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On the Calculation of Reaction Free Energies in Solution: A Comparison of Current Approaches

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Abstract

The result of the application of different approaches based on the ideal gas/rigid rotor/harmonic oscillator (IGRRHO) model, commonly used in popular software packages, for the calculation of free energies in solution is compared with that of *ab initio* molecular dynamics for a process involving ligand exchange in palladium complexes. The IGRRHO-based approaches considered differ in most cases in the extent to which the rotational and translational contributions are included in the correction. Our study supports the use the free energy values directly obtained from

dispersion-corrected DFT functionals without any correction or with minor corrections at most.

Introduction

The estimation of Gibbs energy, also described as free energy, changes in chemical reactions is the criterion used in mechanistic studies to accept or discard a computed pathway. Thus, the accuracy of Gibbs energy calculations is of great relevance in computational chemistry and continued effort is dedicated to the benchmark of computational methods.¹ In recent years, the accuracy of the internal energy contribution to the Gibbs energy has been a focus of attention. Indeed, improved approximations to Density Functional Theory (DFT), certainly the most used approach to the study of chemical reactivity in catalytic systems, have been proposed. Among these, we acknowledge the introduction of dispersion-corrected functionals, which improved the quality of potential energy surfaces. However, the entropic contribution to the Gibbs energy may be also the source of sizable errors.

In the ideal gas/rigid rotor/harmonic oscillator (IGRRHO) approach, entropy is introduced via the particle-in-a-box / rigid rotor / harmonic oscillator approximation. Accordingly, the translational, rotational and vibrational degrees of freedom are considered independent and the corresponding partition functions are estimated based on the ideal-gas formulas of quantum statistical mechanics. This approach is, by construction, appropriate for gas-phase reactions. However, homogeneous catalysis usually takes place in solution and the evaluation of Gibbs energy changes in solution becomes necessary. The proper method how to perform this evaluation has been a matter of discussion in the last decades. Bulk solvation effects are accounted for in the calculation of the potential energy through the use of continuum models. These models

approximate the averaged behavior of the solvent with a parameterized potential of mean force, and are used to obtain the Gibbs energy of solvation which is added to the potential energy of the system to estimate the potential energy in solution. The handling of the entropic term has happened to be controversial. In particular, calculation of the translational entropy in solution based on the particle-in-a-box model has been questioned. Several approaches have appeared in the literature to address this contribution,^{2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25} several authors have commented on their use^{26,27,28,29,30,31,32,33,34,35,36,37,38,39,40} and many researchers have applied these modified corrections in their investigations.^{41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65} It has been argued that the translational entropy should not be estimated via the particle-in-a-box model for a system in solution. Translational and rotational entropies have been proposed to change significantly in solution as the solvent somehow restricts the movements of the solute with respect to what happens in gas phase.^{2,4,9,11} Some authors have estimated that the total entropy in solution should be about 50-70% of that in the gas phase,^{30,31,32} and different proposals have been put forward to estimate the translational component of the entropy by re-computing or applying a correction to $\Delta S_{\text{trans}}^0$.

To further complicate the issue, the opinion exposed in the previous paragraph is not unanimous. A few authors have pointed out that the standard application of ideal gas/rigid rotor/harmonic oscillator (RRHO) approach could be appropriate.^{66-67,68} Rauk and co-workers examined the origin of the loss of entropy of a substance from gas phase to solution⁶⁶ and found that the most important loss of entropy is due to cavity formation and that no important changes appear in ΔS_{trans} or ΔS_{rot} . Poli and co-workers reported better agreement with experiment when using standard Gibbs energies than when removing the translational and rotational entropy terms.⁶⁷ And Harvey and Fey

found very good quantitative agreement of DFT-D standard Gibbs energies in solution with available kinetic data.⁶⁸ In contrast, they found that there was no agreement when the same functional was used without dispersion.^{69,70,71} Harvey and Sunoj have also assumed in a recent paper that none of these corrections to the IGRRHO approach are necessary.¹

