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On the Calculation of Vibrational Frequencies for Molecules in Solution Beyond the Harmonic Approximation

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Abstract: We report some results on the calculation of vibrational spectra of molecules in condensed phase with accounting simultaneously for anharmonicity and solute–solvent interactions, the latter being described by means of the polarizable continuum model (PCM). Density functional theory force fields are employed as well as a new implementation of the PCM cavity and its derivatives. The results obtained for formaldehyde and simple peptide prototypes show that our approach is able to yield a quantitative agreement with experiments for vacuo-to-solvent harmonic and anharmonic frequency shifts.

Introduction

Infrared (IR) and Raman spectroscopies are among the most powerful techniques for characterizing medium-size molecules, but proper assignment of spectra is often not straightforward especially for unstable species or nonstandard bonding situations. In the last years, development of non-linear techniques (e.g., two-dimensional IR, 2D-IR)¹ has allowed the direct examination not only of vibrational frequencies but also of the specific anharmonicities (both diagonal and off-diagonal) of vibrational modes.² This additional information demands a more quantitative interpretation of the different contributions determining the overall vibrational spectrum.

Thanks to the progresses in hardware and software, the a priori prediction of accurate low-lying vibrational levels of semirigid polyatomic molecules by means of quantum-mechanical (QM) methodologies is becoming viable. It is

now widely recognized that the computation of semidiagonal quartic force fields at the coupled clusters with single, double, and perturbative inclusion of triple excitations³ [CCSD(T)] level in conjunction with sufficiently large basis sets (at least of triple- ζ quality for second-row atoms) followed by an effective second-order perturbative treatment (PT2) usually provides results with an accuracy of the order of 10–15 cm^{−1} for fundamental transitions.^{4–6} Although the perturbative vibrational treatment remains highly cost-effective for quite large systems, the unfavorable scaling of the CCSD(T) model with the number of active electrons limits the determination of quartic force fields to molecules containing at most five to six atoms. Additionally, a simple reduction of computational cost by combining correlated QM methods with a small basis set should not be recommended, due to the quite unpredictable accuracy of the results. Thus, extension of computational studies to larger systems requires cheaper, yet reliable, electronic structure approaches.

Recently, several authors have reported anharmonic force fields for small- and medium-sized semirigid molecules computed by methods rooted in the density functional theory (DFT).^{7–10} Among the functionals tested, the so-called hybrid functionals provide satisfactory results when used with a basis set of at least double- ζ plus polarization quality supplemented by diffuse sp functions. An even more effective

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approach in terms of good accuracy, obtained at a computationally reduced cost, is based on the additivity of DFT anharmonic corrections to CCSD(T) harmonic force fields. This is well-known to further improve the agreement with experimental data.^{11,12}

The next step involves the consideration of environmental effects because most of the experimental determinations (and of the biologically and technologically interesting processes) are performed in the condensed phase. In this framework, continuum solvation methods^{13,14} are particularly attractive due to their reliability coupled to computational costs fully comparable with those of the corresponding computations in the gas phase. We will use in the following the polarizable continuum model (PCM),¹⁵ in view of its physical soundness coupled with effective implementations for several QM models.

Going back to the evaluation of anharmonic force fields, the effectiveness of the PT2 vibrational approach in the gas phase is related to the availability of reliable and relatively fast procedures for computing analytical second derivatives of the energy, with respect to the atomic coordinates and the extracting normal modes. By using a finite difference approach, it is relatively easy to differentiate once more along the direction of the normal modes to obtain all of the third and a subset of the fourth derivatives (the ones with no more than three distinct indexes), which are required in the PT2 model. The key issue for an effective extension to the condensed phase is related to the handling of the cavity containing the solute molecule, which is closely related to the so-called molecular surface. When the derivatives of the energy in solution, with respect to the atomic positions, need to be computed, the molecular surface must be a continuous and smooth function of the same atomic positions. The importance of this issue has been recognized in recent years.^{16–18} Recently, a robust and reliable method fulfilling these characteristics, originally proposed in ref 19, has been extended to second derivatives, and the corresponding fully analytical expression for the second derivatives of the PCM contribution to the energy has been derived and is now available in the Gaussian09 (G09) suite of programs.²⁰

On these grounds, we report in the present work some results related to one of the most challenging issues in the calculation of reliable vibrational spectra in condensed phase, namely, the simultaneous inclusion of anharmonicity and solute–solvent interactions. In view of their importance, most of the results refer to amides and peptides, but the computational approach and the general trends are not specific to given molecular structures and/or solvents, thus, rather providing a first exploration of a much wider topic.

Finally, it is worth remarking that to date QM calculations of anharmonicities that explicitly account for solvent effects have received only little attention in the literature. To the best of our knowledge, the preceding contributions to this matter are very limited,^{21–27} all resorting to fitting of the potential energy surface (PES) and subsequent calculation of anharmonic vibrational levels.

Theoretical Background and Computational Details.

In order to calculate anharmonic vibrational frequencies including solvent effects accurately, the PCM,¹⁴ and in

particular, the integral equation formalism (IEF) version of PCM,^{28–30} has been used in the calculations reported in this paper. It is well-known that standard techniques can be used to compute analytical second derivatives of the energy with respect to the atomic coordinates^{31,32} and to extract the normal modes when dealing with systems in the gas phase. Indeed, by means of a finite difference approach, it is relatively easy to differentiate once more along the direction of the normal modes to obtain all of the third and a subset of the fourth derivatives (the ones with no more than three distinct indexes),^{10,33} which are enough to provide an accurate treatment of the anharmonicity.

