# A Theoretical Study on *trans*-Resveratrol - Cu(I) Complex

Concetta Caglioti[1,2], Antonella De Luca[2], Chiara Pennetta[2], Lorenzo Monarca[1,2], Francesco Ragonese[2], Paola Sabbatini[2], Maria Noelia Faginas Lago[2,3], Andrea Lombardi[2,3], Federico Palazzetti[2(✉)], and Bernard Fioretti[2]

[1] Dipartimento di Medicina e Chirurgia, Università degli Studi di Perugia, piazzale Gambuli 1, 06129 Perugia, Italy

[2] Dipartimento di Chimica, Biologia e Biotecnologie, Università degli Studi di Perugia, via Elce di Sotto 8, 06123 Perugia, Italy

federicopalazzetti@yahoo.it

[3] UdR INSTM di Perugia, via Elce di Sotto 8, 06123 Perugia, Italy

**Abstract.** Resveratrol is a natural occurring phenol, found in peanuts, cocoa, and fruits like for example grapes, blueberries, and strawberries. It has become popular in the last decades for the possible correlation of wine, especially red wine, and cardioprotective properties. It is widely employed in nutraceutics production. It presents stilbenoid structure; in nature there are two isomers, *cis* and *trans*, this latter is the most stable. Here, we present a preliminary investigation on the most stable complex that *trans*-resveratrol forms with Cu(I), an essential trace element in living organisms, that takes part to redox processes, where resveratrol plays an antioxidative role. The structure of *trans*-resveratrol - Cu(I) is optimized in vacuum and in solvents like water and ethanol, by Density Functional Theory methods. Dissociation and solvation energies of the complex are calculated. Infrared spectra are calculated and compared with experimental data, available in literature.

**Keywords:** Density functional theory · Nutraceutics · IR spectra

## 1 Introduction

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a stilbenoid, a class of natural phenols. It is formed by a phenol and a resorcinol group connected by an ethylene radical (Fig. 1). It is present in *cis* and *trans* isomers, although this latter is the most stable and common. In nature, it is found essentially in *Polygonum cuspidatum* [1], a flowering plant already employed in the traditional Chinese medicine. It became very popular for the reduced incidence of coronary heart disease in countries with high consumptions of saturated fats and red wine [2], this latter suggested a correlation between resveratrol and cardioprotective properties. Grape is in fact one of the main sources of resveratrol. Other plants containing this natural phenol are blueberries, strawberries, ribes, peanuts, cocoa, and *itadori* tea.

Resveratrol has antioxidant, chemopreventive and anticancer properties [3]. It has been proved to regulate proteins and enzyme activity [4]. Preclinical studies reported a

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2022
O. Gervasi et al. (Eds.): ICCSA 2022 Workshops, LNCS 13382, pp. 237–248, 2022.
https://doi.org/10.1007/978-3-031-10592-0_18

positive effect in anti-glioblastoma therapy [5]. Its effects have been studied on mitochondrial biogenesis of granulosa cells, suggesting beneficial effects on the physiology of female reproductive system, with possible therapeutic implications [6]. Solid formulations have been produced to overcome the low solubility in water and improve bioavailability (see for example [7]).

Computational chemistry has been largely employed both to support experimental studies or to predict chemical properties of this molecule, mostly for the *trans* isomer. Iuga *et al.* [8] applied quantum chemistry to investigate the antioxidant activity of *trans*-resveratrol toward hydroxyl and hydroperoxyl radicals. Density Functional Theory, DFT, was employed by Mazzone *et al.* [9] and by Benayahoum *et al.* [10] to study antioxidant mechanisms of resveratrol and its analogues. Other computational and theoretical studies were devoted to study homolytic and heterolytic bond cleavage in the hydroxyl radical [11] and its interactions with hemoglobin [12]. Frau *et al.* studied the chemical reactivity of the *cis* and *trans* isomers by Molecular Electron DFT [13, 14]. The isomerization process was accurately described by Feng and Chatterjee [15]. Kores *et al*. applied inverse molecular docking to investigate new potential human targets for this molecules [16]. Very recently, Nakajima *et al.* reported a computation-guided asymmetric synthesis of resveratrol dimers [17].

Interaction of resveratrol with metal ions have been studied both to investigate antioxidant activity and in view of biological studies on the interaction of this molecule with essential trace elements in living organisms [18–20]. Copper has the capability of switching the two oxidation forms Cu(II) and Cu(I). This feature plays an important role in biochemical processes related to the electron transfer processes in proteins and enzymes, and in redox reactions producing free radicals. Resveratrol acts as prooxidant in presence of Cu(II), producing reactive oxygen species. The oxidation process leads to the formation of a phenoxide radical and reduction of Cu(II) to Cu(I).

In this paper, we report a preliminary study of the complex *trans*-Resveratrol - Cu(I), here denoted as [Resv]$Cu^+$. DFT has been used to calculate the dissociation energy of the complex, *i.e.* the difference in energy between the stable complex and resveratrol - Cu(I) isolated. Solvation energy was also calculated for water and ethanol solvents. This latter has been studied in view of possible applications in analytical chemistry. Vibrational spectra of [Resv] $Cu^+$ in vacuum, in water and in ethanol have been calculated and discussed in relations to the experimental data obtained by infrared multiple-photon dissociation (IRMPD) spectroscopy [19].

