 [6] or GAUSSIAN09 [7] with the $6-31+G(d)$ basis set. Unless otherwise noted, all frequencies are real. Alternative starting structures were tried in many cases to check for additional stable conformations. Thermodynamic quantities are those given in GAUSSIAN. Some computational results are summarized in the tables. Full details are available as pdf files from the principal author.

Results and Discussion. – The compounds studied and their experimental p*K*(Li) values are compiled in *Table 1* listed in order of decreasing p*K*(Li). Most of the compounds exist in solution as a single or dominant conformation. Some, such as dibenzyl ketone, **25**, can have several conformations. We generally checked the most reasonable structures and chose that with the lowest energy. In principle, one should

Table 1. *Compounds Computed with Their Experimental* p*K(Li) Values Relative to the SSIP of Fluorenyllithium Assigned the Value of 23.90* (per hydrogen)

	Carbon acid	p*K*(Li)	Ref.
1	Benzene	39.5	[8]
2	2-Phenyl-1,3-dithiane	29.4	[9]
3	2-[1,1′-Biphenyl-4-yl]dithiane	28.2	[9]
4	Adamantylacetylene	23.7	[10]
5	1,2,4,5-Tetrafluorobenzene	23.1	[8]
6	Hexamethyldisilazane (HMDS)	23.05	[11]
7	4-(Methylamino)[1,1′-biphenyl]	22.09	[11]
8	*N,N*-Diethyl-2,2-diphenylacetamide	22.02	[12]
9	Pentafluorobenzene	21.5	[8]
10	*1*-(Diphenylacetyl)pyrrolidine	21.11	[12]
11	*N,N*-Dimethyl-2,2-diphenylacetamide	20.78	[12]
12	2-[1,1′-Biphenyl-4-yl]-*N,N*-diethylacetamide	20.36	[12]
13	[1,1′-Biphenyl-4-yl]methyl phenyl sulfoxide	20.1	[13]
14	2-[1,1′-Biphenyl-4-yl]-*N,N*-dimethylacetamide	19.77	[12]
15	Benzyl phenyl sulfone	19.5	[13]
16	Diphenylamine	19.05	[14]
17	[1,1′-Biphenyl-4-yl]methyl phenyl sulfone	18.8	[13]
18	*p*-Phenylisobutyrophenone	15.86	[15]
19	*p*-(Phenylsulfonyl)isobutyrophenone	14.69	[16]
20	6-Phenyltetralone	14.22	[17]
21	2-Benzyl-6-phenyltetralone	13.96	[18]
22	Carbazole	13.48	[19]
23	2-Phenylcyclohexanone	12.69	[20]
24	2-[1,1′-Biphenyl-4-yl]cyclohexanone	12.31	[21]
25	Dibenzyl ketone	11.62	[22]
26	2,6-Diphenyltetralone	11.14	[23]
27	*p*-Phenylbenzoylacetone	1.78	[24]
28	1,4-Diphenylbutane-1,3-dione	0.51	[24]

determine a *Boltzmann* distribution of all of the conformations and use the resulting energy. The lowest-energy structure, however, would dominate such a distribution, and we used only its computed energy instead. Other required approximations probably do not justify a more elaborate treatment.

Where more than one equivalent hydrogen is involved, the pK values have generally been corrected for statistics in the original articles. The two β-diketones **27** and **28** are exceptions. Both are present in THF mostly as the enol undoubtedly with intramolecular H-bonding, but the pK is based on the small amount of diketone present and assigned a statistical factor of 2. The diketone was used as the parent because the computation of H-bonding in THF is not straightforward and would introduce a new variable.

