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Importance of the Electron Correlation and Dispersion Corrections in Calculations Involving Enamines, Hemiaminals, and Aminals. Comparison of B3LYP, M06-2X, MP2, and CCSD Results with Experimental Data

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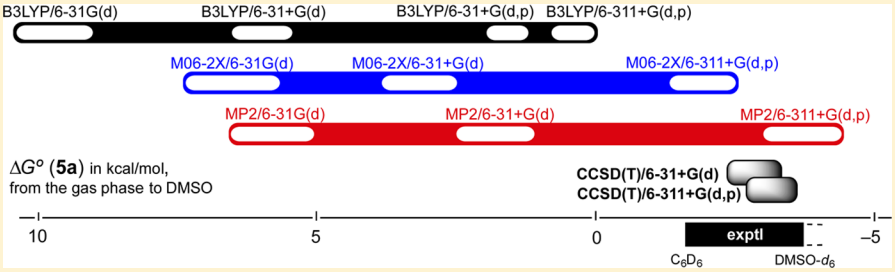
Supporting Information



ABSTRACT: While B3LYP, M06-2X, and MP2 calculations predict the ΔG° values for exchange equilibria between enamines and ketones with similar acceptable accuracy, the M06-2X/6-311+G(d,p) and MP2/6-311+G(d,p) methods are required for enamine formation reactions (for example, for enamine **5a**, arising from 3-methylbutanal and pyrrolidine). Stronger disagreement was observed when calculated energies of hemiaminals (*N*,*O*-acetals) and aminals (*N*,*N*-acetals) were compared with experimental equilibrium constants, which are reported here for the first time. Although it is known that the B3LYP method does not provide a good description of the London dispersion forces, while M06-2X and MP2 may overestimate them, it is shown here how large the gaps are and that at least single-point calculations at the CCSD(T)/6-31+G(d) level should be used for these reaction intermediates; CCSD(T)/6-31+G(d) and CCSD(T)/6-311+G(d,p) calculations afford ΔG° values in some cases quite close to MP2/6-311+G(d,p) while in others closer to M06-2X/6-311+G(d,p). The effect of solvents is similarly predicted by the SMD, CPCM, and IEFPCM approaches (with energy differences below 1 kcal/mol).

INTRODUCTION

The revival of the chemistry of enamines and iminium salts as a consequence of the development of the field of organocatalysis is outstanding.[1] To account for the reactions disclosed or developed, many research groups have carried out calculations based on the density functional theory (DFT) of the species and transition states presumably involved in these catalytic processes.[2] Sometimes, DFT calculations have been used to design new organocatalysts before synthesizing them, to try to increase the chances of success.

There have been many warnings about the shortcomings of diverse functionals, especially regarding the use and abuse[3] of the popular B3LYP method[4] by many organic chemists (such as ourselves). For example, Schleyer et al. and Schreiner et al. reported the systematic errors of B3LYP and related functionals in computing the energies of hydrocarbons,[3a−d] Tirado-Rives and Jorgensen studied a large set of compounds, including isomerization enthalpies for O- and N-containing molecules,[3g] Houk et al. evaluated the case of Diels−Alder additions,[3h] and Hoffmann, Schleyer, and Schaefer asked for more caution in the energy predictions and common sense in the terminology.[3i] More recently, Houk et al. estimated the sources of error in the reaction enthalpies for aldol, Mannich, and α-aminohydroxylation reactions.[3j] Among the handicaps of several DFT methods to provide reliable energy values, an important one is that they do not take into account the London dispersion forces; in simple terms, they do not consider the weak attraction between pairs of nonpolar atoms and between pairs of molecules arising from the interaction of instantaneous multipoles. Other more modern DFT methods, such as M06-2X by Truhlar et al.,[5] which give results closer to those obtained by the Møller−Plesset theory (MP2, for example),[6] are known to perform much better in this regard. More recently, Grimme et al. have included dispersion-corrected terms in DFT methods (DFT-D, DFT-D3), achieving much more reliable results.[7] These algorithms have been implemented in the ORCA package[8] and in the 2013 version of Gaussian 09.[9] Assessment of dispersion corrections in DFT methods is a hot topic.[3f,7] Dispersion-corrected MP2 calculations have also been reported.[10]

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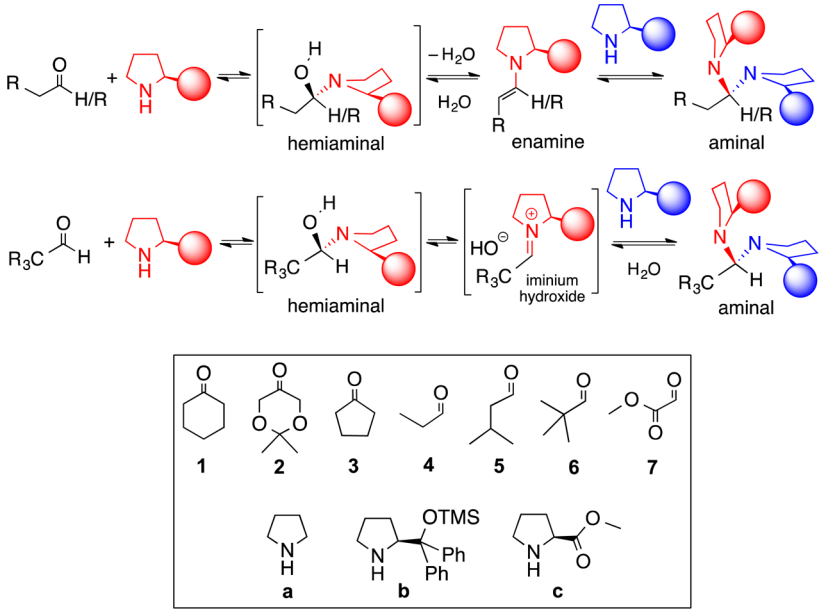
Scheme 1. Equilibria among Hemiaminals, Enamines, and Aminals from Carbonyl Compounds 1−7 and Secondary Amines a−c



