

Comparison between implicit and hybrid solvation methods for the determination of pK_a of mono-protonated form of 13²-(demethoxycarbonyl) pheophytin *a* in methanol[†]

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Abstract. Both implicit solvation method (dielectric polarizable continuum model, DPCM) and hybrid solvation method (cluster–continuum model) were adopted to calculate the pK_a of mono-protonated form of 13²-(demethoxycarbonyl) pheophytin *a* (Pheo) in methanol. In the cluster–continuum model calculations, we considered only 1 solvent molecule attached explicitly and others treated implicitly whereas in the DPCM calculations all the solvent molecules were treated implicitly. DPCM calculations were carried out on Pheo, PheoH⁺, Pheo-CH₃OH and PheoH⁺-CH₃OH in methanol solution. The aim of these calculations was to determine the free energy changes involved in the deprotonation of PheoH⁺ (ΔG_{sol}) and finally to obtain the corresponding pK_a value. DPCM calculations were carried out employing the restricted open-shell density functional treatment (ROB3LYP) using the 6-31G(*d*) basis set to determine the free energy of solvation of bare Pheo and PheoH⁺ and of the clusters, Pheo-CH₃OH and PheoH⁺-CH₃OH in methanol. *In-vacuo* geometries of all the species were obtained by performing optimizations at ROB3LYP level using the 6-31G(*d*) basis. Electronic energies of all the species were then obtained by carrying out single point DFT calculations using 6-311+G(2*d*, 2*p*) basis set on the respective optimized geometries. Differences in thermal energy and molecular entropy were calculated by carrying out frequency calculations at ROB3LYP/STO-3G level on the optimized geometries of the truncated models. The optimized geometries of the clusters display intermolecular hydrogen bonding interactions. The pK_a values of PheoH⁺ calculated by DFT–DPCM and cluster–continuum methods are 6.12 and 4.70 respectively while the observed value is 4.14. The hydrogen bonding interaction between the solute and the solvent can be attributed for the good performance of the cluster–continuum model over pure continuum model.

Keywords. Dielectric polarizable continuum model; cluster–continuum model; pK_a .

1. Introduction

Over the years, extensive research has been conducted to determine the pK_a value of molecules in a medium.¹ Different groups have adopted various methods to incorporate the effect of solvation in the calculation of pK_a .² Jorgensen *et al* pioneered the use of *ab initio* methods coupled with free-energy perturbation to incorporate the effect of the solvent.³ Shields *et al* employed the CPCM continuum solvation method to calculate the free energy differences of solvation of 20 phenols and their anions in water. The obtained absolute pK_a values exhibited standard deviations of less than 0.4 pK_a unit.⁴ Riveros *et al* calculated the pK_a s of 17 species (values ranging from –10 to 50) by adopting the *ab initio* MP2 level

of calculation and including the solvent effects by the cluster–continuum model, a hybrid model that combines both the explicit and implicit solvation treatments. The cluster–continuum model considers gas-phase clustering by explicit solvent molecules and the cluster is then solvated by a dielectric continuum. The results obtained by the cluster–continuum model showed that much better agreement was obtained between the calculated and experimental values by employing the hybrid model in comparison to that obtained by pure continuum methods like SM5.42R and PCM.⁵

We adopt both explicit and implicit solvation treatments⁶ via ONIOM (our Own N-layer Integrated molecular Orbital molecular Mechanics)⁷ and PCM (polarizable continuum model) respectively.⁸ In this paper, we compare pure and hybrid continuum methods in the calculation of the pK_a value of 13²-(demethoxycarbonyl) pheophytin *a* (pheo) in methanol.