The Li salts were computed as contact ion pairs but an important question concerns the number, 2 or 3, of THF molecules coordinated with the Li. This question was thoroughly discussed in our previous article [3]. In short, at low temperatures (liquid N_2), Li appears to be generally tetracoordinate but as the temperature approaches room temperature, the greater entropy of free THF becomes important, and the Li now is at least in part tricoordinate. In some cases, such as some β-diketones and sulfoxides,

Table 2. *Energies in kJ/mol for* Eqn. 2 *at Different Theory Levels*

	RHF + ZPE	MP2 + ZPE	MP2 + G	mPW1 + ZPE	mPW1 + G
1	0.000	0.000	0.000	0.000	0.000
2	– 67.716	– 111.245	– 99.950	– 89.600	– 81.479
3	– 69.140	– 114.131	– 102.479	– 94.167	– 86.778
4	– 110.747	– 98.4240	– 104.534	– 102.957	– 101.334
5	– 115.925	– 124.542	– 117.038	– 112.333	– 109.080
6	– 125.972	– 152.337	– 140.701	– 123.024	– 116.726
7	– 118.524	– 132.972	– 128.419	– 128.950	– 125.563
8	– 125.026	– 174.599	– 164.215	– 152.654	– 137.560
9	– 123.569	– 133.407	– 126.087	– 120.122	– 118.200
10	– 132.486	– 184.552	– 172.194	– 161.900	– 144.443
11	– 138.332	– 184.138	– 170.325	– 163.823	– 146.159
12	– 137.252	– 168.662	– 156.642	– 155.850	– 141.336
13	– 134.316	– 163.362	– 155.029	– 150.084	– 140.564
14	– 140.226	– 171.775	– 156.949	– 157.712	– 141.452
15	– 140.619	– 169.885	– 145.531	– 148.587	– 140.128
16	– 146.578	– 177.976	– 171.186	– 152.967	– 148.065
17	– 141.249	– 170.044	– 158.998	– 150.100	– 138.577
18	– 145.974	– 180.794	– 173.476	– 161.984	– 154.436
19	– 152.678	– 184.253	– 178.348	– 167.453	– 161.236
20	– 137.936	– 156.230	– 153.235	– 149.623	– 145.669
21	– 145.922	– 187.374	– 182.249	– 168.425	– 159.729
22	– 174.677	– 196.547	– 191.125	– 174.356	– 173.893
23	– 182.561	– 221.477	– 210.282	– 199.125	– 184.585
24	– 180.508	– 214.522	– 203.363	– 202.689	– 190.388
25	– 177.820	– 217.696	– 203.379	– 197.769	– 178.800
26	– 171.688	– 215.462	– 206.296	– 194.687	– 183.043
27	– 285.736	– 293.115	– 283.726	– 290.001	– 281.817
28	– 290.960	– 311.419	– 300.290	– 295.667	– 293.151

internal coordination reduces the driving force for tetracoordination. Our pK(Li) measurements were usually done at 25° where tricoordination is expected to be important. Ideally, the amounts of RLi·2S and RLi·3S (where S is solvent) present should be computed and the combined amounts used for correlation with experiment. In practice, this type of computation would be quite difficult, in part because the equilibria now involve different units and differences in standard states between gas phase computations, and experiments in solution would need to be included. Instead, we treated all of the Li salts as disolvated in the isodesmic-like *Eqn. 2*.

Several theory levels were used but all are with the 6–31+G(d) basis set. The lowest is *Hartree–Fock* (*HF*). MP2 Calculations are with frozen core at the HF geometry. For the DFT calculations, the question is which one to use of the dozens now available. We chose to use the hybrid functional mPW1PW91 [25]. This functional is incorporated in the GAUSSIAN program and has been widely used (SciFinder gives over 500 references to its use). Comparisons with other functionals have generally been positive, especially when combined with the 6–31+G(d) basis set [26][27]. We have