Indeed, in order to apply the approach described in the previous paragraph to calculations in solution, some issues must be addressed. First, the PCM requires a molecular cavity to be defined in the dielectric continuum to host the solute, typically using a set of interlocking spheres centered at the positions of the atoms (*vide infra*). The surface of this cavity needs to be discretized into finite elements (historically called *tesserae*) so that the surface integrals required by the solvation model can be effectively calculated. Once the PCM equations are solved, each surface element is assigned a portion of the apparent surface charge (ASC) that represents the solvent polarization due to the presence of the solute. This ASC is typically expressed in terms of a collection of point charges located at representative points of the surface elements. When the derivatives of the energy in solution, with respect to the atomic positions, need to be computed, the issue to be addressed is whether the definition and discretization of the molecular surface is a continuous and smooth function of the same atomic positions.

In recent years, the importance of this issue has been recognized^{16,17} mainly because smooth energy derivatives are needed in the study of solvent effects on the equilibrium structure of molecules. The simplest approach to address the problem of continuity and discretization of the cavity is to focus primarily on the geometrical details of how the surface elements are generated and how the regions of intersection of the spheres are handled, while the fact that the ASC is apportioned in point charges is usually considered a problem of minor importance. In the late 90s, a discretization scheme able to provide a smooth partition of both the molecular surface and the ASC was proposed by York and Karplus (YK).¹⁹ According to the YK approach, the generation of the surface area elements is smooth because elements from one sphere can penetrate somewhat into nearby spheres, while their surface area is reduced using a smooth switching function. Clearly, such a method would be impossible to apply as long as the ASC is partitioned in point charges as there is no guarantee that two surface elements from two different spheres will not be superimposed in the intersection region of the two spheres. The natural solution to this problem is to drop the use of point charges in favor of a continuous description of the ASC using a set of charges each described by a small three-dimensional Gaussian function. In fact, two (or more) charges represented by Gaussian functions can be exactly superimposed, and their interaction energy does not diverge, as it would do if point charges were used. The obvious drawback of the YK scheme

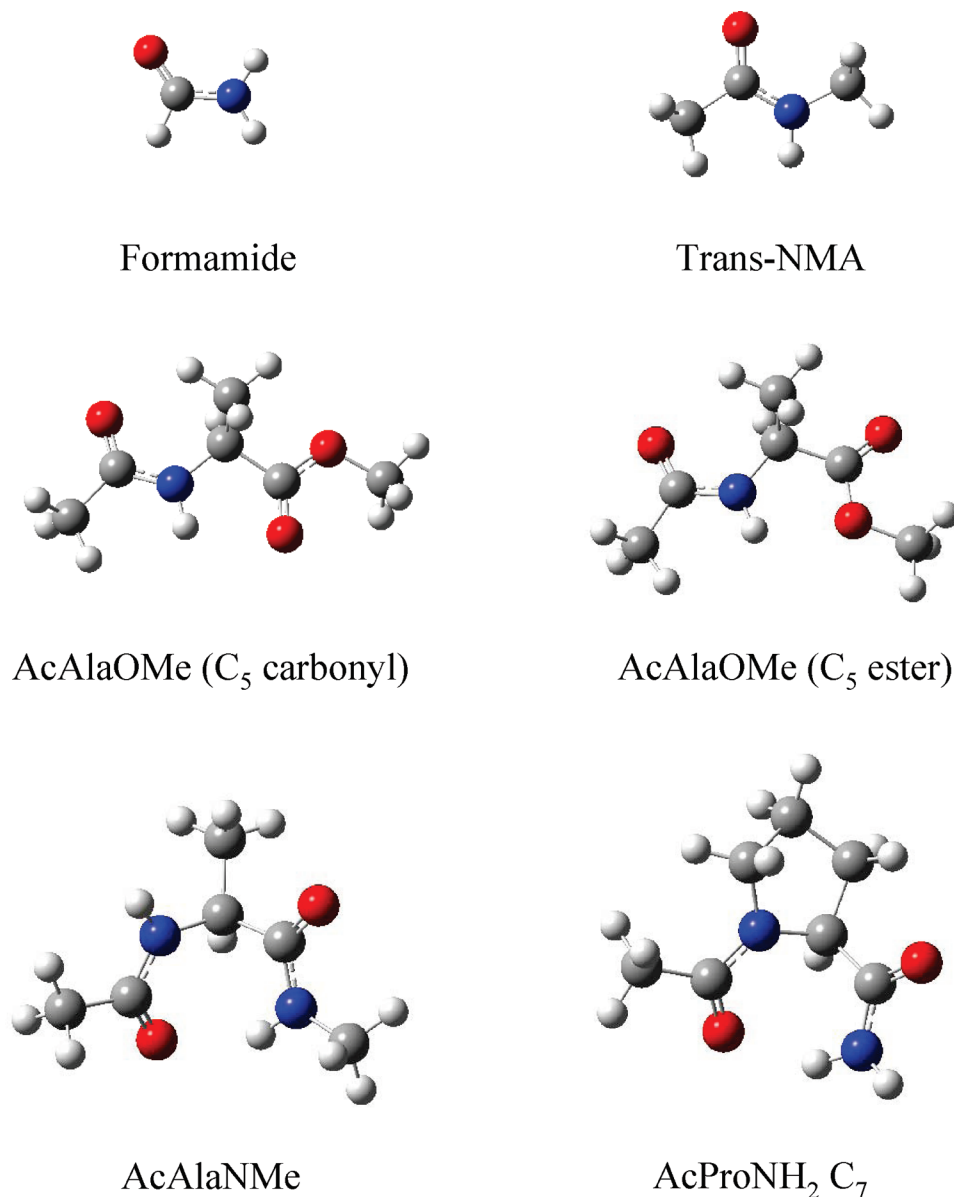


Figure 1. Structures of mono- and dipeptides studied in the present paper.

is that every interaction among the ASC charges and between the ASC charges and the solute becomes an integral over all space.