[†]Dedicated to the memory of the late Professor S K Rangarajan

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2. Methodology

2.1 Dielectric polarizable continuum model (DPCM)

For a deprotonation process in a solvent medium, the free energy change (ΔG_{sol}) as per the PCM method is given by

$$\begin{aligned}\Delta G_{sol} &= \Delta G_g - \Delta G_{solv}(\text{AH}^+) + \Delta G_{solv}(\text{A}) + \Delta G_{solv}(\text{H}^+) \\ &= \Delta G_g + \Delta\Delta G_{solv}.\end{aligned}\quad (1)$$

Here the gas phase change is written as $\Delta G_g = \Delta E_{elec} + \Delta E_{therm} - T\Delta S_{mol}$, where E_{elec} , E_{therm} and S_{mol} refer to the electronic energy, thermal energy and the entropy of the species involved. The quantity ΔG_{solv} is the free energy change involved due to solvation of the concerned molecule, and is to be obtained by DPCM method. Furthermore,

$$\Delta\Delta G_{solv} = -\Delta G_{solv}(\text{AH}^+) + \Delta G_{solv}(\text{A}) + \Delta G_{solv}(\text{H}^+).\quad (2)$$

2.2 Cluster-continuum model (CCM)

The free energy change involved in the deprotonation, ΔG_{solv} , is given from the Cluster-Continuum method by⁵

$$\begin{aligned}\Delta G_{sol} &= \Delta G_g - \Delta G_{solv}^*(\text{AH}^+) + \Delta G_{solv}^*(\text{A}) + \Delta G_{solv}(\text{H}^+) \\ &= \Delta G_g + \Delta\Delta G_{solv}.\end{aligned}\quad (3)$$

where $\Delta G_{solv}^*(\text{A}) = n\Delta G_{vap} + \Delta G_{c\text{omplexion}}^* + \Delta G_{solv}(\text{AS}_n)$. Here n represents the number of solvent molecules treated explicitly and S stands for the solvent. The free energy change due to vaporization (ΔG_{vap}) of CH_3OH is taken as 37.4 kJ/mol,⁹ and as we have treated 1 molecule of CH_3OH explicitly, the value of n is equal to 1.

2.3 Calculations

The gas phase deprotonation Gibbs energy (ΔG_g) is reported for a standard state of 1 atm. Conversion to a standard state of 1M solution is achieved through the relation⁴

$$\Delta G_g(1\text{M}) = \Delta G_g(1\text{atm}) + RT \ln(24.46).\quad (4)$$

The ΔG_{solv} terms correspond to a standard state of 1 M solution.

Application of the Sackur-Tetrode equation give the value of $G_{\text{gas}}(\text{H}^+)$ as -6.28 kcal/mol.¹⁰ Truhlar *et al* obtained the absolute solvation free energy of the proton in methanol as -263.5 kcal/mol by applying the cluster pair approximation.¹¹ The ΔG_{sol} values calculated employing the DPCM and the cluster-continuum methods ((1) and (3) respectively) can be used to obtain $\text{p}K_a$ value using the relation

$$\text{p}K_a = \frac{\Delta G_{sol}}{2.303RT} = \frac{\Delta G_{sol}(\text{in kcal/mol})}{1.3644},\quad (5)$$

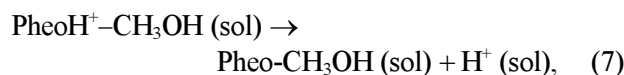
at 298.15 K.

3. Application

The deprotonation reactions considered are as follows



for DPCM, and



for CCM.

4. Computational details

All computations are done by using GAUSSIAN 03 software.¹²

4.1 Geometry optimization

The structure of 13²-(demethoxycarbonyl) pheophytin *a* (Pheo) is shown in figure 1. Geometry optimizations of Pheo, PheoH^+ , $\text{Pheo}-\text{CH}_3\text{OH}$, $\text{PheoH}^+-\text{CH}_3\text{OH}$ and CH_3OH are performed employing the ROB3LYP methodology at the 6-31G(*d*) level (figure 2).

4.2 Electronic and thermal energies

Electronic energies of the neutral and protonated form of Pheo-*a* both in the presence and in the absence of 1 explicit CH_3OH molecule are obtained by carrying out single point calculations at ROB3LYP/6-311+G(2*d*, 2*p*) level on the respective *in-vacuo* optimized geometries. Thermal energies (including the zero point vibrational corrections) and entropies are obtained for the optimized truncated models employing the ROB3LYP methodology at the STO-3G level (figure 3).