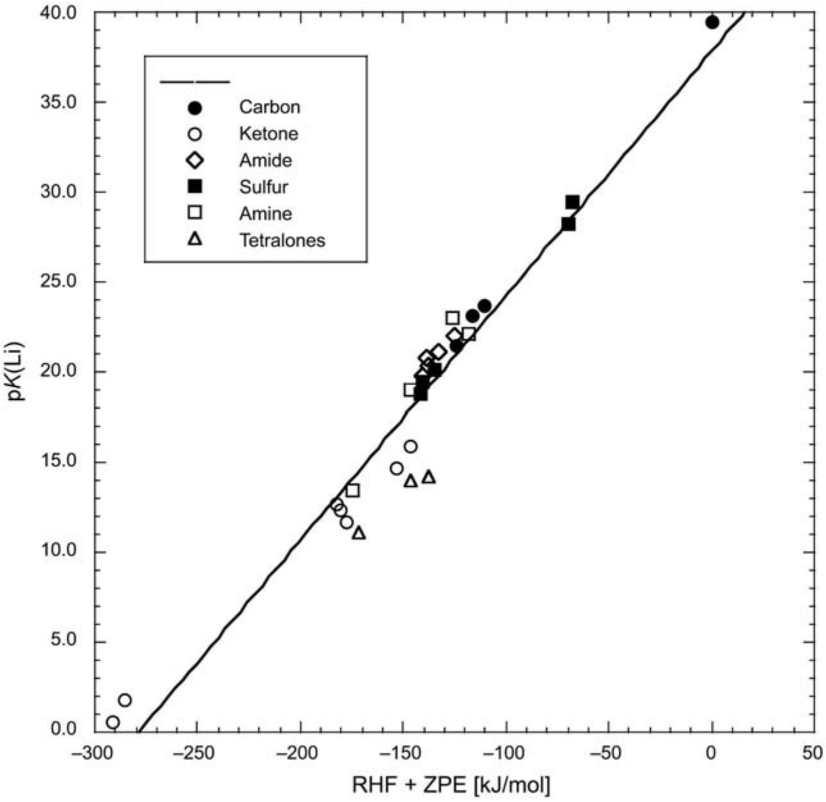

Fig. 1. *Correlation of* pK*(Li) with* Eqn. 2*,* Hartree–Fock *plus unscaled ZPE*. The equation of the regression line shown is $37.813 \pm 1.049 + (0.1356 \pm 0.0068)x$; $R^2 = 0.938$.

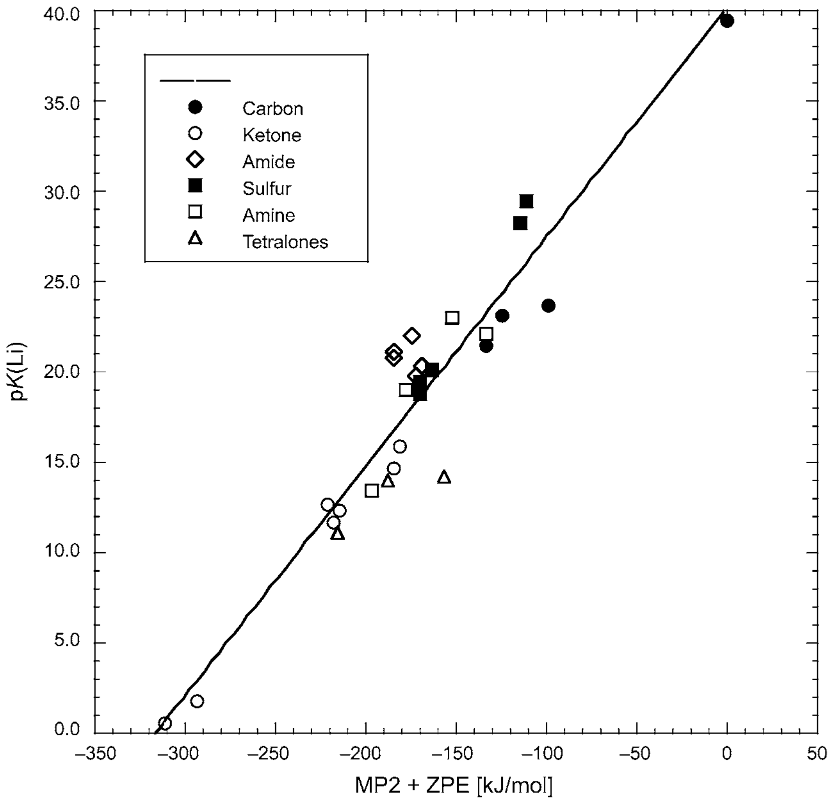

Fig. 2. *Correlation of* p*K(Li) with* Eqn. 2, *MP2 plus unscaled HF ZPE.* The equation of the regression line shown is $40.169 \pm 1.493 + (0.1269 \pm 0.0082)x$; $R^2 = 0.901$.

used this functional previously to interpret aspects of organolithium chemistry [28][29]. The results for *Eqn. 2* at the different theory levels are collected in *Table 2*.

