Kinetic and Equilibrium Lithium Acidities of Substituted Toluenes: Semitheoretical Brönsted Correlations

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S *Supporting Information*

ABSTRACT: *Semitheoretical* Brönsted correlations are compared between previously measured experimental rates of hydrogen isotope exchange of substituted toluenes labeled in the α-position and relative equilibrium acidities computed at several theory levels. The Brönsted correlations show less scatter at the Hartree—Fock level than at higher theory levels. This effect is rationalized on the basis of enhanced steric effects in the more constrained structures of the higher theory levels.

Log Experimental Exchange Rate

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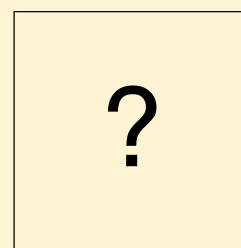
Computed Equilibrium Acidity (H-F, DFT, MP2)

INTRODUCTION

In 1924, Brönsted and Pedersen[1] showed that the rate of the base-catalyzed part of the decomposition of nitramide is dependent on the basicity of the anionic catalyst as measured by the equilibrium acidity constant of the conjugate acid. Their relationship is commonly written today as eq 1.

$$\log(k/k_o) = \beta \log(K/K_o) \tag{1}$$

Indeed, they show what is most probably the first example in the literature of a linear plot of log k vs log K. They assumed that a corresponding relation would apply for acid catalysis, and shortly thereafter, Brönsted and Guggenheim[2] provided a specific example in the mutarotation of glucose. Brönsted[3] generalized this discovery in a long review article.[4] Not long thereafter, Hammett[5] recognized the Brönsted Catalysis Law as the prototype of a *linear free energy* relation between rates and equilibrium constants.[6] Many more such relations are now available.[7,8]

Brönsted also considered that there should be a comparable relation between the *rate* of dissociation of an acid and its equilibrium acidity constant, and several such relations were subsequently experimentally established. One of the most comprehensive early correlations between kinetic and equilibrium acidities is that of Pearson and Dillon[9] for relatively acidic carbon acids such as ketones, esters, nitriles, etc. Extension of this approach to weakly acidic hydrocarbons, however, was more difficult because of a paucity of equilibrium pK data. The first attempt to apply the Brönsted correlation to hydrocarbons appears to be that of Dessy et al.,[10] who in 1962 included cyclopentadiene, phenylacetylene, and fluorene in a study of deuterium exchange rates in aqueous DMF containing triethylamine compared with pK_a's assigned by McEwen.[11] The rates of deuterium exchange have provided a convenient measure of kinetic acidities since the late 1930s.[12] Shatenshtein

has provided many such measurements with potassium amide in liquid ammonia,[13,14] but far fewer equilibrium pK's are available.[15,16]

Williams has suggested another approach; namely, making use of computational quantum methods.[17] Williams and Austin[18] computed both the transition-state energy and reaction energy for a model proton-transfer reaction in order to test some properties of the Brönsted slope β of the correlation between these energies. In previous Brönsted correlations, both arguments are experimental numbers. In their application, both arguments are theoretical numbers to give what could be called a theoretical Brönsted correlation. Their study made use of mimics of substituent effects with the semiempirical AM1 method and would now be considered to be a rather low level theory but the principle is established. The obvious next step is a semitheoretical Brönsted correlation, in which one argument is experimental and the other is theoretical. Note the important difference from common applications of theory in which experimental quantities are compared with theoretical models *of the same quantity*. In a typical semitheoretical Brönsted correlation, kinetic acidities would be compared with theoretical models of the corresponding equilibrium acidities. In a recent example, we showed that experimental kinetic acidities of various aryl hydrogens as measured by hydrogen isotope exchange kinetics with lithium cyclohexylamide (LiCHA) in cyclohexylamine (CHA) give an excellent Brönsted-type correlation with computed ion pair acidities.[19] In the present paper, we extend the same approach to the benzylic hydrogens of substituted toluenes.