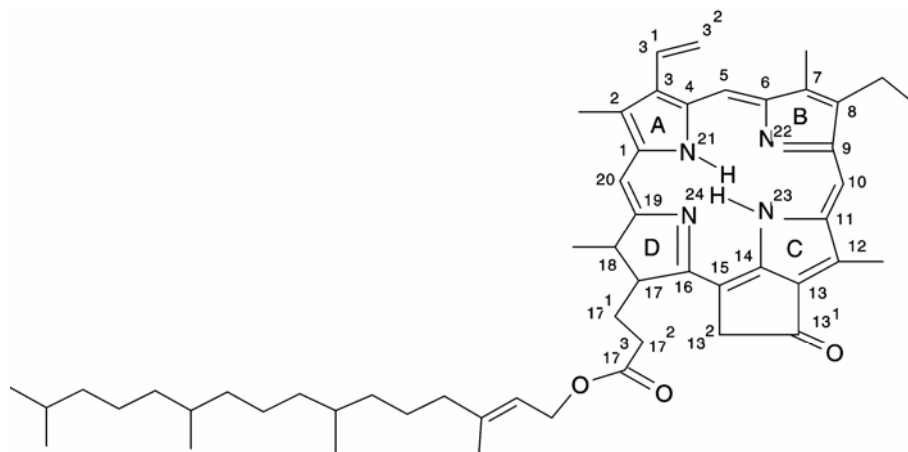


Figure 1. Structure of the whole molecule of 13²-(demethoxycarbonyl) pheophytin *a* showing the numbering on atoms present.

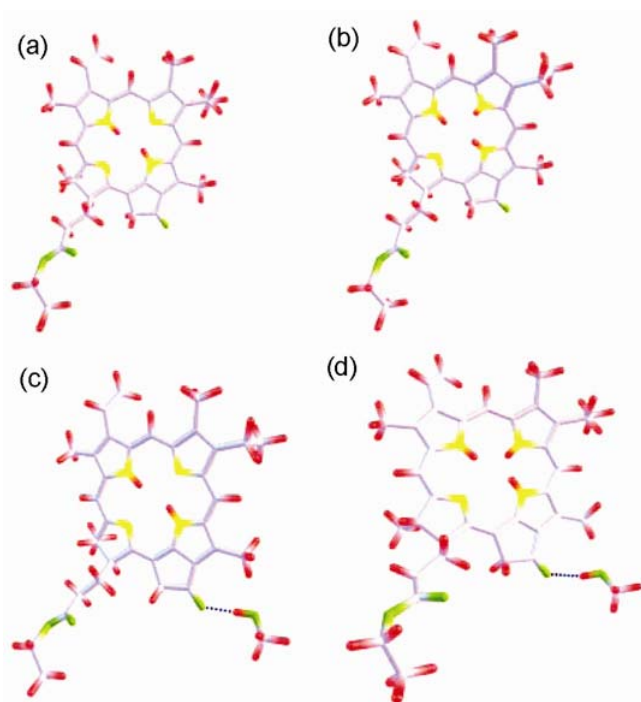


Figure 2. Optimised geometries of (a) Pheo, (b) PheoH⁺ and (c) Pheo-CH₃OH and (d) PheoH⁺-CH₃OH. The colour coding scheme used for representing different atoms is as follows: C atoms → purple, H atoms → red, N atoms → yellow and O atoms → green colour. Figures 2(c) and (d) show the hydrogen bonding interactions of Pheo and PheoH⁺ with the explicit CH₃OH moiety.