A completely different approach to the estimation of free energy is taken in the field of *Ab Initio* Molecular Dynamics (AIMD).⁷² Here, numerical simulations are performed to investigate the behavior of extended model systems, which include explicitly the solvent. Specialized simulation techniques are used to estimate thermodynamic quantities on the basis of classical statistical mechanics. Chemical intuition guides the researcher in the choice of reaction coordinates along which the system probability distribution is sampled. The outcome of the simulation is thus a potential of mean force for a physically achievable process, which incorporates solvent effects as well as the intrinsic interaction between the reactive moieties. Some of us have applied these techniques with success in the field of homogeneous catalysis.^{73,74,75} The transformation from AIMD simulation results to thermodynamical magnitudes is not trivial and contains its own approaches, but it is important to emphasize that they are completely unrelated to those of the IGRRHO treatment.

Despite being based on different model systems and approximations, the IGRRHO-based and AIMD-based approaches attempt to estimate in practice the same quantity: a free energy change in a chemical process. For the sake of exactitude, it has to be mentioned here that the two methods use the term free energy for slightly different magnitudes, in the case of IGRRHO calculations the Gibbs energy is computed (G) whilst in the case of AIMD simulations the Helmholtz energy (A) is computed. The difference between them is the term $p\Delta V$, including pressure and change of volume.

$p\Delta V$ is expected to be very small in liquids because a significant change in the volume is not expected to take place during the reaction. Therefore, we assume that Helmholtz and Gibbs energies should be essentially the same for the systems under study. And we will use the somehow ambiguous free energy label for the remaining of this manuscript.

It thus appears of interest to perform a comparison between the results of the two general approaches: IGRRHO-based and AIMD-based. To this goal, we have focused on a ubiquitous phenomenon in homogeneous catalysis, namely speciation reactions, for which available experimental data are scarce. We have experience in the study of Suzuki-Miyaura cross-coupling by DFT means,^{41,76} including the analysis of the importance of the coordination number in the active catalyst for which a correct evaluation of the association/dissociation energies is key.^{77,78,79,80} We have also previously analyzed the issue *via ab initio* molecular dynamics simulations.⁸¹

Computational Details

The Gaussian09 package⁸² has been used to run the DFT calculations and the thermal contributions to the free energy based on the IGRRHO approximation, which is the default method of the package. The DFT functional PBE-D3 has been used. It corresponds to the PBE functional⁸³ plus the correction for dispersion effects proposed by Grimme (DFT-D3).⁷¹ The 6-31+G** basis set⁸⁴ has been used for all atoms except for palladium, where the SDD basis set with the associated ECP⁸⁵ has been applied. The continuum solvent model SMD⁸⁶ has been used to model the toluene solvent. Please note that up to two toluene molecules have been included explicitly in the calculations to account for their role as ligand. The species under study present a variety of possible isomers. The conformational variety was taken into account in two different ways: taking the lower energy geometries of our previous study,⁸⁷ and taking representative