The second issue to address in order to be able to compute anharmonic vibrational frequencies in solution is that the YK scheme, described in the previous paragraph, must be generalized to second derivatives and applied to the calculation of derivatives with respect to atomic position of the PCM contribution to the energy. The formalism of the derivatives of the PCM contribution to the energy and the terms arising from the second derivatives of the surface discretization has been already reported.^{34–36} However, they have never been implemented free from any approximation.

In recent years, the YK methodology has been extended to second derivatives, and the corresponding fully analytical expression for the second derivatives of the PCM contribution to the energy has been derived and implemented in the code and is now available in the G09 suite of programs.²⁰ The complete continuous surface charge formalism of PCM within the YK discretization scheme and all the implementa-

tion details are beyond the scope of this paper.³⁷ Here we just want to underline the fact that this state-of-the-art implementation fulfills all the requirements needed to carry out further numerical differentiation of the energy in solution along the normal modes and, thus, to compute solvent effects on anharmonic normal modes reliably.

Formaldehyde and some simple mono- and dipeptide prototypes (see Figure 1) were chosen for comparison with a previous study by Wang and Hochstrasser³⁸ on the calculation of amide modes anharmonicity in vacuo.

All structures were optimized at the DFT level by using the B3LYP hybrid functional³⁹ and the 6-311++G(d,p) basis set both in vacuo and solution. Solvent effects were described through a continuum approach by means of the IEF^{28–30} version of PCM,¹⁵ as implemented in the G09.²⁰ The molecular cavity surrounding the molecular solute was built by interlocking spheres, according to G09 default settings. The size of the cavity was also varied by applying different choices of the cavity size scaling factor α .

Free energy gaps and Boltzmann populations in vacuo were obtained by including zero-point and thermal contributions. The same quantities in solvent were obtained in a similar way by further including nonelectrostatic (repulsion, dispersion, and cavitation) energy contributions,¹⁴ calculated over the same cavity used in the evaluation of the electrostatic term.

Anharmonic terms were obtained by the perturbative approach as reported in refs 10 and 33. Fermi resonances were handled in all calculations by suitable settings in the G09 anharmonic calculations. Although G09 can selectively calculate anharmonicities for a selection of normal modes, due to the limited size of the systems under study the calculations were done on all normal modes.

Results and Discussion

In this section, the calculation of anharmonic frequencies for formaldehyde and some simple mono- and dipeptide prototypes are reported. The discussion of the results is organized as follows. First, the PCM approach is tested against experiments in the case of formaldehyde in acetonitrile, in order to establish the quality of the PCM results in reproducing solvent to vacuo shifts as a function of the choice of the size of the PCM molecular cavity surrounding the solute.

Then, the model is applied to the description and prediction of anharmonic shifts of the amide vibrations of simple mono- and dipeptide prototypes in aqueous solution.

Formaldehyde in Acetonitrile: Benchmark of the Molecular Cavity with Respect to Experiment. Before discussing in detail the result of the calculation, it is mandatory to spend a few words on the construction and use of the molecule-shaped cavity. This is one of the most important features which distinguishes the PCM from other continuum models making use of much simpler cavities, such as spheres or ellipsoids, which in many cases are not well suited to reproduce the whole solvent effect.⁴⁰ As a matter of fact, the shape and size of the molecular cavity are the only adjustable parameters in cavity-based models (for a given solvent, i.e., once the dielectric constant has been set), and thus they are responsible for the uncertainty and arbitrariness of the results of the calculations.^{14,25,40}

The choice of the molecular cavity in PCM is not univocal, such as in the self-consistent isodensity polarized continuum model (SCIPCM) approach,⁴¹ but depends on the number, position, and radii of the spheres which are used to build the cavity itself. In the current implementation of PCM, the spheres are placed on the molecule nuclei, but the number of spheres (i.e., the number of nuclei in the same sphere) and their radii are adjustable parameters, whose choice is far from being trivial and often is left to the code default settings or to user's sensibility. However, the importance of a good definition of the radii is well-known; many studies can be quoted^{25,42,43} but, until now, no definitive rules have been found.

In principle, the size and shape of the molecular cavity cannot be defined once and for all, it has only a limited physical meaning (the interface between the solute and the

solvent) but a crucial numerical role, being the boundary in the definition of the PCM operators.

The definition of the molecular cavity in PCM calculations has been done so far basically in two different ways. The simplest (and the original one) consists of using one sphere for each atom, with the radius equal to the atomic van der Waals radius (Bondi⁴⁴ and Pauling⁴⁵ sets of radii are often used), whereas the other one is the use of an united-atom type cavity,⁴² with radii obtained by fitting the solvation free energy at a given QM level with the corresponding experimental values. Of course the fitting with respect to solvation free energy is only one of many possible criteria, any molecular property being, in principle, exploitable for obtaining a reliable fitting and the best parameters for the cavity.