Fig. 1 shows a plot of p*K*(Li) *vs.* the energies of *Eqn. 1* at the *Hartree–Fock* level plus the unscaled zero-point energy (ZPE). The unscaled ZPE were used because scaling factors for organolithium vibrations are unknown. For added insight, the compounds were sorted unto several types: carbon: **1**, **4**, **5**, **9**; ketone: **18**, **19**, **23**, **24**, **25**, **27**, **28**; amide: **8**, **10**, **11**, **12**, **14**; sulfur: **2**, **3**, **13**, **15**, **17**; amine: **6**, **7**, **16**, **22**; tetralone: **20**, **21**, **26**.

The correlation in *Fig. 1* is generally better than that obtained previously using Me_2O in place of THF [3]. In particular, ketones fit the correlation better although tetralones (open triangles in *Fig. 1*) still deviate conspicuously. These deviations could result from neglected solvation effects or simply reflect limitations of the *HF* method. *Fig. 2* shows the same p*K*(Li) values compared to MP2 plus the *HF* ZPE. The correlation is much poorer with greater scatter. It seems surprising that MP2 should be worse than *HF*. The calculated energy plus ZPE gives the energy at 0 K, whereas the p*K* data refer mostly to room temperature. To correct the calculations to 25°, the *HF* 'sum

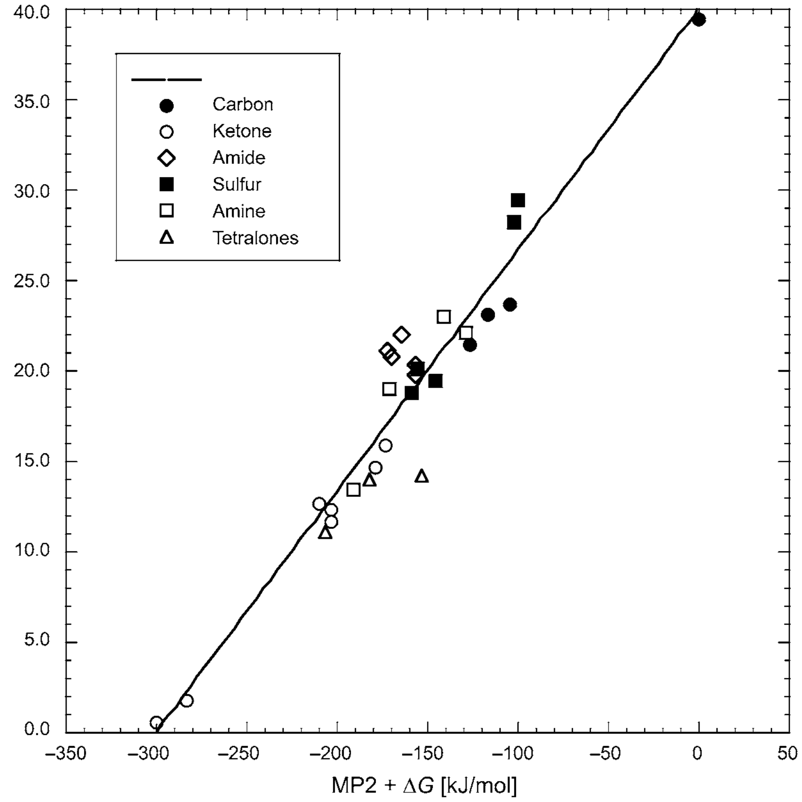

Fig. 3. *Correlation of* p*K(Li) with* Eqn. 2*, MP2 plus thermal correction to* Gibbs *Free Energy.* The equation of the regression line shown is $40.038 \pm 1.246 + (0.1332 \pm 0.0072)x$; $R^2 = 0.928$.