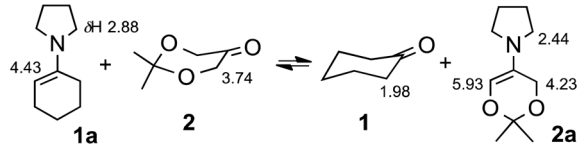
Our interest lies in the performance of DFT methods when providing insight into enamine- and iminium-based catalytic reactions and the design of new catalysts. In fact, in the past ten years, we have carried out B3LYP calculations with different basis sets in connection with several master's degrees and PhD theses. Some of those results have appeared as Supporting Information or in the main text of publications by our group[11] or in collaboration with other research groups.[12] The present study, thus, had two goals: (a) to check how reliable these former results were (as a self-criticism, which may also serve to rectify or reevaluate other results, if necessary); (b) to determine which methods, among the most popular, are appropriate for calculating equilibria involving hemiaminals (*N*,*O*-acetals) and aminals (*N*,*N*-acetals) summarized in Scheme 1.[13]

Hemiaminals are expected to be short-lived species in amine-catalyzed processes of carbonyl compounds with α-hydrogens, such as **1**−**5**, as they quickly dehydrate to give the active species, i.e., enamines (although significant proportions of H_2O in the medium may militate against this dehydration). Anyway, hemiaminals are crucial intermediates in the formation of either enamines or iminium salts and might explain some exchange reactions. Moreover, when the carbonyl compounds do not have enolizable hydrogens (such as **6** and **7**), hemiaminals might be detected since enamines cannot be formed, provided that carboxylic acids are absent otherwise iminium salts are favored. Although not productive, aminals are also plausible intermediates,[11a] depending on the relative amount of amine(s) in the medium (especially toward the end of the reaction, when starting materials are partially exhausted). They may also be involved in exchange reactions, if two amino groups or different amines are present in the medium.

RESULTS AND DISCUSSION

Equilibria between Enamines and Ketones. We first evaluated the relative thermodynamic stability of enamines. Table 1 shows the equilibrium reaction between the enamine from pyrrolidine and cyclohexanone (**1a**, prepared independently and isolated) and 2,2-dimethyl-1,3-dioxan-5-one (1,3-dihydroxyacetone isopropylidine acetal, **2**). For this isodesmic reaction (not hypothetical but real), B3LYP, M06-2X, and MP2 calculations, with geometries optimized with different basis sets, predicted similar total energy values (between −3.2 and −4.1 kcal/mol).[14] When thermal and entropy corrections were included, the predicted $\Delta G°$ values were also quite close. There are no significant differences between ΔE and $\Delta G°$, as there is the same number of similar molecules on both sides of the chemical equation.

Table 1. Calculated vs Experimental $\Delta G°$ Values for the Equilibrium between Enamines 1a and 2a and Their Ketones



	ΔE (kcal/mol)
B3LYP/6-31G(d)	−3.5
B3LYP/6-31+G(d)	−3.5
B3LYP/6-311+G(d,p)	−3.6
M06-2X/6-31G(d)	−3.8
MP2/6-31+G(d)//B3LYP/6-31G(d)	−4.0
MP2/6-31+G(d)//B3LYP/6-31+G(d)	−3.7
MP2/6-31+G(d)	−3.7
MP2/6-311+G(d,p)//B3LYP/6-31G(d)	−4.1
MP2/6-311+G(d,p)//B3LYP/6-31+G(d)	−4.1
CCSD(T)/6-31+G(d)//B3LYP/6-31+G(d)	**−3.2**

	$\Delta G°$(kcal/mol)	$\Delta G°_{(C_6H_6)}$[a]	$\Delta G°_{(DMSO)}$[a]
B3LYP/6-31G(d)	−3.1[b]	−3.3	−3.9
M06-2X/6-31G(d)	−3.4	−3.6	−4.2
MP2/6-31+G(d)	−3.6[c]	−4.2	−5.2
CCSD(T)/6-31+G(d) //B3LYP/6-31+G(d)	**−3.1**	**−3.7**	**−4.7**

K_{eq} ≈ 160 (C_6D_6)	K_{eq} ≈ 540 (DMSO-d_6)
$\Delta G°_{exp}$ ≈ −3.0 kcal/mol	$\Delta G°_{exp}$ ≈ −3.6 kcal/mol

[a]Solvent effects were estimated by means of the SMD method (see the main text). [b]This value changes to −3.4 kcal/mol using the vibrational frequency scaling factors for B3LYP/6-31G(d) (see SI); all DFT $\Delta G°$ values given henceforward are without scaling. [c]The same result with MP2/6-31G(d), taking into account or not the scaling corrections.

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The solvent effects were calculated by means of the SMD method,[15a] but when we compared this with the CPCM and IEFPCM methods the results were similar[15b] (also for other equilibria[15c]). The effect of a nonpolar solvent such as benzene, with respect to the gas phase, was predicted to be quite small (a decrease of ΔG° of 0.2−0.6 kcal/mol), as expected; it was quite general or was assumed to be general and was not always calculated. The effect of a polar solvent such as DMSO lowered the calculated ΔG° value more (0.8−1.3 kcal/mol). When we determined, by ^{1}H NMR spectroscopy, the K_{eq} values for such an exchange reaction (**1a** + **2** = **1** + **2a**) in C_6D_6 and in DMSO-d_6,[16] the agreement between the predicted and experimental values was very good. Bearing in mind the inherent approximations of MO calculations, the experimental errors (as the equilibrium constants were determined from peak integrations in the ^{1}H NMR spectra, at relatively high concentrations), the presence of several conformers for many of the molecules studied (from which we have only selected that of the lowest energy for the calculation of the Gibbs free energy values, or free enthalpy values, as usual), and how the solvent effects were calculated in our study (implicit solvent models, single-point calculations), the agreement is surprisingly excellent.

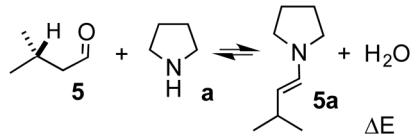
Thus, for the equilibrium shown in Table 1, with species with similar electronic delocalization and steric hindrance on both sides, the simplifications and errors are compensated for. Higher level calculations, such as CCSD(T) calculations also indicated in Table 1 (bottom), are not required for these types of equilibria, as computational chemists recognize.