However, in some way this is an ill-posed question as the difficulty of representing a complex phenomenon, such as solvent effects, cannot be limited to a check on a single property. On the other hand, it is also quite impossible to find a universal definition of the best parameters valid for any kind of phenomenon, process, or property. The best strategy is probably to adopt a given set of cavity parameters chosen among sufficiently 'safe' values (for example those derived from some experimental data or from well established theoretical models) and then to check the stability of the results obtained under this assumption by varying the same parameters in a range, without giving up on the reliability of the model. If the choice adopted is sufficiently sound, then the set of computed results will not be dramatically affected by reasonable variations of the parameters involved in the cavity definition.²⁵

As far as the reproduction of anharmonic solvent to vacuo frequency shifts for formaldehyde in acetonitrile is concerned, we would like to underline the fact that the reason for the choice of such a system is two-fold. First, considering that we are basically interested in testing the performance of the method as a function of the cavity parameters, formaldehyde is a sufficiently small carbonyl compound for which a great number of calculations can be run in a reasonable time. Second, being that the IR spectrum of formaldehyde is relatively simple, experimental results reported in the literature should be reasonably accurate. Notwithstanding this, the analysis reported, involving a specific QM level of calculation (B3LYP/6-311++G**) and a given solvation method (PCM-IEF), is not exhaustive, implying that other choices would have possibly given different results.

Calculated harmonic and anharmonic frequencies of formaldehyde in the gas phase together with their experimental counterparts taken from refs 26 and 27 are reported in Table 1. The comparison between calculated and experimental data is satisfactory, thus showing the adequacy of the chosen combination of DFT functional and basis set. As expected, the introduction of anharmonic effects substantially increases the agreement between calculated and experimental absolute frequency values, being ν_3 the best case (-2 cm^{-1}) and $2\nu_5$ and $2\nu_2$ the worst cases (88 and -81 cm^{-1} , respectively).

Table 1. Calculated B3LYP/6-311++G** Harmonic and Anharmonic Frequencies (in cm^{-1}) of Formaldehyde in the Gas Phase

	harmonic	anharmonic	exptl ^a
ν_4	1202	1181	1167
ν_6	1260	1240	1249
ν_3	1531	1499	1501–1500
ν_2	1815	1789	1745–1746
$2\nu_2$		3558	3470–3472
ν_1	2885	2722	2782
ν_5	2942	2762 ^b	2843

^a From refs 26, 27. ^b The calculated value is 2722 cm^{-1} if Fermi resonance is considered.

Calculated harmonic and anharmonic frequency values of formaldehyde in acetonitrile are reported in Tables 2 and 3, respectively, as a function of the size of the molecular cavity around the solute. In all cases, the cavity is built by one sphere on each atom, with the radius equal to G09 default settings, i.e., $R(\text{C}) = 1.926$, $R(\text{O}) = 1.75$, and $R(\text{H}) = 1.443$ Å. As it appears from the examination of the data, a definite trend of absolute values is not evident. Although, at least in principle, values obtained increasing the cavity size should go toward values in vacuo (where the size of the hypothetical cavity is virtually infinite); this is observed only in the case of harmonic frequencies, whereas, as far as anharmonic terms are concerned, larger fluctuations can be noticed. The tendency to reach in vacuo values is less evident and seems to depend on the normal mode under consideration. From the results obtained it could be speculated that higher frequency modes tend to the limit more slowly. In all tables, SMD refers to the use of the optimized cavity reported by Truhlar and co-workers⁴⁶ available in G09.

Moving to the comparison between calculated and experimental absolute values, as expected, the inclusion of anharmonic corrections substantially improves the prediction of experimental values. Of course, the discrepancy between absolute values not only depends on the representation of solvent effects but also is strongly influenced by the QM level of description.

In order to get better insight into solvent induced effects and to remove the intrinsic uncertainty due to the particular choice of the QM level, the frequency shift obtained moving from vacuo to solvent should be evaluated. In the latter case, in fact, only the quality of the solvation model is put into evidence.

Solvent to vacuo shifts are reported in Table 4, as a function of the size of the cavity, and the comparison with experiment is shown in a pictorial way in Figure 2. The quality of the agreement with experiment strongly depends on the cavity size, being generally better for larger cavities. The best agreement for formaldehyde in acetonitrile seems to be obtained with $\alpha = 1.3$, i.e., a cavity a bit larger than the default setting in G09 ($\alpha = 1.1$). Figure 2 also shows values previously calculated by Begue et al.,^{26,27} using a fitting of the PES calculated by exploiting the SCIPCM continuum model.⁴¹ Both the quality of our PCM results with $\alpha = 1.3$, which is very close to the one obtained by Begue et al., and the agreement with the experimental data are very satisfactory thus confirming the reliability of the PCM

approach to model solvent effects on vibrational properties and spectroscopies^{25,47–51} also in the case of tricky effects, such as anharmonic ones.

To end this section, it is worth noticing that the SMD cavity, which has been parametrized using a large training set of neutral and ionic solvation free energies for various solutes in water and organic solvents, i.e., is specific for the quantitative description of solvation energies, seems not to be adequate to describe vibrational anharmonic frequencies. Such an inaccuracy is reasonably due to the fact that the SMD cavity is the smallest of the series of exploited cavities, so that the use of larger cavities is to be advised for the evaluation of solvent effects on vibrational frequencies by means of the PCM.

Amide Modes in Peptide prototypes. As already mentioned in the Introduction, IR spectroscopy can be very useful to identify and characterize peptide structure, conformational preference, and reactivity in solution. Thus, it is important to give an accurate and a detailed theoretical description of peptide vibrational spectra in order to put a clear interpretation on the experimental evidence.

In this section, a few mono- and dipeptide prototypes in water solution (Figure 1) are considered, and the focus is on amide-A, -I, and -II, which are the most exploited for peptide structure determination.

Calculated harmonic and anharmonic frequencies of selected modes of formamide and *trans*-*N*-methyl acetamide (NMA) in the gas phase are listed in Table 5, where the experimental values^{52,53} are also shown for comparison. The agreement between calculated and experimental values is very good, and the results are even better than those obtained for formaldehyde, thus confirming the appropriateness of the chosen combination of DFT functional and basis set for the description of amide modes (the calcd vs exptl discrepancies are of the order of few cm^{-1}).