Table 1. Relative Rates for Tritium Exchange of Substituted Toluene−α−t's with LiCHA in CHA Compared to ($\Delta(E(\mathrm{RHF}) + \mathrm{H})$ in kcal mol^{-1}) of eq 2 at Different Theory Levels with the 6-31+g(d) Basis Set[a]

substituted toluene, subst	rel rate[b]	S = Me$_2$O, HF	S = THF, HF	S = THF, mPW1	S = THF, MP2
H	1.00	0	0	0.0000	0.0000
o-methyl	0.60	0.3658			
m-methyl	0.60	0.1682	0.1562	0.0935	−0.5993
p-methyl	0.31	1.2550	1.3247	1.1841	0.3771
o-fluoro	12	−1.8675	−2.0174	−1.6529	−2.9192
m-fluoro	22	−2.8240	−2.9775	−2.6751	−3.0622
p-fluoro	0.73	0.3577	0.1010	0.8064	0.4945
m-methoxy	2.1	−0.7969	−3.9521	−0.5372	−1.8110
p-methoxy	0.091	2.7610	−1.1772	2.9782	1.6911
m-trifluoromethyl	60	−3.3114	2.6029	−4.0186	−6.3680
p-trifluoromethyl	180	−4.8833	−5.3194	−5.9695	−6.5305
m-trimethylsilyl	1.01	0.2272			
p-trimethylsilyl	1.57	−1.1973			

[a] S is the solvent in eq 2. [b] Reference [23]

COMPUTATIONAL METHODS

Computations were run with GAUSSIAN03[20] or GAUSSIAN09[21] at several theory levels: Hartree−Fock, the hybrid functional mPW1PW91,[22] and MP2, with geometries optimized at the same level. The basis set used in all cases is 6-31+g(d). In many cases, alternative starting structures were used to search for other optimized structures, and in some cases, particularly with ortho and meta substituents, a second optimized structure was sometimes obtained having an energy difference of generally less than 0.1 kcal mol^{-1} but occasionally somewhat greater. The lower energy structure was used for the correlations.

Examples of these alternative structures are included in the Supporting Information. The energies reported in the tables and figures are based on the electronic energy plus the thermal energy correction to room temperature (E + H) as given by GAUSSIAN. These enthalpy corrections include the zero point energy (ZPE). Complete details are given in the Supporting Information.

RESULTS AND DISCUSSION

Several decades ago, we measured the rates of hydrogen isotope exchange catalyzed by lithium cyclohexylamide (LiCHA) in cyclohexylamine (CHA) of a number of substituted toluenes labeled with deuterium or tritium in the methyl group.[23] The purpose was to establish a Hammett $\sigma\rho$ correlation; the result ρ = 4.0 shows that the transition state has carbanionic character. In the present study we compare these rates with theoretically computed acidities in order to extend our previous study[19] of arene positions to conjugated benzylic systems.

Lithium ion pair acidities in THF solution are defined by eq 1 in which R$_o$H is an arbitrarily assumed standard which we take as fluorene. Log K_{ip} gives the pK difference between RH and R$_o$H. These differences are converted to absolute values, expressed as pK(Li), by assigning to fluorene the value pK(Li) = 22.90 (per hydrogen) for its solvent-separated lithium salt.[24] Because the pK_a of fluorene is 22.90 (per hydrogen) in DMSO,[25] this otherwise arbitrary choice allows a direct comparison of the relative ion pair pK(Li) values with the pK_a's in DMSO. Over a period of several decades, we have measured a number of such pK(Li) values in THF.

$$\mathrm{RH} + \mathrm{R_o^-Li^+} \overset{K_{ip}}{\underset{}{\rightleftarrows} } \mathrm{R^-Li^+} + \mathrm{R_oH} \qquad (1)$$

We showed recently that the pK(Li) values of many compounds whose lithium salts are contact (or tight) ion pairs, CIP, in THF are well modeled by Hartree−Fock (H−F)
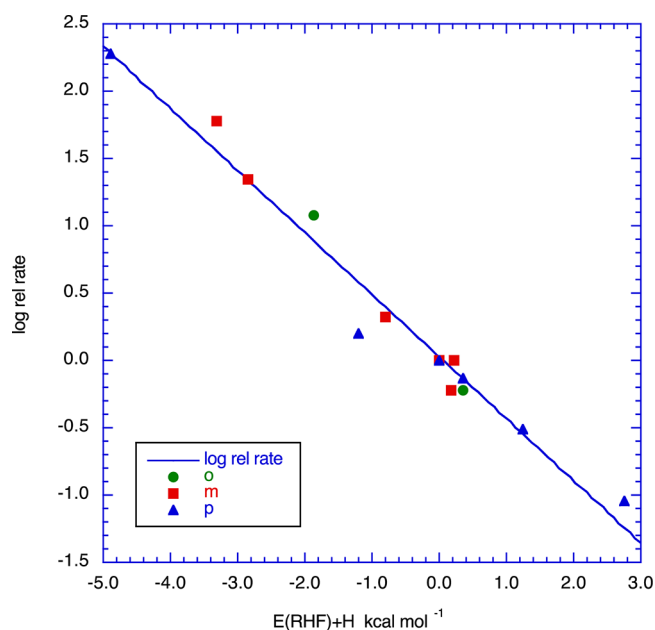