We obtained similar excellent agreements for equilibrium reaction between enamine **1a** and cyclopentanone (**3**) to give **1** and (1-cyclopentenyl)pyrrolidine (**3a**), for which we experimentally determined K_{eq} = 2.0 ± 0.2 (C_6D_6) and K_{eq} = 2.1 ± 0.2 (DMSO-d_6). At various calculation levels, using geometries optimized with different basis sets, the predicted reaction energies were practically the same; for example, single-point calculations with the MP2/6-31+G(d) and MP2/6-311+G(d,p) methods provided practically identical results starting from different geometries, as shown in more detail in Supporting Information (SI).

Formation of Enamines from Aldehydes and Pyrrolidine. In sharp contrast, for the formation of enamines, the use of large basis sets and diffuse functions gave much lower free energy values. The cases of pyrrolidine enamines of propanal (from **4**, Scheme 1, to its enamine **4a**) and 3-methylbutanal (from **5** to enamine **5a**) were first studied. The details are given in SI. Table 2 summarizes the essential points for the case of **5a**. Only M06-2X/6-311+G(d,p), MP2/6-311+G(d,p), CCSD(T)/6-31+G(d), and CCSD(T)/6-311+G(d,p) predict that these equilibria are shifted to the right, close to experimental data (the M06-2X value being closer to our experiments in C_6D_6 and the MP2 and CCSD values closer to our experiments in DMSO-d_6). Thus, when there is only one conjugate species in the chemical equation, the better the treatment of the electron correlation, the better the agreement with the experimental value, as expected.

It is worth noting that the CCSD(T)/6-31+G(d) and CCSD(T)/6-311+G(d,p) results are almost identical. Thus, for the enamines examined here it is not necessary to use the CCSD(T)/6-311+G(d,p) method, which is much more expensive: each structure with >14 atoms in the second period required >14 days with 6 processors working together.

Table 2. Calculated vs Experimental ΔG° Values, in kcal/mol, for the Formation of Enamine 5a from Aldehyde 5

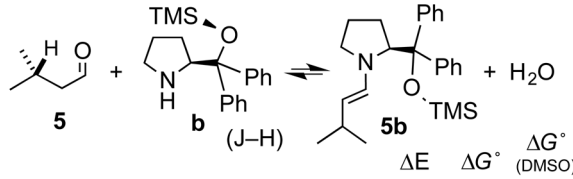


	ΔE	ΔG°	ΔG° (DMSO)
B3LYP/6-31G(d)	10.0	10.4	9.0
B3LYP/6-31+G(d)	5.9	6.4	5.5
B3LYP/6-31+G(d,p)	1.3	1.9	1.3
B3LYP/6-311+G(d,p)	0.5	0.8	0.0
M06-2X/6-31G(d)	7.4	7.3	5.7
M06-2X/6-31+G(d)	3.9	3.8	2.5
M06-2X/6-311+G(d,p)	–1.6	–1.4	–2.3
MP2/6-31G(d)//B3LYP/6-31G(d)	6.5	6.9	5.1
MP2/6-31+G(d)//B3LYP/6-31G(d)	2.0	2.5	1.1
MP2/6-311+G(d,p)//B3LYP/6-311+G(d,p)	–3.3	–3.0	–4.3
MP2/6-311+G(d,p)//M06-2X/6-311+G(d,p)	–3.5	–3.3	–4.6
CCSD(T)/6-31+G(d)//B3LYP/6-31+G(d)	**–2.8**	**–2.4**	**–3.2**
CCSD(T)/6-311+G(d,p)//B3LYP/6-311+G(d,p)	**–3.1**	**–2.8**	**–3.5**

K_{eq} = 14.3 (C_6D_6) K_{eq} ≥ 500 (DMSO-d_6)
ΔG°_{exp} = –1.6 kcal/mol ΔG°_{exp} ≤ –3.7 kcal/mol

For the sake of comparison, the reaction yielding enamine **5b** from 3-methylbutanal and the Jørgensen−Hayashi catalyst (henceforward J−H, see **b**)[1,17] is shown in Table 3. Whereas

Table 3. Calculated vs Experimental ΔG° Values, in kcal/mol, for the Formation of Enamine 5b from Aldehyde 5



	ΔE	ΔG°	ΔG° (DMSO)
B3LYP/6-31G(d)	14.8	15.8	14.3
B3LYP/6-31+G(d)	10.2	11.9	10.5
B3LYP/6-311+G(d,p)	5.1	6.1	4.9
M06-2X/6-311+G(d,p)//B3LYP/6-311+G(d,p)	0.5	1.6	0.2
MP2/6-311+G(d,p)//B3LYP/6-311+G(d,p)	–5.0	–4.0	–5.8

K_{eq} ≈ 20 (DMSO-d_6), ΔG°_{exp} ≈ –1.8 kcal/mol

the B3LYP/6-311+G(d,p) numbers predict that the equilibrium is very shifted to the left, which does not agree with the experimental fact, MP2/6-311+G(d,p) calculations predict an equilibrium too shifted toward **5b** (overestimation of the dispersion energy). M06-2X/6-311+G(d,p) gives an intermediate value. It can be assumed again that CCSD(T) methods would provide results between M06-2X and MP2 (of Table 3), again closer to the experimental ones, but we did not perform these calculations (they would have been too costly).

Formation of Hemiaminals. With all this background, we were ready to examine related equilibria that, to the best of our knowledge, have never been subjected to the scrutiny of high-level calculations.