Considering that we are interested in evaluating effects due to an aqueous solvent, we have chosen to report the PCM results obtained by using $\alpha = 1.25$, which is consistent with the characteristics of the medium.

Selected harmonic and anharmonic frequencies of the amide modes for the systems chosen are reported in Table 6, and calculated anharmonicities are reported and compared with experimental findings taken from the literature in Table 7. The values in the table are obtained as follows:

$$\Delta_{ii} = 2\nu_i - \nu_{2i} \quad (1)$$

$$\Delta_{ij} = \nu_i + \nu_j - \nu_{ij} \quad (2)$$

Diagonal anharmonicities are larger than those of off-diagonal ones, and amide-A anharmonicities are larger than those of amide-I and -II, which are almost comparable for all molecules.

The comparison between calculated and experimental data shows a very good correlation between the two sets (see also Figure 3). Our PCM values are always within three error bars and generally correlate with experiments better than the data previously reported by Wang and Hochstrasser,³⁸ obtained from B3LYP/6-31+G** calculations in vacuo. Also worth noting, the ca. 30 cm^{-1} difference in reproducing

Table 2. Selected Harmonic Frequencies (in cm^{-1}) of Formaldehyde in Acetonitrile^a

	$\alpha = 1.1$	$\alpha = 1.15$	$\alpha = 1.2$	$\alpha = 1.25$	$\alpha = 1.3$	$\alpha = 1.4$	SMD	exptl ^b
ω_4	1214	1213	1212	1211	1210	1209	1219	
ω_6	1257	1257	12587	1258	1258	1258	1255	1247
ω_3	1526	1527	1528	1528	1529	1529	1521	1503
ω_2	1783	1786	1790	1792	1795	1798	1774	1723–1726
ω_1	2921	2917	2914	2911	2908	2904	2918	2797–2808
ω_5	2992	2986	2982	2978	2975 ^c	2969	2987	2876

^a Calculated data at the B3LYP/6-311++G** level with various choices of the molecular cavity. The cavity is made by four interlocking spheres centered at atoms, with the following radii values: $R(\text{C}) = 1.926$, $R(\text{O}) = 1.750$, and $R(\text{H}) = 1.443$ Å, each multiplied by the α factor in the table. ^b From refs 26 and 27. ^c It is 2822 with Fermi resonance.

Table 3. Selected Anharmonic Frequencies (in cm^{-1}) of Formaldehyde in Acetonitrile^a

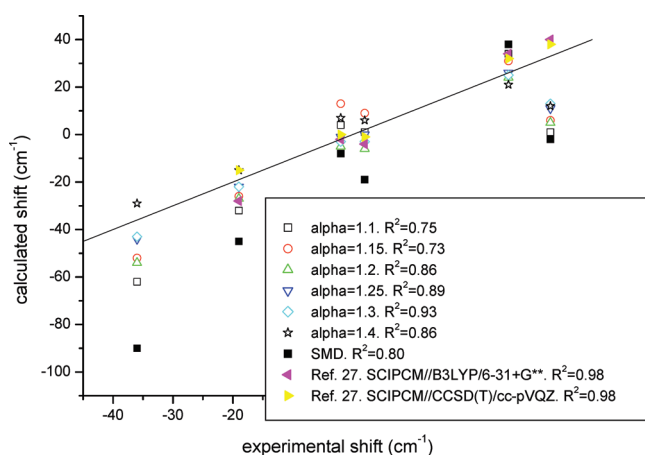
	$\alpha = 1.1$	$\alpha = 1.15$	$\alpha = 1.2$	$\alpha = 1.25$	$\alpha = 1.3$	$\alpha = 1.4$	SMD ^b	exptl ^c
ν_4	1190	1193	1175	1185	1193	1190	1219	
ν_6	1244	1253	1235	1239	1237	1247	1232	1247
ν_3	1500	1508	1493	1499	1496	1505	1480	1503
ν_2	1757	1762	1761	1766	1767	1774	1744	1723–1726
$2\nu_2$	3496	3506	3504	3514	3515	3529	3468	3434
ν_1	2756	2753	2746	2748	2747	2743	2760	2797–2808
ν_5	2763	2768	2767	2773	2775	2774	2760	2876

^a Calculated data at the B3LYP/6-311++G** level with various choices of the molecular cavity. The cavity is made by four interlocking spheres centered at atoms, with the following radii values: $R(\text{C}) = 1.926$, $R(\text{O}) = 1.750$, and $R(\text{H}) = 1.443$ Å, each multiplied by the α factor in the table. ^b The SMD cavity for formaldehyde in acetonitrile is $R(\text{C}) = 1.85$, $R(\text{O}) = 2.186$, and $R(\text{H}) = 1.2$ Å and $\alpha = 1.00$. ^c From refs 26 and 27.

Table 4. Anharmonic Solvent to Vacuo Sol–Vac Shifts (in cm^{-1}) of Formaldehyde^a

	$\alpha = 1.1$	$\alpha = 1.15$	$\alpha = 1.2$	$\alpha = 1.25$	$\alpha = 1.3$	$\alpha = 1.4$	SMD ^b	exptl ^c
$\Delta\nu_4$	9	12	−6	4	12	9	38	
$\Delta\nu_6$	4	13	−5	−1	−3	7	−8	−2
$\Delta\nu_3$	1	9	−6	0	−3	6	−19	3/2
$\Delta\nu_2$	−32	−26	−27	−22	−22	−15	−45	−23/−19
$\Delta 2\nu_2$	−62	−52	−54	−44	−43	−29	−90	−36
$\Delta\nu_1$	34	31	24	26	25	21	38	15/26
$\Delta\nu_5$	1	6	5	11	13	12	−2	33

^a Calculated data at the B3LYP/6-311++G** level with various choices of the molecular cavity. The cavity is made by four interlocking spheres centered at atoms, with the following radii values: $R(\text{C}) = 1.926$, $R(\text{O}) = 1.750$, and $R(\text{H}) = 1.443$ Å, each multiplied by the α factor in the table. ^b The SMD cavity for formaldehyde in acetonitrile is $R(\text{C}) = 1.85$, $R(\text{O}) = 2.186$, and $R(\text{H}) = 1.2$ Å and $\alpha = 1.00$. ^c From refs 26 and 27.