Figure 1. Semitheoretical Brönsted plot of log relative rate of protodetritiation of substituted toluene−α−t's with LiCHA in CHA compared to computed lithium ion pair acidites relative to toluene, eq 2, S = Me$_2$O. The regression line shown is $y = 0.0283 \pm 0.0511 - (0.4609 \pm 0.0242)x$; $R^2 = 0.971$.

calculations if the effect of solvent is modeled by coordination of the lithium cation with donor solvent molecules. For most compounds, we found that coordination with two dimethyl ethers (eq 2. S = Me$_2$O) is sufficient.[26] Equation 2 is set up relative to toluene (Bn = benzyl) for convenience. The kinetic results are given as rates relative to toluene, and this choice permits a direct comparison.

$$\mathrm{RH} + \mathrm{BnLi \cdot 2S} = \mathrm{RLi \cdot 2S} + \mathrm{BnH} \qquad (2)$$

Equation 2 is of the isodesmic type in which the equilibrium constants are unitless and in which some other types of solvent interactions are expected to cancel. The results summarized in Table 1 form the basis for the plot in Figure 1.

The correlation is found to be excellent with $R^2 = 0.97$. Even ortho substituents, which often deviate in such correlations, fit well. The point for the p-CF$_3$ group is noteworthy. Because of decomposition during the kinetic run, its relative reactivity of
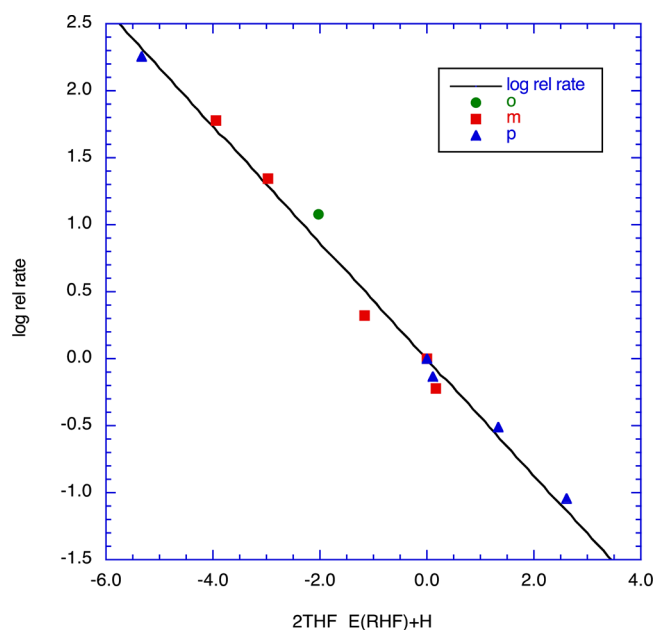
Figure 2. Semitheoretical Brönsted plot of log relative rate of protodetritiation of substituted Brönsted toluene-α−t's with LiCHA in CHA compared to HF computed lithium ion pair acidities relative to toluene, eq 2, S = THF. The regression line shown is $y = -0.002 \pm 0.045 - (0.4447 \pm 0.0174)x$; $R^2 = 0.987$.
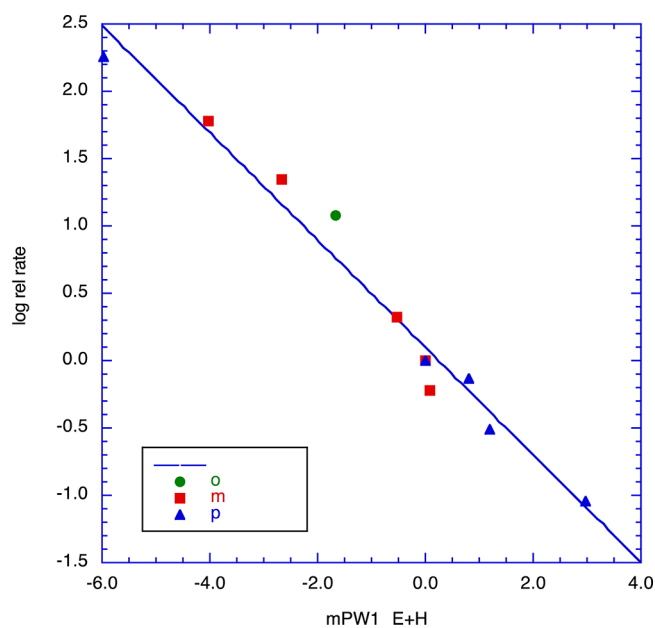