When a simple hemiaminal, or *N*,*O*-acetal, such as **HA-4a** (Table 4) was calculated at different levels of theory, it was noted that B3LYP, with different basis sets, predicted ΔG°(DMSO) values of 11.6−13.7 kcal/mol; that is to say, when there were no differences in conjugation (electronic

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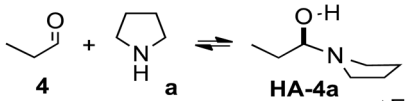
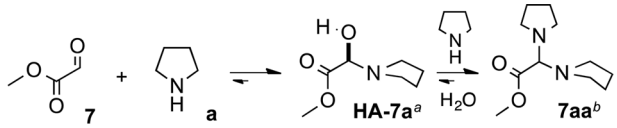
Table 4. Calculated ΔG° Values, in kcal/mol, for the Formation of the Hemiaminal Related to 4a (HA-4a)



	ΔE	ΔG°	ΔG° (DMSO)
B3LYP/6-31G(d)	−6.9	8.7	11.6
B3LYP/6-31+G(d)	−5.7	9.9	13.7
B3LYP/6-311+G(d,p)	−5.9	9.8	13.6
B2PLYP-D3/6-311+G(d,p)//B3LYP/6-31+G(d)	−9.6	6.0	10.1
wB97XD/6-311+G(d,p)//B3LYP/6-31+G(d)	−14.5	1.1	4.9
M06-2X/6-31G(d)	−16.8	−1.2	1.9
M06-2X/6-31+G(d)	−16.0	−0.4	3.4
M06-2X/6-311+G(d,p)	−16.8	−0.9	2.8
MP2/6-311+G(d,p)//B3LYP/6-31+G(d)	−15.6	0.0	3.1
MP2/6-311+G(d,p)//B3LYP/6-311+G(d,p)	−15.7	0.1	3.2
CCSD(T)/6-31+G(d)//B3LYP/6-31+G(d)	**−13.0**	**2.4**	**6.2**
CCSD(T)/6-311+G(d,p)//B3LYP/6-311+G(d,p)	**−13.6**	**2.1**	**5.4**

Table 5. Calculated ΔG° Values, in kcal/mol, for the Reactions of Methyl Glyoxylate with Pyrrolidine



	ΔE	ΔG°	ΔG° (DMSO)	ΔE	ΔG°	ΔG° (DMSO)
B3LYP/6-31+G(d)	−12.9	2.4	4.9			
B3LYP/6-311+G(d,p)	−13.0	2.5	4.9	1.3	1.5	0.0
B2PLYP-D3/6-311+G(d,p)//B3LYP/6-31+G(d)	−17.4	−2.1	0.6			
wB97XD/6-311+G(d,p)//B3LYP/6-31+G(d)	−21.4	−6.1	−3.7			
M06-2X/6-31+G(d)	−23.8	−8.5	−5.9			
M06-2X/6-311+G(d,p)//B3LYP/6-311+G(d,p)	−24.3	−8.7	−6.3			
M06-2X/6-311+G(d,p)	−24.5	−9.3	−6.8			
MP2/6-31+G(d)//B3LYP/6-31+G(d)	−21.6	−6.3	−3.8			
MP2/6-311+G(d,p)//B3LYP/6-311+G(d,p)	−22.2	−6.6	−4.6	−7.6	−7.4	−8.9
CCSD(T)/6-31+G(d)//B3LYP/6-31+G(d)	**−20.4**	**−4.9**	**−2.5**			
CCSD(T)/6-311+G(d,p)//B3LYP/6-311+G(d,p)	**−20.5**	**−5.0**	**−2.8**			

[a]With EtOCOCHO (7′) in C_6D_6 the first equilibrium, the formation of hemiaminal, was quickly shifted to the right (to **HA-7′a**). [b]By contrast, the homologue of aminal **7aa** (**7′aa**) appeared slowly (a few days at rt to reach the second equilibrium, unless catalytic amounts of PhCOOH were added), though it was also fully shifted to the right.

delocalization) on either side of the chemical equation, small differences were obtained between using smaller or larger basis sets. The ΔG°(DMSO) values calculated with M06 and MP2 were 10 kcal/mol lower (1.9−3.2 kcal/mol). No experimental data are available for comparison since, as known, aldol reactions take place quickly in this case, via the enamine that is rapidly formed by dehydration of the hemiaminal and/or via base catalysis.

Due to the lack of experimental values regarding hemiaminals, we carried out additional calculations using dispersion-corrected DFT methods,[18] such as B2PLYP-D3 and wB97XD, just to check the effect of such corrections. We did not plan to systematically compare a long series of these DFT functionals. It is worth noting that wB97XD/6-311+G(d,p) gave ΔG°(DMSO) = 4.9 kcal/mol, an intermediate value between the two extremes mentioned in the preceding paragraph, although closer to the M06 and MP2 values. This value was also close to that of 5.4 kcal/mol predicted by our highest level calculation, that is, using the CCSD(T)/6-311+G(d,p) method. In other words, B3LYP methods are not reliable in these cases, as they predict that the attack of secondary amines on carbonyl groups are much less exothermic than expected, so that, once the entropic term is included, the equilibria are shifted too far to the left to allow for the detection of hemiaminals. By contrast, high-level calculations predicted that the equilibrium in Table 4 (ΔG° in DMSO) was not so shifted to the left. These observations held in other cases in which the carbonyl groups are sterically more hindered and, consequently, the hemiaminals are more crowded (such as the reaction of **3** with pyrrolidine to yield **HA-3a**, and of **6** with pyrrolidine to yield **HA-6a**, included as SI in an expanded Table 4).

To study one example of hemiaminal formation with the equilibrium shifted to the right, we chose methyl glyoxylate (methyl glyoxalate, methyl 2-oxoacetate, **7**), where the presence of an EWG linked to the carbonyl may relatively stabilize[19] the corresponding hemiaminal, **HA-7a**. Within each level of theory (see Table 5, first equilibrium), the use of smaller or larger basis sets almost did not affect the calculated reaction energies (as mentioned for other cases in which the differences in electronic delocalization of the molecules involved in the equilibria are not important).

The B3LYP calculations suggested that the first equilibrium of Table 5 was shifted slightly to the left, whereas M06-2X and MP2 indicated that it was shifted far to the right. The experimental fact, using commercially available ethyl glyoxylate (OHC−COOEt, 7′), is that the equilibrium is shifted far to the right, in such a way that we could not measure the equilibrium constant due to its high value (full conversion of 7′ and pyrrolidine into **HA-7′a** in C_6D_6). Our most reliable calculations, CCSD(T), suggested that the error in the B3LYP calculations can be around 7.5 kcal/mol. On the other hand, M06-2X and MP2, again with respect to CCSD(T), overestimated the stability of the **HA-7a** by 3.4−4.0 kcal/mol and 1.3−1.8 kcal/mol, respectively.

It can be observed that CCSD(T)/6-31+G(d) and CCSD(T)/6-311+G(d,p) values do not differ too much. The former, although generally less reliable, is a good approach to the latter, at least with regard to the formation of this and previous hemiaminals. Again, wB97XD/6-311+G(d,p) gave results intermediate between MP2/6-311+G(d,p) and CCSD(T)/6-311+G(d,p), all of them close to each other.