of electronic and thermal free energies' as given by GAUSSIAN were added to the MP2 results, although it is well-known that this procedure has its own problems. The computed vibrations are all harmonic, whereas in practice many vibrations have hindered rotations and have lower entropy than calculated. For the THF units coordinated to Li, much of the vibrational entropy is contributed by vibrations that are less than 100 wavenumbers. Such vibrations are frequently highly anharmonic and contribute large errors in entropies [30]. Nevertheless, by casting the results in the form of an equilibrium as in *Eqn. 2*, many vibrations, especially of THF coordinated to Li, are similar in both sides of the equilibrium and their associated errors might be expected to cancel. In fact, *Fig. 3*, which presents a plot of MP2 plus the thermal corrections to ΔG at 298 K, is a substantial improvement over *Fig. 2*.

We next explore the use of the hybrid DFT method mPW1PW91. The optimized structures are generally similar to the corresponding *HF* structures showing only relatively small changes in bond distances and angles.

A plot of pK(Li) *vs.* the mPW1PW91 energy + ZPE (calculated from the mPW1PW91 vibrations), *Fig. 4*, gives results better than the MP2 correlations in

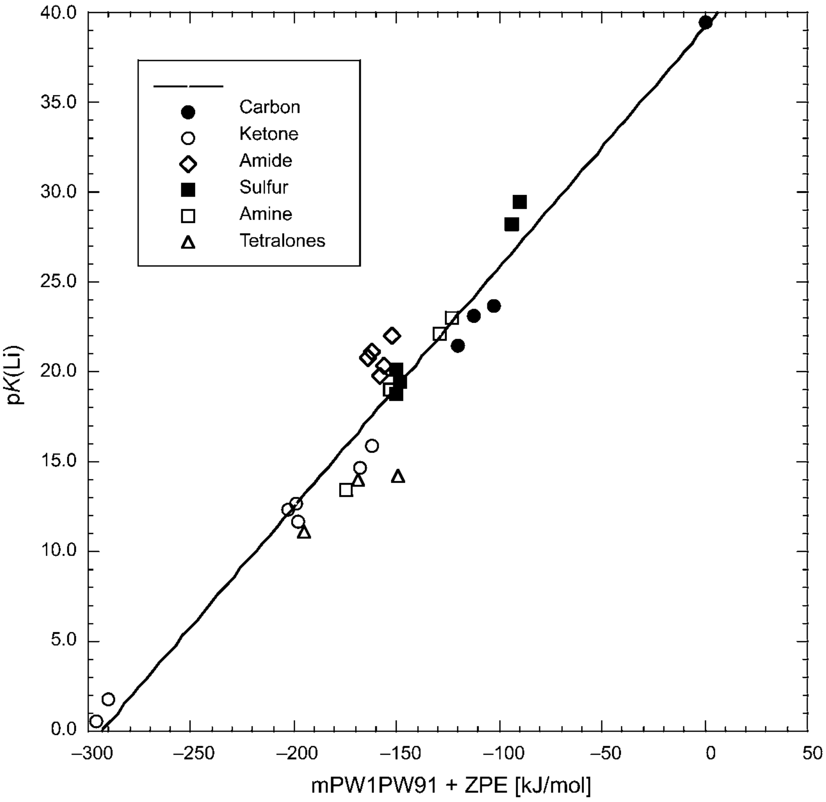

Fig. 4. *Correlation of* p*K(Li) with* Eqn. 2, *mPW1PW91 plus ZPE.* The equation of the regression line shown is $39.154 \pm 1.164 + (0.1333 \pm 0.0070)x$; $R^2 = 0.932$.