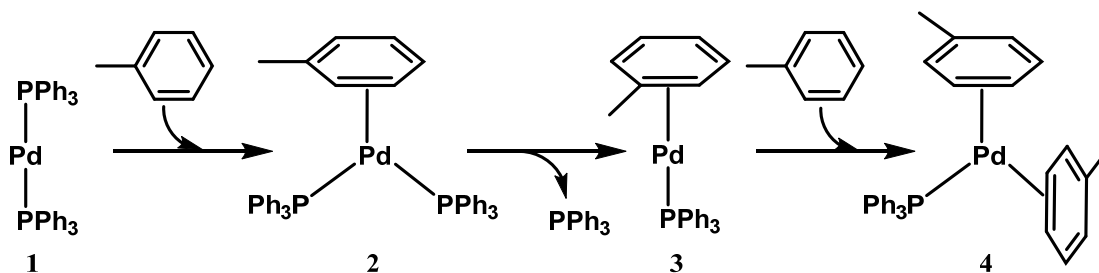
geometries from the AIMD simulations detailed below. All energies presented are free energies in solution and in kcal mol⁻¹. Frequency calculations were carried out at 1 atm and 298.15 K. This corresponds to a concentration of the palladium complexes of 4.1 10⁻² M. This concentration is very close to that in the AIMD simulations (see below) and consequently we did not introduce reference state corrections. The concentration of the toluene solvent is on the other hand certainly very different. In this case we decided not to introduce further corrections because the description of solvation energies with implicit and explicit solvent models is a controversial issue^{88,89} in itself which is outside the scope of the current work. A data set collection of the computational results for the IGRRHO calculations is available in the ioChem-BD repository.⁹⁰

AIMD simulations were performed to study the (Tol)Pd(PPh₃) ↔ (Tol)₂Pd(PPh₃) equilibrium. The simulation protocol is the same as described in ref 81. The model system included the Pd(PPh₃) complex and 1000 toluene molecules. This corresponds to a concentration of the palladium complexes of 9.4 10⁻³ M. A QM/MM intermolecular potential was employed to reduce the computational cost of the simulation.⁹¹ The MM potential used for toluene was based on the RESP procedure.⁹² Density Functional Theory (DFT)^{93, 94} was used for the QM part, in the form of the PBE-D3⁸³ exchange-correlation functional with a dispersion correction.⁷¹ A double-ζ plus polarization (DZVP)⁹⁵ basis set and plane waves (with a cutoff of 300 Ry) were used to expand valence orbitals and electron density, respectively.⁹⁶ Core electrons were described using pseudopotentials.^{97,98,99} Simulations at constant volume and temperature (300 K) were performed according to the Born–Oppenheimer approach using the CP2K program package.¹⁰⁰ Umbrella sampling simulations were performed to compute the potential of mean force (pmf) along the coordinate represented by the coordination number (CN)

between Pd and the center of mass of two toluene molecules.¹⁰¹ CN parameters were defined as in our previous study.⁸¹ Initial structures were taken from a previous unbiased simulation in which the process was observed. The reaction path (from 1.0 to 1.85) was explored using 18 windows spaced by 0.05 units. In each window, the value of the CN was restrained by a harmonic potential with spring constant $500 \text{ kcal mol}^{-1} \text{ CN}^{-2}$. 13 ps were simulated for each window, of which the last 10 ps were used for data analysis. Umbrella integration was used to reconstruct the potential of mean force (pmf).¹⁰² The free energy difference was then approached as the difference between the pmf of the two systems involved.

Results and Discussion

We have investigated computationally three different processes relevant in palladium-catalyzed coupling reactions: i) the coordination of a toluene molecule to the bis(triphenylphosphine) palladium complex $\text{Pd}(\text{PPh}_3)_2$ (**1**) to form the tricoordinated complex $(\text{Tol})\text{Pd}(\text{PPh}_3)_2$ (**2**), ii) the dissociation of one phosphine from complex **2** to form the linear complex $(\text{Tol})\text{Pd}(\text{PPh}_3)$ (**3**), and iii) the coordination of a second toluene molecule to **3** to form the complex $(\text{Tol})_2\text{Pd}(\text{PPh}_3)$ (**4**), see Scheme 1. *Ab initio* molecular dynamic simulations on the $\text{Pd}(\text{PPh}_3)_2$ and $\text{Pd}(\text{PPh}_3)$ complexes in presence of toluene molecules had led to an estimation of the relative free energy for the toluene coordination of $1.8 \pm 0.6 \text{ kcal mol}^{-1}$ (energy of **2** respect to **1**), and for the dissociation of a phosphine in $(\text{Tol})\text{Pd}(\text{PPh}_3)_2$ (**2**) of $17.3 \pm 0.6 \text{ kcal mol}^{-1}$ (energy of **3** respect to **2**).⁸¹ In the present paper we have determined using the same methodology the relative free energy of $(\text{Tol})_2\text{Pd}(\text{PPh}_3)$ (**4**) with respect to **3**. IGRRHO calculations were performed on the same system at the same level of theory as for the AIMD simulations.