Figure 3. Semitheoretical Brönsted plot of log relative rate of protodetritiation of substituted toluene-α−t's with LiCHA in CHA compared to mPW1 computed lithium ion pair acidities relative to toluene, eq 2, S = THF. The regression line shown is $y = 0.098 \pm 0.067 - (0.3986 \pm 0.0248)x$; $R^2 = 0.970$.

Figure 4. Comparison of structures obtained for BnLi·2THF with HF/6-31+g(d) (above) and mPW1PW91/6-31+g(d) (below).

Figure 5. Semitheoretical Brönsted plot of log relative rate of protodetritiation of substituted toluene-α−t's with LiCHA in CHA compared to MP2-computed lithium ion pair acidities relative to toluene, eq 2, S = THF. The regression line shown is $y = -0.20 \pm 0.11 - (0.366 \pm 0.032)x$; $R^2 = 0.941$.

180 was only approximate,[23] but its agreement with the correlation suggests that the assigned relative rate is actually quite accurate. The slope of −0.46 is typical of Brönsted correlations. It is also in agreement with the slope of −0.5 found by Veracini and Gau[27] for rates and equilibria in hydrocarbon solvent of some benzyllithiiums coordinated to TMEDA. Their work is limited to hydrocarbon substituents
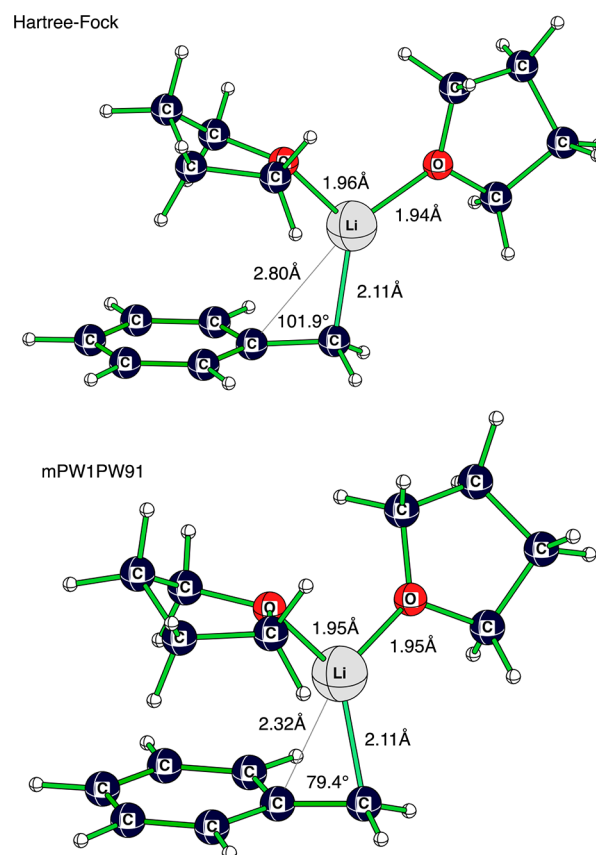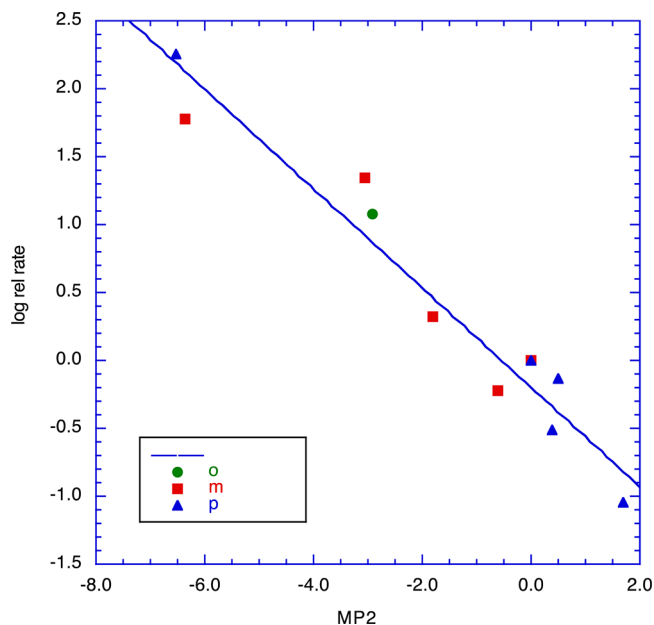
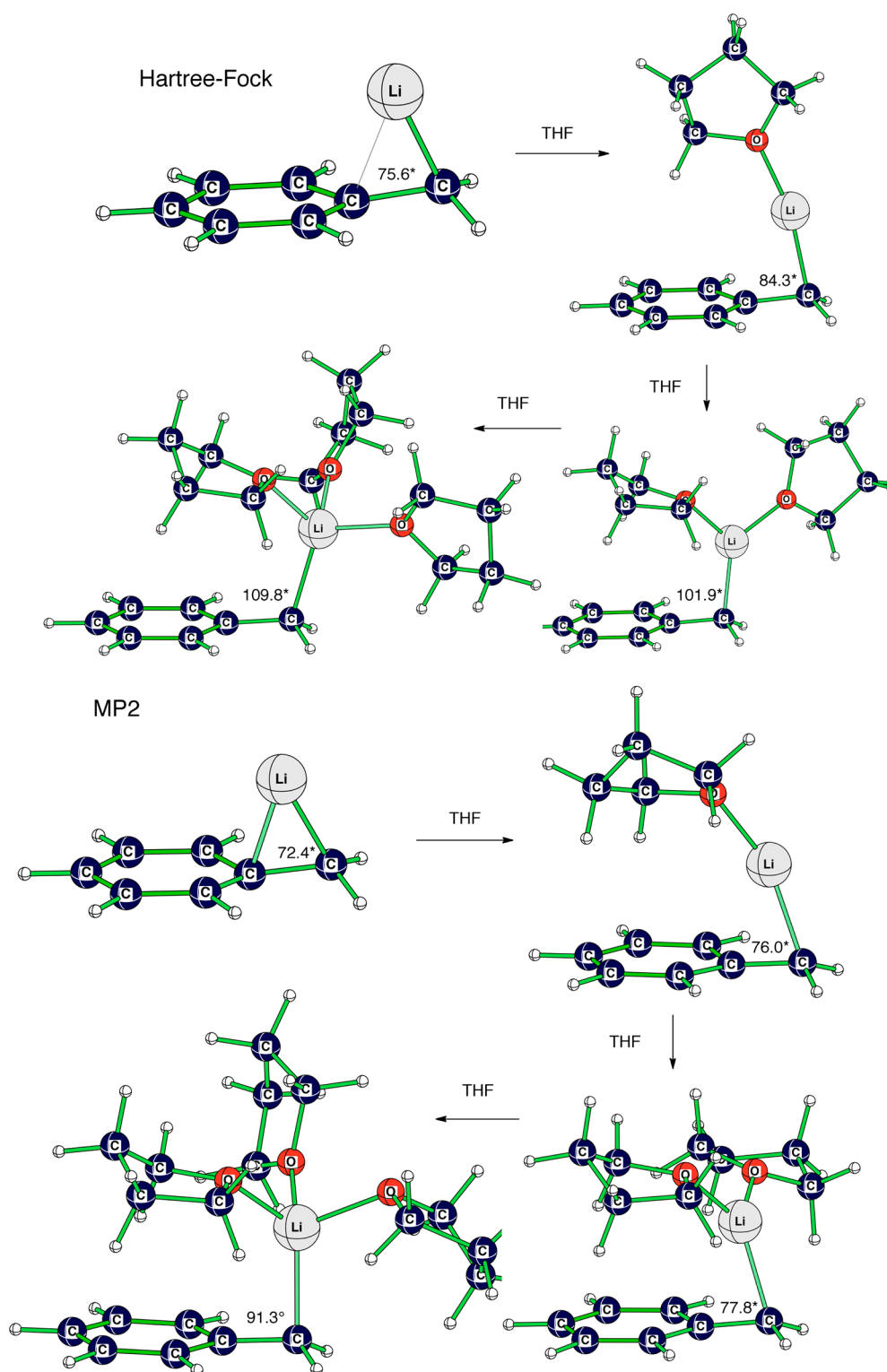and covers a relatively small range, but where their work overlaps with ours the agreement is good.

Figure 6. Progressive coordination of THF to lithium in benzyllithium results in opening the bond angle at the benzylic carbon, but the effect is greater at the Hartree–Fock level (above) than at MP2 (below).