Formation of Aminals from Hemiaminals. The conversion of hemiaminal **HA-7a** into aminal **7aa** (that is, equilibrium **HA-7a** + **a** = **7aa** + H_2O, Table 5, right side) was also calculated. B3LYP indicated that it is slightly endothermic, while according to MP2 it is highly exothermic and, as expected for an equilibrium involving two molecules on both sides (small differences in entropy), the ΔG° values indicated that the possible equilibrium is completely shifted to the right. Experimentally, we observed that this was the case in the NMR tube, using the hemiaminal of ethyl glyoxylate (**HA-7′a**). The conversion was slow, even in the presence of an excess of pyrrolidine, but it sufficed to add a catalytic amount of benzoic acid to the NMR tube to cause an almost immediate and quantitative transformation of the hemiaminal, **HA-7′a**, into the aminal, **7′aa**.[20] Overnight treatment of 7′ with 210 mol % of pyrrolidine, in the presence of 4-Å MS, also gave **7′aa** quantitatively.

The reaction of **7** with the Jørgensen−Hayashi catalyst (**b**) was also computationally examined, and the results were parallel (see SI, addendum to Table 5). With the commercially

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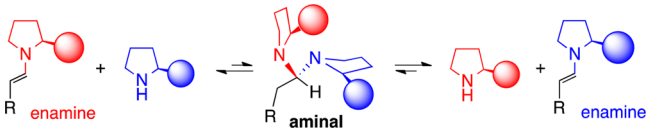
available ethyl glyoxylate (7′), we were able to determine the equilibrium constant for the formation of hemiaminal **HA-7′b** (7600 M^{-1}, that is, above 7000 $L{\cdot}mol^{-1}$). It was feasible since this first equilibrium is in practice less shifted to the right (in comparison with the reaction of 7′ with pyrrolidine to give **HA-7′a**), while the second equilibrium (formation of aminal **7′bb**) did not intervene, as it was slower and not so favorable.

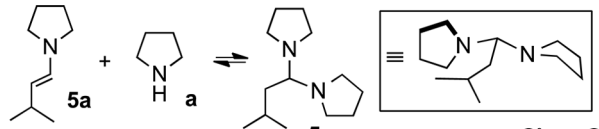
Formation of Aminals from Enamines. We also examined the formation of aminals from the addition of amines to enamines; that is, we calculated the first step of the general equilibria shown in Scheme 2.

Scheme 2. Plausible Equilibria between Enamines and Aminals



The energies of aminal **5aa** at different levels of theory and then the free enthalpy for equilibrium **5a** + **a** = **5aa** (aminal from 3-methylbutanal and pyrrolidine) were calculated. A brief summary is shown in Table 6. Here the gap between B3LYP/6-311+G(d,p) and the other methods was larger than ever. The ΔE values of M06-2X, wB97XD, and CCSD(T) were practically identical. The values predicted by M06-2X/6-311+G(d,p) agreed with the experimental ones, even more than those coming from CCSD(T)/6-31+G(d). In the light of the corresponding results shown in Table 5, we assume that CCSD(T)/6-311+G(d,p), not calculated, would give a value even closer to M06-2X and the experimental one. Using the experimental value in DMSO as the reference, the error (underestimation) of B3LYP/6-311+G(d,p) was around 14.5 kcal/mol (in DMSO) while the overestimation of the dispersion corrections by MP2/6-311+G(d,p) was only around 3 kcal/mol (also in DMSO). It is well established that B3LYP methods are very often inappropriate for energy calculations, but here we show how large they may be when moderately crowded molecules such as **5aa** are involved.

Table 6. Calculated vs Experimental $\Delta G°$ Values, in kcal/mol, for the Formation of Aminal 5aa from 5a and Pyrrolidine



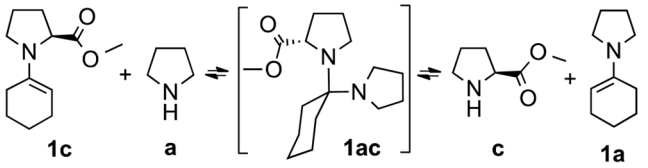
	ΔE	ΔG°	ΔG° (C_6H_6)	ΔG° (DMSO)
B3LYP/6-311+G(d,p)	−3.5	12.4	14.9	15.8
wB97XD/6-311+G(d,p)//B3LYP/6-311+G(d,p)	−19.0	−3.1	−0.5	0.4
M06-2X/6-311+G(d,p)	−19.1	−2.5	0.2	1.2
MP2/6-311+G(d,p)//B3LYP/6-311+G(d,p)	−21.0	−5.0	−2.6	−1.8
CCSD(T)/6-31+G(d)//B3LYP/6-31+G(d)	**−18.9**	**−2.9**	**−0.2**	**0.7**

$K_{eq} \approx 0.24$ $L{\cdot}mol^{-1}$ (C_6D_6); $\Delta G°_{exptl} \approx 0.8$ kcal/mol

$K_{eq} \approx 0.11$ $L{\cdot}mol^{-1}$ (DMSO-d_6); $\Delta G°_{exptl} \approx 1.3$ kcal/mol

Equilibria between Enamines (via aminals). Table 7 compares two equilibria between enamines and secondary amines. In the first, where the conjugation and steric hindrance on both sides are similar: (i) the size of the basis set is not significant; (ii) the B3LYP errors are small; (iii) all the other methods give values quite close to the experimental ones. Experimentally, under the reaction conditions (with nearly equimolar amounts of the secondary amine, in NMR tubes at 25 °C), we did not detect aminal **1ac**, so it is indicated within brackets. The $\Delta G°$ value (gas phase) calculated at the M06-2X/6-311+G(d,p) level for the **1c** + **a** = **1ac** equilibrium is 3.2 kcal/mol (to be compared with $\Delta G° = -2.5$ kcal/mol, also in the gas phase at the same level, for the **5a** + **a** = **5aa** equilibrium shown in Table 6).