4.3 Solvation energy

The ΔG_{solv} values for Pheo, PheoH⁺, and Pheo-CH₃OH and PheoH⁺-CH₃OH in methanol are obtained by carrying out single point DFT-DPCM cal-

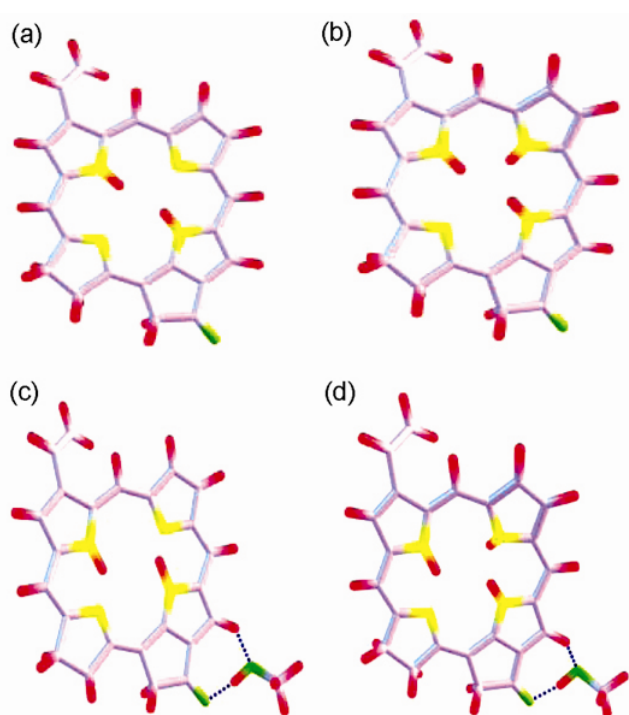


Figure 3. Structures of the truncated models with all substituents except the vinyl group replaced by hydrogen (a) Pheo, (b) PheoH⁺, (c) Pheo-CH₃OH and (d) PheoH⁺-CH₃OH. These are used in the estimation of differences in thermal energy and molecular entropy. Figures 3(c) and (d) show the hydrogen bonding interactions of Pheo and PheoH⁺ with the explicit CH₃OH moiety. The colour coding scheme used for representing different atoms is as follows: C atoms → purple, H atoms → red, N atoms → yellow and O atoms → green colour.

culations at ROB3LYP/6-31G(d) level on the vacuum optimized geometries. The dielectric constant (ϵ) of methanol used in SCRF calculations

Table 1. Calculation of the electronic energy term (E_{elec}).

Species	Electronic energy (E_{ele}) in a.u.	
	6-31G(<i>d</i>) ^a	6-311+G(2 <i>d</i> , 2 <i>p</i>) ^b
Pheo	-1801.3188	-1801.8454
PheoH ⁺	-1801.7267	-1802.2498
Pheo-CH ₃ OH	-1917.0482	-1917.6255
PheoH ⁺ -CH ₃ OH	-1917.4544	-1918.0279
CH ₃ OH	-115.7144	-115.7698

^aOptimizations using the ROB3LYP methodology^bSingle-point calculations using the ROB3LYP methodology**Table 2.** Calculation of the contribution of thermal energy (E_{therm}) and entropy factor ($-TS$) towards the free energy of deprotonation. We have used 1 a.u. = 627.51 kcal mol⁻¹.

Species	Thermal energy E_{therm} in kcal/mol ^a	Entropy (<i>S</i>) in cal/mol-K	$-TS$ in kcal/mol
Pheo	254.895	151.956	-45.306
PheoH ⁺	263.993	155.889	-46.478
Pheo-CH ₃ OH	293.800	170.673	-50.886
PheoH ⁺ -CH ₃ OH	302.774	173.343	-51.682
CH ₃ OH	36.396	56.633	-16.885

^aOptimizations and frequency calculations at ROB3LYP/STO-3G level of calculation**Table 3.** Calculation of the gas phase deprotonation Gibbs energy change (ΔG_g) for standard states of 1 atm [ΔG_g (1 atm)] and 1 M [ΔG_g (1M)].

Reaction	ΔE_{elec}	ΔE_{therm}	$-T\Delta S$	ΔG_g (1 atm) ^a	ΔG_g (1 M)
	(kcal/mol)				
PheoH ⁺ (s) → Pheo (s) + H ⁺ (s)	247.485	-9.098	1.172	239.558	241.445

^a ΔG_g (1 atm) = ΔE_{elec} + ΔE_{therm} - $T\Delta S$ **Table 4.** Calculation of the free energy change due to solvation (ΔG_{solv}), obtained from DFT-DPCM single point calculations at ROB3LYP/6-31G(*d*) level on the vacuum optimized geometries.