**Figure 2.** Formaldehyde in acetonitrile. Correlation between experimental and calculated sol–vac frequency shifts; values in cm^{-1} . Experimental data taken from ref 27.

amide-I mode of *trans*-NMA is reasonably due to the discarding of the directional component of the hydrogen-bond effects, so that resorting to a supermolecule approach (*trans*-NMA + water clusters) would probably go toward

Table 5. B3LYP/6-311++G** Harmonic and Anharmonic Frequencies (in cm^{-1}) of the Amide-A, -I, and -II Modes of Formamide and *trans*-NMA in the gas phase

	formamide		<i>trans</i> -NMA	
	calcd	exptl ^a	calcd	exptl ^b
ω_A	3716		3643	
ω_I	1791		1744	
ω_{II}	1618		1559	
ν_A	3513		3493	3498
ν_{2A}	6943		6843	
ν_I	1760	1755	1713	1708
ν_{2I}	3504		3408	
ν_{II}	1577	1580	1501	1511
ν_{2II}	3150		2989	
ν_{AI}	5271		5203	
ν_{III}	3338		3213	

^a Ref 52. ^b Ref 53.

the right direction. However, part of the effect is also due to the use of DFT wave functions.

***trans* (s)-N-Methyl Acetylproline Amide.** As confirmed by previous studies,⁴⁸ the PCM is able to give a reliable description of conformational effects and spectroscopic properties, such as IR/VCD, Raman/VROA, UV/CD, ORD, and NMR of *trans* (s)-N-acetylproline amide (AcProNH₂)

Table 6. B3LYP/6-311++G** Harmonic and Anharmonic Frequencies (in cm^{-1}) of the Amide-A, -I, and -II Modes of Various Mono- and Dipeptides in Water^a

	formamide	<i>trans</i> -NMA	AcAlaOMe (ester)	AcAlaOMe (carbonyl)	AcProNH ₂ (C ₇)
ω_A	3704	3645	3628	3603	3455
ω_I	1735	1690	1698	1690	1714
ω_{II}	1621	1549	1532	1537	1604
ν_A	3510	3508	3464	3424	3283
ν_{2A}	6938	6876	6783	6702	6412
ν_I	1704	1653	1672	1657	1676
ν_{2I}	3393	3290	3326	3297	3334
ν_{II}	1565	1558	1514	1492	1547
ν_{2II}	3112	3102	3011	2970	3078
ν_{AI}	5212	5158	5132	5076	4958
ν_{III}	3265	3210	3183	3149	3218

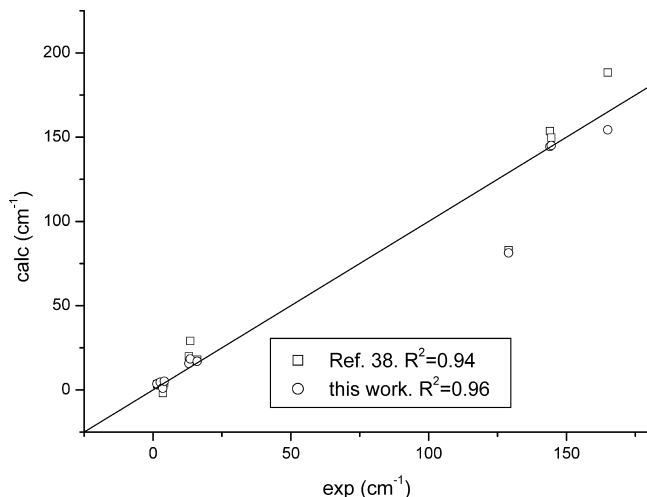
^a The PCM cavity is defined in terms spheres centered on each atom with the following radii: $R(C) = 1.926$, $R(O) = 1.750$, and $R(H) = 1.443$ Å, further multiplied by $\alpha = 1.25$.

Table 7. B3LYP/6-311++G** Calculated Amide Anharmonicities (cm^{-1}) of Various Mono- and Dipeptides in Water^a

		Δ_{AA}	Δ_{II}	Δ_{II}	Δ_{AI}	Δ_{II}
formamide	exptl	129				
	calcd	81.3	15.8	18.6	2.4	5.0
<i>trans</i> -NMA	exptl		16			3.5 ± 0.5
	calcd	140.4	17.0	12.8	4.0	1.0
AcAlaOMe (C5 ester)	exptl	144 ± 7			1.4 ± 0.4	
	calcd	145.1	17.5	16.6	3.6	2.1
AcAlaOMe (C5 carbonyl)	exptl	144 ± 7			2.6 ± 0.8	
	calcd	144.5	17.5	14.7	4.6	1.1
AcProNH ₂ (C7)	exptl	165 ± 15^b	13 ± 2	13 ± 2	3.5^b	4.1 ± 0.6
	calcd	154.4	18.4	15.7	1.3	5.2

^a Experimental findings taken from ref 38, and references therein are also reported for comparison. The PCM cavity is defined in terms spheres centered on each atom with the following radii: $R(C) = 1.926$, $R(O) = 1.750$, and $R(H) = 1.443$ Å, further multiplied by $\alpha = 1.25$.