Table 7. Calculated vs Experimental $\Delta G°$ Values, in kcal/mol, for the Exchange of the 1-Cyclohexenyl Group between Secondary Amines a and c



	ΔE	ΔG°	ΔG° (DMSO)
B3LYP/6-31+G(d)	−2.5	−2.8	−1.7
B3LYP/6-311+G(d,p)	−2.6	−2.8	−1.7
wB97XD/6-311+G(d,p)//B3LYP/6-31+G(d)	−1.4	−1.6	−0.5
M06-2X/6-31+G(d)	−1.7	−0.9	0.2
M06-2X/6-311+G(d,p)	−1.7	−1.6	−0.6
MP2/6-311+G(d,p)//B3LYP/6-31+G(d)	−0.2	−0.4	0.6
MP2/6-311+G(d,p)//M06-2X/6-31+G(d)	−0.4	−0.5	1.4
CCSD(T)/6-31+G(d)//B3LYP/6-31+G(d)	**−1.1**	**−1.3**	**−0.2**

$K_{eq} = 8.4 \pm 0.8$ (C_6D_6); $\Delta G°_{exptl} \approx -1.3$ kcal/mol

$K_{eq} = 6.7 \pm 0.9$ (DMSO-d_6); $\Delta G°_{exptl} \approx -1.1$ kcal/mol

Finally, in Table 8, where the large substituent may actually give rise to steric hindrance, the size of the basis set is insignificant, as in the preceding table, but now the gap between B3LYP/6-311+G(d,p) and the other methods is more important. While MP2/6-311+G(d,p) surprisingly predicts positive $\Delta G°$ values (generally attributed to an overestimation of the dispersion corrections), the M06-2X/6-311+G(d,p) results are close to the available experimental value in C_6D_6. By the way, spectra were not registered in DMSO-d_6 because of the partial cleavage of the O−Si bond, in this and other cases in which equilibria are reached slowly. Although the exchanges of Tables 7 and 8 may also occur through partial hydrolysis of the enamines if a trace of water was present in the NMR tubes, what matters here is the position of the equilibria.

CONCLUSIONS

Only when an identical number of similar molecules are on both sides of a chemical equation (similar electronic delocalization, comparable steric hindrance) may the B3LYP energies be partially reliable. The B3LYP methods, which are so efficient for geometry optimizations, give large errors for the

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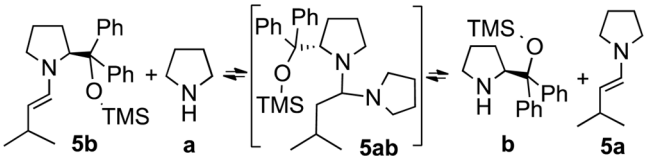
Table 8. Calculated vs Experimental ΔG° Values, in kcal/mol, for the Exchange of an Alkenyl Group between Secondary Amines a and b



	ΔE	ΔG°	ΔG°(DMSO)
B3LYP/6-31G(d)	–4.8	–5.4	–5.3
B3LYP/6-31+G(d)	–4.3	–5.6	–5.0
B3LYP/6-311+G(d,p)	–4.6	–5.3	–4.8
M06-2X/6-311+G(d,p)//B3LYP/6-311+G(d,p)	–2.2	–2.9	–2.6
MP2/6-311+G(d,p)//B3LYP/6-311+G(d,p)	1.7	1.0	1.6

K_{eq} ≈ 75 (C_6D_6) ΔG°_{exptl} ≈ –2.6 kcal/mol

examples shown in Tables 2–6 and 8. Higher-level calculations, for example MP2 and/or M06-2X, with large basis sets, are necessary in these cases. Obviously, this is well-known,[3,7] but we have disclosed here how much all these methods underestimate or overestimate the electron correlation and London dispersion forces regarding enamines, hemiaminals, and aminals. Top-level calculations cannot always be efficiently carried out, but the outcomes have been compared with experimental ΔG° values in C_6D_6 and/or DMSO-d_6 solutions reported here for the first time. Although a study of the performance of dispersion-corrected DFT methods was outside the scope of this work, we observed that wB97XD/6-311+G(d,p) gives energy values very close to CCSD(T), for hemiaminals and aminals.

For the formation of simple enamines, the CCSD(T) free enthalpy values were almost intermediate between the M06-2X/6-311+G(d,p) and MP2/6-311+G(d,p) values (see the case of **5a**, Figure 1, left). For the equilibria of formation of hemiaminals, the M06-2X/6-311+G(d,p) values were systematically more exoergic than the MP2/6-311+G(d,p) and CCSD(T) results, as graphically indicated in Figure 1 (center) for the case of hemiaminal **HA-7a**. Finally, for the formation of aminals from enamines and secondary amines, the MP2/6-311+G(d,p) energies were more negative than those determined experimentally and/or predicted by CCSD(T) and M06-2X/6-311+G(d,p), as shown in Figure 1 (right) for the equilibrium between **5a** and **5aa** in the gas phase. For more crowded molecules (such as enamines from the J–H catalyst), the classical MP2 fails, as the energies are further overestimated (updated methods[7,10] would be needed). Anyway, what is clear is that the energy values predicted by B3LYP/6-311+G(d,p) for the three equilibria of Figure 1 (corresponding to Tables 2, 5, and 6, respectively) are wrong; those predicted by B3LYP with smaller basis sets, not included in Figure 1 for the sake of simplicity, are worse (left), similar (center), and paradoxically some kcal/mol lower (right). We hope that these conclusions will be useful to others and help avoid mistakes that we made years ago.

EXPERIMENTAL SECTION

Computational Methods. The calculations were carried out with the Gaussian 09 package (Revision D.01, 2013)[9] with methods B3LYP[4] M06-2X,[5] MP2,[6] and CCSD(T).[21] The ORCA package was also used in a few cases for the sake of comparison.[8] The stationary points were characterized by frequency calculations. Gibbs free energies (free enthalpies) at 298.15 K for all the reactions were calculated on the basis of the rigid rotor/harmonic oscillator approximation. The solvent effects were calculated by means of the SMD method,[15a] but also the CPCM and IEFPCM methods were sometimes used, again for the sake of comparison. The effect of scaling factors was evaluated on the equilibrium of Table 1 for the B3LYP/6-31G(d) and MP2/6-31G(d) methods;[22] as no significant differences were noted (see SI), these corrections were not considered in the remaining equilibria (Tables 2–8), for the sake of simplicity.