Scheme 1. Dissociation and association reactions under study.

The free energies of the reactions in Scheme 1 obtained using the standard IGRRHO methodology are presented in the first row of Table 1. Comparison with potential energies (see SI) show that association processes have an important energy penalty coming from the entropic term ($-T\Delta S$) of about 15-20 kcal mol⁻¹. Conversely a similar amount of free energy is gained in dissociations.

The new AIMD simulation resulted in a value of $\Delta G = 0.7 \pm 0.5$ kcal mol⁻¹ for the coordination of a second toluene molecule to $(\text{Tol})\text{Pd}(\text{PPh}_3)$ (**3**). The results of the AIMD simulations are reported in the second row of Table 1, setting complex **1** as the origin of energies. Comparison of the free energies of the IGRRHO and AIMD simulations results in a very good agreement between the two methodologies, with a maximum difference of 2.4 kcal mol⁻¹.

The next block in Table 1 (five rows) reports the values obtained upon applying a first type of modifications of the IGRRHO approach. The first approach considered (third row in the Table) was used by Sakaki, Takayama, Sumimoto and Sugimoto (STSS) and consists of completely removing the translational and rotational terms of the entropy and thermal energy from the free energy leaving only the vibrational entropy as thermal correction, ΔG_{vib} .^{8,9,10} With this simple approach the authors did not intend to get the free energy value but a range of energies in which the real value should be found. The real value should be then between ΔG_{vib} and ΔG_{IGRRHO} . The reasoning behind this is the intuitive suppression of movements in solution respect to gas phase mentioned in the

Introduction. A minor variation of this approach was put forward by Tanaka, Yamashita, Chung and Morokuma (TYCM), where only the translational term was suppressed (fourth row in Table 1).¹⁷ Another approach along the same line, by Deubel and Lau (DL)¹⁴ (fifth row in Table 1), proposes to compensate the perceived overestimation of the free energy correction in solution by using as free energy correction one half of the free energy in gas phase with opposite sign.^{13,42} Plata and Singleton (PS)³² (sixth row in Table 1), proposed the use of one half of the free energy correction in gas phase but without changing the sign.^{44,45,46,47,48} Tobisch (ST)¹² (seventh row in Table 1) proposed the use of two thirds of the gas phase correction upon comparison with experimental data.¹⁰³

The next block in the Table includes treatments which use other tools to estimate the translational and rotational entropic contributions to the free energy in solution. One of the proposed models to improve the translational entropy is a variation of the Sackur-Tetrode equation within the *free volume theory*. The Sackur-Tetrode equation considers that the molecules have no volume, an approximation which can stand in gas phase but not in solution where most of the volume is occupied by the solvent. The *Free volume theory* takes into account the molecular volume, defined as the volume enclosed by the van der Waals surface of the molecule.²⁶ A simplified version of this model was developed and applied by Okuno.³ The model was further developed by Mammen, Shakhnovich, Deutsch and Whitesides (MSDW). The results of its application are in the eighth row of Table 1.⁵ Others have proposed similar approaches,²⁹ see SI.