Recently, we have been able to surmount the limitation of using dimethyl ether as a computational model for THF and have used THF itself for S in eq 2.[26] A comparison of eq 2 with S = THF compared to S = Me$_2$O is shown in Figure S1 (Supporting Information). The computational results are summarized in Table 1 with details available in the Supporting Information. The correlation is almost exact with R^2 = 0.995.

This correspondence shows that dimethyl ether can be an effective model for THF, particularly for those cases in which electronic effects dominate and steric effects are not important. As expected from this close correspondence, a Brönsted plot using the computed relative acidities with coordinated THF (Figure 2) is excellent. Indeed, the correlation is slightly better than with Me$_2$O and validates this computational model for the

acidities of substituted toluenes in a region where experimental acidities are difficult to obtain.

The RLi·2THF model was also tested with the hybrid density functional mPW1PW91,[22] (hereafter referred to as mPW1) which gives an excellent correlation with the set of experimental lithium acidities.[28] We therefore expected this functional to give a superior Brönsted correlation with the exchange rates. The results plotted in Figure 3 show a satisfactory correlation with $R^2 = 0.970$ but slightly inferior to that in Figure 2.

These results raise the obvious question: why is H−F at least as good as the presumably better hybrid density functional in this type of Brönsted correlation? There is an important difference in the computed structures from the two methods. Figure 4 compares the optimized structure of BnLi·2THF with both methods. The bond distances are about the same and the three ligands to Li are close to trigonal in both cases: The sum of angles about lithium is 360.0° for the H−F structure and 358.3° for the mPW1 structure. In both cases, the O−Li−O plane is twisted from the axis of the benzene ring: The two $C(ipso)−C(H_2)−Li$-O dihedral angles are 34° and −145° for H−F compared to 69° and −128° for mPW1. The biggest and most important difference is the C−C−Li angle at the benzylic carbon, a constrained 79.35° for mPW1, and a more open 101.87° for H−F. This puts the lithium in the mPW1 structure within bonding range of the ipso-carbon, 2.32 Å, and increases steric interactions of a coordinated solvent with the benzylic ring. To determine which structure is closer to reality, the structure was also optimized at the MP2/6-31+g(d) level. The resulting structure is similar to mPW1. Bond distances are slightly less, the ligands around lithium are close to trigonal (sum of angles = 359.2°) and the O−Li−O plane is twisted somewhat less from the benzene line (the two dihedral angles are 70° and −99°) but the crucial angle at the benzylic carbon is 77.8°, close to that for mPW1.

Several other structures were optimized at MP2/6-31+g(d) to compare with the mPW1 results. In general, the structures compare quite well; in particular, the bond angles at the benzylic carbon are generally about 2 degrees less than for mPW1 and more acute than 90°. The corresponding Brönsted plot (Figure 5) is distinctly poorer than that for mPW1.

As shown in Figure 6, at the H−F level progressive coordination of THF to the lithium of benzyllithium results in greater opening of the bond angle at the CH_2 group. The effect is less pronounced with MP2 such that only with full coordination does this angle become greater than 90°. This effect can be rationalized on the basis that the electrostatic attraction of the coordinating solvent dipoles to lithium also involves repulsion to the anionic ring which has the effect of moving the lithium assembly away from the ring and thus widening the angle at the benzylic carbon. Electron correlation included in the MP2 method effectively reduces this electrostatic repulsion between ligand and ring such that this angle stays more acute. One result is that steric interactions between ligand and ring are enhanced relative to the transition state for proton transfer with the remarkable result that Brönsted correlations are less effective at the higher theory level!

This interpretation is consistent with another feature of these results. A plot of the relative H−F acidities vs MP2 (Figure S2, Supporting Information) has a slope of 0.83 ± 0.08; that is, a structural change has a greater effect on the MP2 acidity than on H−F, another indication that steric effects are enhanced in the more congested MP2 structure. A comparable plot of

mPW1 vs MP2 has a slope of 0.91 ± 0.08, a lesser effect than H−F but still significant.

CONCLUSION

Semitheoretical Brönsted correlations can be effective to, in effect, extrapolate from a region where equilibrium measurements, such as acidities, are feasible to regions where direct measurements are not possible. Differences in the way different substituents or other structural changes are handled, however, can result in higher theory levels being less effective in such correlations. This caviat is perhaps not much different from the known effect that some structural changes or substituent effects have in causing deviations from purely experimental Brönsted correlations or, indeed, any linear free energy relationhips.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Tables of computational results. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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