Starting Materials and General Information. All the carbonyl compounds used in this work (**1**–**7**) are known, and most of them are commercially available; they were dried over 4-Å MS before use. 1,3-

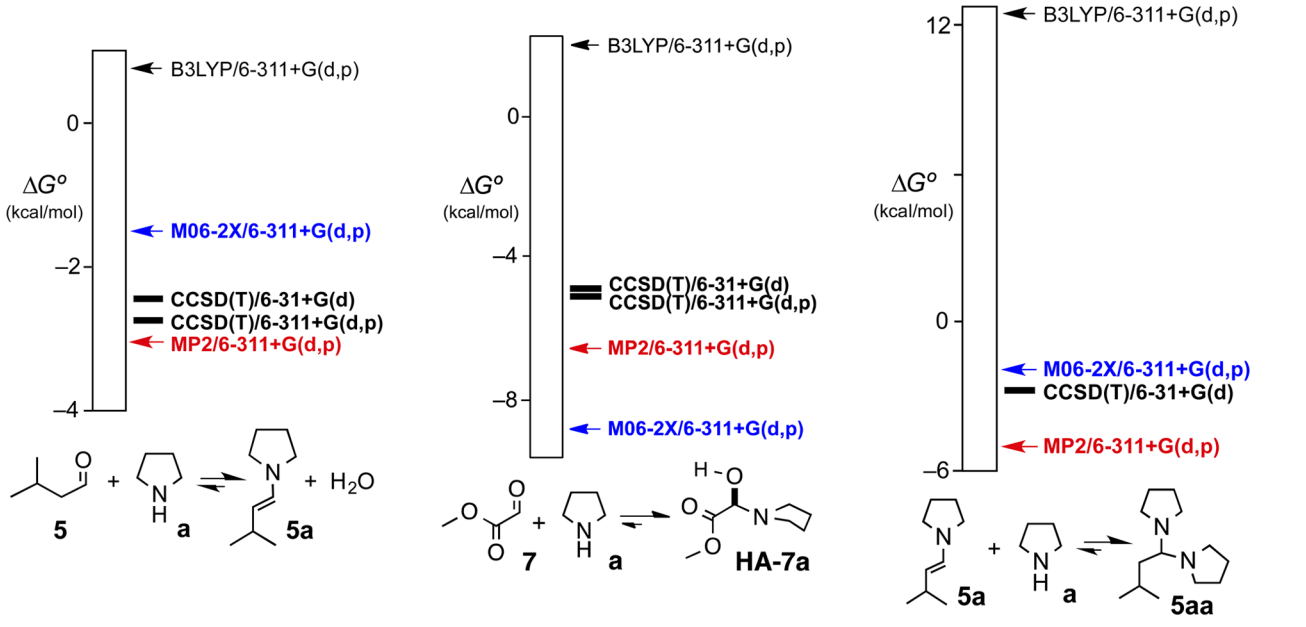


Figure 1. Comparison of calculated ΔG° values in the gas phase for the reactions of formation of enamine **5a** (left), hemiaminal **HA-7a** (center), and aminal **5aa** (right) from the corresponding carbonyl compounds (left, center) or enamine (right).

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Dihydroxyacetone isopropylidene acetal (2,2-dimethyl-1,3-dioxan-5-one, **2**) was prepared according to the procedure of Enders et al.,[23] although we purified the compound by flash column chromatography over silica gel (CH_2Cl_2) instead of by distillation. A technical grade, commercially available mixture of ethyl glyoxylate (**7′**) and toluene (50%) was purified by flash chromatography (95:5 to 1:1, hexanes/ethyl acetate, to remove toluene and polymeric material), followed by fractional distillation[24] at 20 mbar under N_2 (and stored after dilution with C_6D_6). Enamine **1a** is commercially available. Most NMR spectra were registered in C_6D_6 and in anhydrous DMSO-d_6. ^{1}H NMR spectra were recorded on 400 MHz spectrometers, with 5 s of mixing time. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (C_6D_5H in C_6D_6 at 7.16 ppm, CD_3SOCHD_2 in DMSO-d_6 at 2.50 ppm); data are reported in the following order: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants in hertz, integration. ^{13}C NMR spectra were recorded on 100.6 MHz instruments with proton decoupling; chemical shifts are reported in ppm with the solvent as the internal standard (C_6D_6, δ 128.06 ppm; DMSO-d_6, δ 39.52 ppm). The most relevant cross-peaks of 2D NMR experiments are marked on the spectra; HSQC cross-peaks belonging to CH and CH_3 are tagged in blue and those to CH_2 in red. FTIR spectra of **HA-7′a** and **7′aa** in their liquid form (oils) were registered; only the main absorptions, in cm^{-1}, are given. The mass spectra were obtained by the electrospray ionization (ESI+, TOF) technique.

Reactions of formation of enamines, hemiaminals, and aminals, as well as exchange reactions, were generally carried out and/or followed in standard NMR tubes by mixing appropriate amounts of reactants or reagents; details for the determination of the equilibrium constants from the ^{1}H NMR integrations of relevant peaks are given as SI.

Representative Procedure for the Preparation of Enamines. A solution of L-proline methyl ester (compound **c**, 2.05 g, 15.9 mmol), cyclohexanone (compound **1**, 1.64 mL, 15.9 mmol), and *p*-toluenesulfonic acid ($TsOH·H_2O$, 60 mg, 0.31 mmol) in cyclohexane (40 mL) was heated at reflux temperature in a Dean−Stark apparatus for 5 h. Removal of the solid (salt of the proline derivative and TsOH) by filtration or decantation, evaporation of the solvent under vacuum, addition of CH_2Cl_2 and coevaporation (two or three times) in the rotary evaporator, and removal of residual solvents and cyclohexanone with a vacuum pump afforded enamine **1c** as a yellow oil (practically quantitative yield),[25] which was analyzed by NMR and used without further purification (to avoid its easy hydrolysis). Enamines **1a**,[26] **2a**,[27] **3a**,[28] **5a**,[29] and **5b**[30] (in this last case no TsOH was added, to avoid partial desilylation of the OTMS group and subsequent reactions) were similarly prepared in >95% yields.