Figs. 2 and *3*. The farthest outlier is 6-phenyltetralone although the other two tetralones compare well with the ketone group. Applying the ΔG thermal corrections (from the mPW1PW91 vibrations) to 298 K in *Fig. 5* gives the best correlation of all with R^2 being a respectable 0.95 for experimental results covering a range of almost 40 pK units. The carbon groups and amines fit the correlation well. The tetralones still deviate the farthest but not much more than some of the ketones. At least some of the variations that still exist in this correlation might well be the result of considering all of the Li compounds to be coordinated with only two THF molecules. Significant amounts of fully coordinated Li-atoms are undoubtedly still present in these solutions at 25°, and their neglect is expected to result in differences from the computed model.

One additional feature requires comment. The slopes in all of these figures are well-defined and all are significantly lower than the expected slope, 0.1753, given by $RT\ln 10$ (kJ/mol at 25°), the energy equivalence of pK, These reduced slopes probably result from the polar character of the solvent compared to gas-phase computations; that is, they are probably the result of 'dielectric solvation' [3][29][31][32]. This effect is often

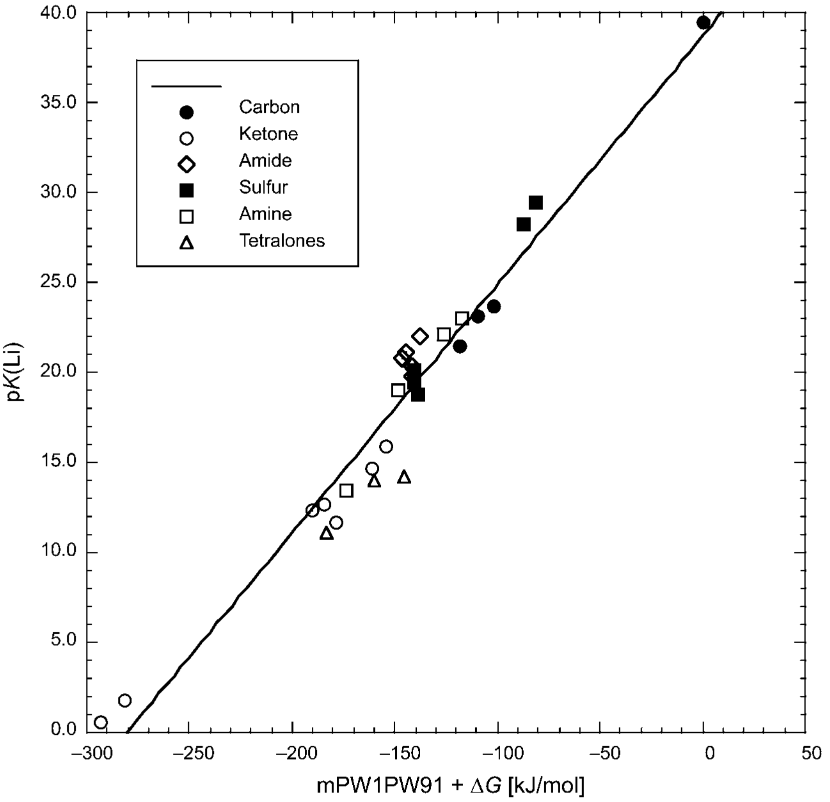

Fig. 5. *Correlation of* p*K(Li) with* Eqn. 2, *mPW1PW91 plus* ΔG. The equation of the regression line shown is $38.684 \pm 0.978 + (0.1379 \pm 0.0062)x$; $R^2 = 0.950$.

not considered in theoretical studies of solution chemistry and points up the value of correlations with experimental results.

This work was supported in part by a *Senior Scientist Mentor Award* from the *The Camille and Henry Dreyfus Foundation*. Most of the calculations were done at the Molecular Graphics and Computation Facility, College of Chemistry, UC Berkeley, supported by *National Science Foundation* grants CHE-0233882 and CHE-0840505. We thank Dr. *Kathleen A. Durkin* of this facility for assistance.