A related correction was obtained by Martin, Hay and Pratt (MHP) by modifying the gas phase standard state (ninth row in Table 1).⁶ MHP propose to correct the gas-phase entropy with a pressure parameter $P = \rho_{\text{solvent}}RT$. In practice, this represents just adding a correction factor dependent on the solvent (4.3 and 3.2 kcal mol⁻¹ for water and toluene

respectively). With the same idea other authors changed the pressure when setting up the frequency calculations.^{6,15,104,105,106} The final row in this block (tenth row in Table 1) corresponds to the proposal by Wertz (DHW).² The idea is to break the solvation entropies in three steps: i) compression of the gas phase solute from 1 atm to $V_{m,liq}$, ii) entropy lost when going from the gas at its liquid-phase density to liquid (intermolecular interactions of a dilute solution), and iii) expansion of the solute from $V_{m,liq}$ to the density of the desired solution. This approach was used by Cooper and Ziegler to obtain an expression of $\Delta S_{sol} = -4.1 - 0.20\Delta S_{gas}$ cal.mol⁻¹.K⁻¹ for toluene.⁷

The last block in Table 1 has only one row, eleventh, and corresponds to a different approach. Ribeiro, Marenich, Cramer and Truhlar (RMCT) studied the use of vibrational frequencies computed and concluded that low-frequency molecular vibrations (below 100 cm⁻¹) calculated under the harmonic oscillator approximation have systematic errors in the determination of their entropy contribution. To solve this problem the authors suggested setting all frequencies below 100 cm⁻¹ to exactly this value, so that their contribution to the entropy is not overestimated.¹⁶ This strategy was applied in the study of a rhodium-catalyzed cycloaddition by Li et al.⁴³ The authors found equal results for the rate limiting step of the reaction when applying or not this correction, and differences from 0 to 4 kcal mol⁻¹ along the free energy profile. A slightly more sophisticated approach achieving similar results was also reported by Grimme,¹⁸ see SI. Recently, Paton and Funes-Ardoiz have developed the freely available GoodVibes script that performs these two corrections automatically from Gaussian output files.¹⁰⁷ It must be remarked that this last type of corrections are not specifically focused on the treatment of reactions in solution, and follow therefore a different philosophy. They have been included in this work only for the sake of completion.

Table 1. Relative free energies in kcal mol⁻¹ for species **1**, **2**, **3** and **4** for IGRRHO and AIMD and applying different corrections.

	1 Pd(PPh ₃) ₂	2 (Tol)Pd(PPh ₃) ₂	3 (Tol)Pd(PPh ₃)	4 (Tol) ₂ Pd(PPh ₃)	Mean absolute differences vs. AIMD ^d
IGRRHO ^a	0.0	1.6	16.7	21.9	1.6
AIMD^b	0.0	1.8	19.1	19.8	0.0
STSS ^c	0.0	-16.2	18.7	6.3	10.6
TYCM	0.0	-13.2	19.0	8.3	7.5
DL	0.0	-24.6	17.5	2.6	15.0
PS	0.0	-7.2	17.6	15.2	5.0
ST	0.0	-4.3	18.1	17.5	3.1
MSDW	0.0	-2.5	16.7	17.8	2.9
MHP	0.0	-1.6	16.7	18.7	2.3
DHW	0.0	-1.9	16.8	18.5	2.4
RMCT	0.0	-1.3	15.7	20.6	2.5

^aCalculations within the Ideal Gas/Rigid Rotor/Harmonic Oscillator (IGRRHO) approach. ^bResults from simulation by *Ab Initio* Molecular Dynamics (AIMD). ^c These authors did not intend to estimate the free energy in solution but instead to locate its possible maximum. ^d Mean absolute values of the differences between the considered approach and the AIMD energies.

A detailed description of the corrections considered and of the all results obtained is included in the Supporting Information. According to the STSS correction, the actual relative free energy of **2** should be found between 1.6 ↔ -16.2 kcal mol⁻¹, **3** between 16.7 ↔ 18.7 and **4** between 21.9 ↔ 6.3 kcal mol⁻¹. If we take the AIMD free energies as reference, we can see that the inclusion of the correction to achieve a range of energies

does not really improve the results. The correction clearly overestimates the solvation effect. The TYCM correction produces values closer to those of AIMD, but the overestimation is still clear. Application of the DL approach of reducing the entropy to the half and changing the sign produces the bigger discrepancies with the AIMD results, the mean absolute difference reaching 15 kcal mol⁻¹. The PS correction, using only 50% of the gas phase entropy and keeping its sign results in values closer to those given by the dynamics and the mean of the absolute differences decreases to 5.0 kcal mol⁻¹. The ST approach taking two thirds of the gas phase entropy gives closer results with mean absolute differences of 3.1 kcal mol⁻¹.