^b Experimental value for AcProNHMe.⁵⁸

**Figure 3.** Selected mono- and dipeptides (see text). Correlation between experimental and calculated anharmonicities; values in cm^{-1} . Experimental values taken from ref 38 and references therein. Calculated values at the B3LYP/6-31+G** level in vacuo, taken from the same reference, are also reported.

in aqueous solution and, thus, can be confidently applied to evaluate anharmonic effects for this system in water and CH_2Cl_2 .

It has been shown⁴⁸ previously, that only 3_{10} helix I and C_7 are stable minima in the gas phase, whereas three structures, i.e., 3_{10} helix I, P_{II} , and C_7 , with different conformational weights, coexist in water. In particular, AcProNH₂ assumes almost exclusively the C_7 conformation

(with only 1% of the 3_{10} helix I) at room temperature in the gas phase. The situation changes in water solution, where P_{II} , 3_{10} , and C_7 structures are present, and their percentage populations are 68, 28, and 4%, respectively. The combination of such a conformational ranking with PCM calculated response and spectroscopic properties led to a very good description of experimental spectra, thus showing, once again, the reliability of the PCM approach to describe the solvation of AcProNH₂.

Moreover, discrepancies between calculated (harmonic) and experimental vibrational frequencies were in the range of $30\text{--}50\text{ cm}^{-1}$, which coincides with that between calculated harmonic and anharmonic amide-I frequencies in the gas phase for the methylated analogue (see Wang and Hochstrasser, ref 38). Thus, AcProNH₂ seems an ideal candidate for further testing the current implementation of PCM anharmonic frequency evaluation. In the following tables, the attention will be focused on amide-I modes only, for which experimental results are available in the literature.^{54–56} Data obtained for other amide modes are reported in the Supporting Information.

Calculated anharmonic amide-I frequencies of the three conformers together with amide-I–amide-I off-diagonal anharmonicities are reported in Table 8 for three different cavities, i.e., the G09 default value, the $\alpha = 1.25$ value, and the cavity exploited in ref 48. The inspection of the table reveals that vibrational anharmonic frequencies are sensitive to the peptide conformation, in close analogy with harmonic ones. In all cases, going beyond the harmonic approximation decreases the absolute values of a few tenths of cm^{-1} , i.e.,

Table 8. B3LYP/6-311++G** Calculated Amide I Anharmonic Frequencies and Anharmonicities (cm^{-1}) of the Various Conformations of AcProNH₂ in Water, with Different Choices of the Molecular Cavity

	C_7	3_{10}	P_{II}	average	exptl ^a
$\alpha = 1.25$					
ω_i	1714	1711	1696		
ω_j	1652	1677	1647		
ν_i	1676	1681	1665	1676	1650
ν_j	1614	1639	1615	1617	1608
Δ_{ij}	1.24	0.08	0.80	1.07	
Ref 48					
ω_i	1677	1667	1682		
ω_j	1632	1650	1642		
ν_i	1647	1650	1654	1653	1650
ν_j	1617	1613	1603	1606	1608
Δ_{ij}	0.84	0.41	1.55	1.20	
$\alpha = 1.1^b$					
ω_i	1695	1689	1704		
ω_j	1639	1657	1647		
ν_i	1660	1657	1672	1665	1650
ν_j	1601	1637	1610	1620	1608
Δ_{ij}	2.05	0.12	0.69	0.59	

^a Ref 55. ^b Default value in G09.**Table 9.** B3LYP/6-311++G** Calculated Boltzmann Populations of AcProNH₂ in Water with Different Choices of the PCM Molecular Cavity^a

	C_7	3_{10}	P_{II}
$\alpha = 1.1$	0.34	0.36	0.30
$\alpha = 1.25$	0.68	0.19	0.13
ref 48	0.04	0.28	0.68
SMD	0.00	0.24	0.76
in vacuo ^b	0.99	0.01	0.00

^a All data obtained by including ZPE, thermal ($T = 298$ K), and nonelectrostatic contributions. In vacuo results are reported for comparison. ^b Ref 48.

a similar range as the discrepancy between calculated harmonic and anharmonic amide-I frequencies in the gas phase reported by Wang and Hochstrasser for the methylated analogue.³⁸

Calculated Boltzmann populations for AcProNH₂ in aqueous solution at room temperature, as a function of the size of the molecular cavity, are reported in Table 9. Data refer to 298 K and were obtained by considering free energies corrected for zero point energies (ZPE) and thermal contributions, and with the inclusion of nonelectrostatic solvent effects (cavitation, dispersion, and repulsion; see ref 40 for details). The weight of the C_7 conformer increases with the cavity size, whereas an opposite trend is observed for P_{II} . Such a behavior is expected because by increasing the cavity size, the limit of the in vacuo calculation should be reached. In particular, the picture does not change substantially by passing from $\alpha = 1.1$ (default cavity in G09) to the cavity reported in the previous study (see ref 48) or to the one used in the SMD, even if in the latter case the opposite limit with respect to vacuo is reached (i.e., the weight of the C_7 conformation is negligible). The use of $\alpha = 1.25$ substantially reaches the in vacuo limit where the P_{II} conformer is not present. Indeed, the stabilization of P_{II} is due to its interaction with water.

Calculated and experimental⁵⁵ frequencies are reported in Table 8 (average values).