Species	Free energy change due to solvation (ΔG_{solv}) ^a in kcal/mol
Pheo	24.03
PheoH ⁺	-6.37
Pheo-CH ₃ OH	27.62
PheoH ⁺ -CH ₃ OH	-2.36

^aComputed using $\epsilon = 33.6$

is 33.6. The ΔG_{solv} of the proton in methanol is taken as -263.5 kcal/mol as calculated by Truhlar *et al.*¹¹

5. Results and discussion

Tables 1 and 2 display the values of E_{elec} , E_{therm} and S of all the species involved. Conversion of the

value of ΔG_g from a standard state of 1 atm to a standard state of 1 M following eq. (4) is shown in table 3. Table 4 displays the ΔG_{solv} values obtained by DPCM method for Pheo, PheoH⁺, as well as their cluster with 1 CH₃OH. Table 5 shows the calculation of ΔG_{solv}^* by the cluster-continuum method. The calculated $\text{p}K_a$ value of PheoH⁺ is 6.12 and 4.70 by DPCM and cluster-continuum methods respectively. See Tables 6 and 7.

The $\text{p}K_a$ value 4.70 obtained by cluster-continuum method is in good agreement with the experimental value 4.14 reported by Hynninen.¹³ This can be explained by the presence of a strong intermolecular hydrogen bonding interaction between the solute and the solvent, which is incorporated by the hybrid continuum model. Consideration of a large number of solvent molecules would further improve the result. However, a pure quantum mechanical treatment on a complex of a large number of atoms is still not computationally feasible, and then one

Table 5. Calculation of the free energy of solvation (ΔG_{solv}^*) by cluster continuum method.

Species (A)	$\Delta G_{\text{complexation}}^0$ ^a	$\Delta G_{\text{solv}} (A-\text{CH}_3\text{OH})$	$\Delta G_{\text{solv}}^* (A)$ ^b
	kcal/mol		
PheoH	7.351	27.62	43.876
PheoH ⁺	8.858	-2.36	15.403

$$^a \Delta G_{\text{complexation}}^0 = \Delta G(A-\text{CH}_3\text{OH}) - \Delta G(A) - \Delta G(\text{CH}_3\text{OH})$$

$$^b G_{\text{solv}}^* (A) = n\Delta G_{\text{vap}} + \Delta G_{\text{complexation}}^0 + \Delta G_{\text{solv}} (A-\text{CH}_3\text{OH})$$

Table 6. Calculation of the absolute free energy of deprotonation (ΔG_{sol}) of PheoH⁺ by DFT-DPCM and the corresponding value of $\text{p}K_{\text{a}}$. We have used 1 a.u. = 627.51 kcal/mol.

Reaction	$\Delta G_{\text{g}} (1 \text{ M})$	$\Delta \Delta G_{\text{solv}}$	ΔG_{sol}	$\text{p}K_{\text{a}}$ values	
	kcal/mol			Calcd.	Obsd.
PheoH ⁺ (s) → Pheo (s) + H ⁺ (s)	241.445	-233.1	8.345	6.12	4.14 ^a

^aRef. 13**Table 7.** Calculation of $\text{p}K_{\text{a}}$ of PheoH⁺ by cluster-continuum method.

Reaction	$\Delta G_{\text{g}} (1 \text{ M})$	$\Delta \Delta G_{\text{solv}}$	ΔG_{sol}	$\text{p}K_{\text{a}}$ values	
	kcal/mol			Calcd.	Obsd.
PheoH+CH ₃ OH (s) → Pheo-CH ₃ OH (s) + H ⁺ (s)	241.445	-235.027	6.418	4.70	4.14 ^a

^aRef. 13

would have to resort to a mixed quantum mechanical-molecular mechanical treatment. S K Rangarajan was a source of inspiration to all theoretical electrochemists. He was known for his vast contribution to the field of electrochemistry.¹⁴

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