Representative Example of Enamine Formation (as Monitored by NMR). Pyrrolidine (compound **a**, 4.0 mg, 0.06 mmol) was added to a solution of isovaleraldehyde (3-methylbutanal, **5**, 5.0 mg, 0.06 mmol) in C_6D_6 (0.7 mL) or in anhydrous DMSO-d_6 (0.7 mL) in a vial. The mixture was directly transferred to a NMR tube and ^{1}H NMR spectra were recorded until equilibrium was attained (no additional increase of the peaks of **5a**, usually within 1 h).

Representative Example of an Exchange Reaction. 2,2-Dimethyl-1,3-dioxan-5-one (**2**, 14.0 mg, 0.10 mmol) was added to a solution of **1a** in C_6D_6 (0.7 mL) or in anhydrous DMSO-d_6 (0.7 mL), and ^{1}H NMR spectra were recorded until the relative heights of the peaks of **2**, **1a**, **2a**, and **1** did not change further (usually within 1 h).

Hemiaminal HA-7′a. To ethyl glyoxylate (ethyl oxoacetate, **7′**, 7.2 mg, 0.07 mmol) in C_6D_6 (up to 0.7 mL) was added pyrrolidine (5.0 mg, 0.07 mmol), and the spectra were registered: ^{1}H NMR (C_6D_6) δ 4.92 (s, 1H), 3.91 (qd, J = 7.1, 3.8, 2H), 2.76 (m, 4H), 1.53 (m, 4H), 0.87 (t, J = 7.1, 3H); ^{13}C NMR (C_6D_6) δ 172.3, 82.1, 61.5, 47.1, 24.6, 14.1. Removal of the solvent under good vacuum, without heating, gave **HA-7′a** as a colorless oil (12.0 mg, ca. 100%); FTIR 3430 (br), 1730; HRMS (ESI+) m/z calcd for $C_8H_{16}NO_3^+$ $(M + H)^+$ 174.1125, found 174.1119; the base peak was the corresponding pyrrolidinium ion ($C_4H_8N^+$=$CHCOOC_2H_5$), m/z calcd for $C_8H_{14}NO_2^+$ 156.1019, found 156.1014.

Aminal 7′aa. To ethyl glyoxylate (ethyl oxoacetate, **7′**, 7.2 mg, 0.07 mmol) in C_6D_6 (up to 0.7 mL) was added pyrrolidine (10.0 mg, 0.14 mmol), and the mixture was treated overnight with 4-Å molecular sieves. Filtering and removal of the solvent under good vacuum, without heating, afforded 17.0 mg (ca. 100%) of **7′aa** as an oil; when distillation was attempted at 1 mbar with a much larger volume of sample, only decomposition was noted. ^{1}H NMR (C_6D_6) δ 4.02 (q, J = 7.2, 2H), 3.80 (s, 1H), 2.89−2.72 (m, 8H), 1.60 (m, 8H), 0.99 (t, J = 7.1, 3H); ^{13}C NMR (C_6D_6) δ 169.4, 82.8, 59.8, 49.7, 24.0, 14.7; FTIR 1744; HRMS (ESI+), the $(M + H)^+$ peak, $C_{12}H_{23}N_2O_2^+$, m/z 227.1754, can hardly be observed (even at low voltages and temperatures), while pyrrolidinium ion $C_4H_8N^+$=$CHCOOC_2H_5$, m/z 156.1014, was the main peak; however, registering the spectrum at 25 V, from a solution prepared in anhydrous benzene and diluted just before injection with anhydrous acetonitrile, the $(M + Na)^+$ peak was clearly observed, m/z calcd for $C_{12}H_{22}N_2NaO_2^+$ 249.1573, found 249.1566.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01814.

Details of calculations, copies of NMR and 2D-NMR spectra, and procedures for the determination of equilibrium constants (PDF)

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Notes

The authors declare no competing financial interest.

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(11) For example: (a) Carneros, H.; Sánchez, D.; Vilarrasa, J. *Org. Lett.* **2014**, *16*, 2900−2903. (transfer of alkenyl groups between secondary amines). (b) Sánchez, D.; Castro-Alvarez, A.; Vilarrasa, J. *Tetrahedron Lett.* **2013**, *54*, 6381−6384. (oxazolidinone/enamine ratios). (c) Sánchez, D.; Bastida, D.; Burés, J.; Isart, C.; Pineda, O.; Vilarrasa, J. *Org. Lett.* **2012**, *14*, 536−539 (relative stability of enamines).

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(13) For the sake of simplicity, in this scheme the ball depicted at position 2 of the pyrrolidine ring may be a hydrogen atom or any substituent other than a COOH group (which has a strong tendency to form oxazolidinone rings or, in very polar media, zwitterionic iminium carboxylates) or similar groups. Moreover, R_3CCHO means not only pivalaldehyde and similar branched aliphatic aldehydes but also ArCHO and RCH=CHCHO; in the presence of PhCOOH or other suitable acids as additives, the iminium hydroxide depicted in the second row of Scheme 1, also for simplicity, must be replaced by the corresponding iminium carboxylates (plus water), as expected.

(14) The twist-boat conformer of ketone **2** is drawn in Table 1. It is predicted to be 2−3 kcal/mol more stable than the chair conformer, at all levels.

(15) (a) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378−6396. (b) The SMD, CPCM, and IEFPCM approaches were compared for this case (**1a** + **2** = **1** + **2a**) at the B3LYP/6-31G(d) level, and the predicted $\Delta G°$(DMSO) values were −3.9, −4.6, and −4.6 kcal/mol, respectively. (c) The SMD, CPCM, and IEFPCM approaches were also compared for other equilibria; for example, for the **5** + **a** = **5a** + H_2O equilibrium at the B3LYP/6-31+G(d) level (see Table 2), and the $\Delta G°$(DMSO) values turned out to be 5.7, 5.5, and 5.5 kcal/mol, respectively; at the CCSD(T)/6-31+G(d)//B3LYP/6-31+G(d) level the predicted values were −3.3, −3.5, and −3.5 kcal/mol, respectively.

(16) In DMSO-d_6 (moist, as acquired) the determined K_{eq} value was 670; in DMSO-d_6 dried over 4-Å MS the value is that given in Table 1 (540).

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