Table 10. B3LYP/6-311++G** Calculated Amide-I Harmonic and Anharmonic Frequencies and Anharmonicities (cm^{-1}) of the the Various Conformations of AcProNH₂ in CH₂Cl₂ with $\alpha = 1.3$

	C_7	3_{10}	P_{II}
ω_i	1725	1725	1739
ω_j	1660	1689	1677
ν_i	1688	1685	1690
ν_j	1626	1651	1651
Δ_{ij}	1.8	-0.1	0.1
exptl ^a		1.5 ± 0.4	

^a Ref 57.

In agreement with the results reported in ref 48, an appropriate evaluation of solvent effects on populations is crucial for the correct description of AcProNH₂ spectroscopic properties. In fact, use of the default G09, ref 48, or SMD cavities leads to a prevalence of the P_{II} conformations over the others, with only a very small (or even negligible) amount of the C_7 . On the contrary, use of $\alpha = 1.25$ makes the results go toward in vacuo data, i.e., a prevalence of the C_7 conformation is predicted (see Table 9). The latter ranking, however, makes the average results go farther from experiments. In particular, the use of the cavity previously reported in ref 48 almost matches calculations with experimental values.

To the best of our knowledge, no experimental data for AcProNH₂ anharmonicities in aqueous solution have been reported so far in the literature. However, experimental values in dichloromethane have instead been measured.^{57,58} Thus, our study has been extended to AcProNH₂ in dichloromethane. Data obtained by exploiting $\alpha = 1.3$ are listed in Table 10. Notice that, due to the lower polarity of dichloromethane with respect to water, a slightly larger α value has been chosen in this case. As already pointed out for water, the inclusion of anharmonic effects makes the calculated frequencies decrease, and once again the frequencies of amide-I band are sensitive to the surrounding environment. Even more sensitive are amide-I anharmonicities.

Table 11. B3LYP/6-311++G** Calculated Boltzmann Populations of AcProNH₂ in CH₂Cl₂ with Different Choices of the PCM Molecular Cavity^a

	<i>C</i> ₇	3 ₁₀	<i>P</i> _{II}
α = 1.1	0.63	0.14	0.23
α = 1.25	0.73	0.15	0.12
α = 1.3	0.88	0.05	0.07
SMD	0.07	0.32	0.62
same as ref 48	0.12	0.30	0.58

^a All data obtained by including nonelectrostatic, ZPE, and thermal (298 K) contributions.

ties, which increase even by a factor of 100 moving from one conformation to another.

Comparison of anharmonicities of the single conformers with experimental findings seems to evidence a prevalence of the *C*₇ conformer in the dichloromethane solution or even a mixture with a relevant amount of *C*₇. This is in agreement with previous experimental findings reported in the literature for AcProNH₂ in dichloromethane and deuterated chloroform.^{59,60}

As already pointed out in the previous paragraphs, the comparison between experimental and “average” calculated values is not straightforward and requires accurate and reliable evaluation of molecular properties and also a consistent prediction of the conformation hierarchy. Calculated PCM conformational weights are reported in Table 11.

The picture changes with respect to water (compare Table 9). In fact, the G09 default cavity and the largest α = 1.25 and 1.3 cavity lead to a prevalence of the *C*₇ conformer, whereas other choices, including SMD, show a prevalence of the *P*_{II} conformer, which is, however, consistent neither with the anharmonicity values of Table 10 nor with previous experimental studies.^{59,60}

In summary, by resorting to the results reported in the present study, it seems reasonable to state once again that the choice of a universal definition for the molecular cavity is far from trivial and that such a choice can hugely influence the outcome of the calculation. In particular, as far as the present examples are concerned, it seems reasonable to suggest the use of a larger PCM molecular cavity for the calculations of both molecular properties and conformational effects in medium-polarity solvents, whereas a small cavity is recommended for polar solvents, at least as far as conformational properties are concerned. However, due to a lack of extended studies on this matter in the last years, efforts to get a better parametrization of the molecular cavity seem to be absolutely necessary.

Summary, Conclusions, and Future Developments

We have reported some results related to the description of vibrational spectra of molecules in condensed phase with the simultaneous account of anharmonicity and solute–solvent interactions. The computational approach and the general trends, even if here applied to few small-to-medium sized systems, should not be considered as specific of given molecular structures and/or solvent, so that the present study represents a first exploration of a much wider topic.

The current implementation of the PCM in the Gaussian suite of programs²⁰ yields a continuous surface, which is smooth enough to be further differentiated to obtain the quantities needed for the evaluation of anharmonic vibrational frequencies.

The comparison of the calculated results with their experimental counterparts suggests the use of a molecular cavity of a different size for the evaluation of energetics and vibrational spectroscopic properties, depending on the nature of the solvent. However, this discrepancy could be overtaken by finer parametrization of the nonelectrostatic contributions, which enter the evaluation of the solvation free energy.^{14,61–63} Work in this direction is currently in progress in our group.

Nevertheless, the quality of the results which have been obtained, in connection with the low cost and versatility of the PCM, shows that it is a valuable method for a quantitative description of vacuo-to-solvent harmonic and anharmonic frequency shifts. Also, due to features of the current implementation, which enables the user to discriminate between normal modes and then to choose to perform the calculation only on selected ones, the PCM evaluation of anharmonic frequencies in solution is nowadays applicable to large systems, also by combining the PCM description to QM/MM approaches.

The only real limitation still remaining is the difficulty of the continuum approach to evaluate specific solute–solvent interactions, for which a proper treatment requires, in almost all cases, resorting to techniques rooted in the molecular dynamics.

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Supporting Information Available: Calculated harmonic and anharmonic amide-II, amide-III, and amide-A frequencies of AcProNH₂ in aqueous and dichloromethane solutions. This material is available free of charge via the Internet at <http://pubs.acs.org/>.

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