The use of approaches based on the Sackur-Tetrode equation give in all cases results closer to the uncorrected IGRRHO energies. The mean of the absolute differences between corrected and AIMD values is 2.9, 2.3 and 2.4 kcal mol⁻¹ respectively for MSDW, MHP and DHW. Results after the correction cannot be considered more accurate than prior to its application, when compared to those from AIMD. However, the small size of the modification associated to this method makes the evaluation of its quality inconclusive.

The analysis is even more complicated for the RMCT modification associated to low mode vibrations. It does affect evenly the compounds leading to a mean absolute difference of 2.5 kcal mol⁻¹. It has to be admitted that RMCT and related approaches based on a special treatment of small frequencies seem on a more solid theoretical ground, and therefore its validity cannot be discounted from these results.

It should be noted that most of the modifications to the standard IGRRHO approach discussed above were proposed at a time where the relevance of dispersion corrections in DFT calculations had not been clearly established yet. We can hypothesize that the modifications were necessary because of the poor agreement between measured and

computed free energies, and because these discrepancies were magnified when dissociation processes were involved. Currently we are using DFT functionals which have been carefully parameterized to include dispersion. The relative free energies of the states of the system were recomputed without the dispersion correction to the PBE functional. Species **2**, **3** and **4** are located at 15.4, 16.5 and 31.7 kcal mol⁻¹ above **1** in free energy. The value is similar to the PBE-D one for **3**, but 13.8 and 9.8 kcal mol⁻¹ larger for **2** and **4**. If STSS or DL corrections are applied to these non dispersion-corrected energies, the values become much closer to the AIMD value. One may thus suspect that some of these corrections would not have been proposed if modern dispersion-corrected potential energy-derived values had been available.

Conclusions

The free energy corrections emerging from the direct application of popular computational packages with its usual simplified models based on IGRRHO (harmonic oscillator, rigid rotor, particle-in-a-box) approaches provides an estimate of the free energy changes involved in the ligand exchange processes of palladium complexes in toluene solution that are in reasonable agreement with the free energies emerging from molecular dynamics AIMD calculations. The introduction of some commonly used modifications of these corrections does not provide in any case substantial improvement on the agreement when dispersion-corrected functionals are employed. Removal of rotational and translational free energies (STSS, TYCM approaches) moves the computed energies far away from the AIMD values, as happens with the DL approach. The PS and ST treatments give values closer to AIMD, but this happens also because the modification is small, at least for the particular processes we studied. Modifications based on the Sackur-Terode equation and the *free volume* theory, such as the MSDW, MHP and DHW approaches provide less conclusive results, as the absolute correction is

again small. Changes introduced by the RMCT approach are also small, and we consider that this treatment is more promising because of its theoretical base. We remark that in no case, the modifications to the IGRRHO treatment improve significantly its performance. We suggest that part of the errors historically associated to translational and rotational entropies were in reality product of the lack of dispersion forces in the calculations. We recommend for the calculation of free energies in solution the use of dispersion-corrected DFT functionals to achieve accurate potential energies and the introduction of free energy corrections with the IGRRHO treatments generally accepted for gas phase processes, with minor corrections based on lower frequency treatment at most.

ASSOCIATED CONTENT

Supporting Information.

Extended computational details, equations and details of the corrections to the translational energy presented, Cartesian coordinates and energies of the minima located in the DFT calculations. (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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