REFERENCES

[1] D. Seebach, K. H. Geiss, in 'New Applications of Organometallic Reagents in Organic Synthesis', Ed. G. Seyferth, Elsevier, New York City, 1976, p. 1.
[2] A.-M. Sapse, P. v. R. Schleyer, 'Lithium Chemistry: A Theoretical and Experimental Overview', John Wiley & Sons, Inc., New York, 1995.
[3] A. Streitwieser, J. R. Reyes, T. Singhapricha, S. Vu, K. Shah, *J. Org. Chem.* **2010**, *75*, 3821.
[4] F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456.
[5] L. M. Pratt, *Theochem* **2007**, *811*, 191.

[6] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. G. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian, Inc.*, Pittsburgh PA., 2003.

[7] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adam, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian, Inc.*, Wallingford CT, 2009.

[8] M. Stratakis, P. G. Wang, A. Streitwieser, *J. Org. Chem.* **1996**, *61*, 3145.

[9] L. Xie, A. Streitwieser, *J. Org. Chem.* **1995**, *60*, 1339.

[10] R. Gareyev, A. Streitwieser, *J. Org. Chem.* **1996**, *61*, 1742.

[11] A. Streitwieser, A. Facchetti, L. Xie, X. Zhang, E. C. Wu, *J. Org. Chem.* **2012**, *77*, 985.

[12] A. Facchetti, A. Streitwieser, *J. Org. Chem.* **1999**, *64*, 2281.

[13] A. Streitwieser, G. P. Wang, D. A. Bors, *Tetrahedron* **1997**, *53*, 10103.

[14] J. A. Krom, J. T. Petty, A. Streitwieser, *J. Am. Chem. Soc.* **1993**, *115*, 8024.

[15] A. Abbotto, S. S.-W. Leung, A. Streitwieser, K. V. Kilway, *J. Am. Chem. Soc.* **1998**, *120*, 10807.

[16] F. Abu-Hasanayn, M. Stratakis, A. Streitwieser, *J. Org. Chem.* **1995**, *60*, 4688.

[17] D. Z. Wang, A. Streitwieser, *J. Org. Chem.* **2003**, *68*, 8936.

[18] A. Streitwieser, Y.-J. Kim, D. Z.-R. Wang, *Org. Lett.* **2001**, *3*, 2599.

[19] A. Abbotto, A. Streitwieser, M. Stratakis, J. A. Krom, *J. Am. Chem. Soc.* **1998**, *120*, 1718.

[20] D. Z.-R. Wang, A. Streitwieser, *Can. J. Chem.* **1999**, *77*, 654.

[21] A. Streitwieser, D. Z.-R. Wang, *J. Am. Chem. Soc.* **1999**, *121*, 6213.

[22] R. Gareyev, J. C. Ciula, A. Streitwieser, *J. Org. Chem.* **1996**, *61*, 4589.

[23] D. Z.-R. Wang, Y.-J. Kim, A. Streitwieser, *J. Am. Chem. Soc.* **2000**, *122*, 10754.

[24] A. Facchetti, A. Streitwieser, *J. Org. Chem.* **2004**, *69*, 8345.

[25] C. Adamo, V. Barone, *J. Chem. Phys.* **1998**, *108*, 664.

[26] Y.-K. Han, S. U. Lee, *Theor. Chem. Acc.* **2004**, *112*, 106.

[27] K. E. Riley, Bryan T. Op't Holt, J. K. M. Merz Jr., *J. Chem. Theory Comput.* **2007**, *3*, 407.

[28] A. Streitwieser, E. G. Jayasree, *J. Org. Chem.* **2007**, *72*, 1785.

[29] A. Streitwieser, E. G. Jayasree, F. Hasanayn, S. S.-H. Leung, *J. Org. Chem.* **2008**, *73*, 9426.

[30] C. J. Cramer, 'Essentials of Computational Chemistry', 2nd Edn., John Wiley & Sons, Ltd., West Sussex, 2004.

[31] A. Streitwieser, *J. Org. Chem.* **2009**, *74*, 4433.

[32] A. Streitwieser, K. Shah, J. R. Reyes, X. Zhang, N. R. Davis, E. C. Wu, *J. Phys. Chem. A* **2010**, *114*, 8793.

Received August 7, 2012