## 2 Background

Calculations have been performed by the Gaussian 09 package software [21]. Structure optimizations, as well as single point energies and vibrational spectra, have been calculated by means of Density Functional Theory (DFT) methods, by employing the hybrid functional B3LYP with the Pople basis set 6-31G(d,p), already used by Beneyahoum [10] to optimize the structure of *trans*-resveratrol and the Electron Core Potential LanL2DZ, Los Alamos National Laboratory 2 double ζ, largely employed for metal transition complexes [22].

Dissociation energies of the copper complex were determined by calculating the difference in energy between the complex in its equilibrium geometry and the energies

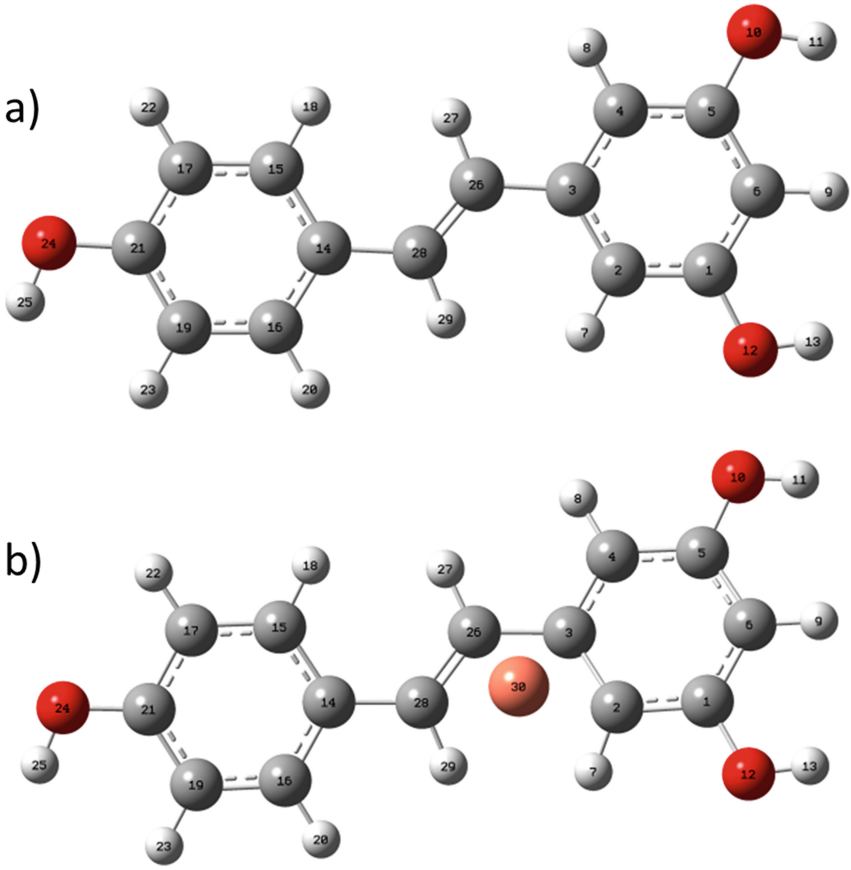


**Fig. 1.** Structures of *trans*-Resveratrol (a) and *trans*-Resveratrol - Cu (I) complex (b) optimized by B3LYP/6-31G(d,p). In orange the Cu atom, in grey the carbons, in white the hydrogens and in red the oxygens. The atoms are labelled by numbers from 1 to 29, the copper is labelled by 30. (Color figure online)

of resveratrol and $Cu^+$ at infinite distance. The solvation energy, for complex dissolved in water and in ethanol was determined by the difference between the energy of the complex in the solvent and in vacuum. The solvent interaction was calculated by applying the IEFPCM model (see for example [23]).

## 3 Results and Discussion

The structure of [Resv]$Cu^+$ was optimized by B3LYP with 6-31(d,p) and LanL2DZ basis sets. Here, we report a comparison of the structures in the neighboring of the $Cu^+$ ion obtained by these two basis sets (Fig. 1). We also compare these geometrical features with those of the *trans*-resveratrol molecule in vacuum to evaluate the effect of the copper ion to the molecule. The atoms we considered are C28, C26, C3, and C2, for which we

calculated the mutual interatomic distances and bond angles, the dihedral angle and their distances from $Cu^+$. Additionally, we calculated the dihedral angle among C16, C28, C26, and C4, to evaluate the coplanarity of the phenol and resorcinol fragments. In Table 1, we report the distances among the four carbon atoms closest to the Cu atom in the complex, C28, C26, C3, and C2, the dihedral angle defined by these four atoms, and the dihedral angle among C16, C28, C26, and C4. In Table 2, we report the bond lengths of $Cu^+$ with four carbon atoms C28, C26, C3, and C2, and the bond angles C27-Cu-C26, C26-Cu-C3, and C3 - Cu - C2. This calculations aim at comparing the structure changes related to the coordination with the copper ion and the geometries predicted by the two basis sets both in vacuum and in the cases when a solvent is considered. The geometrical features of resveratrol calculated by the two basis sets are similar, while remarkable differences are observed in the copper complex. Comparison between the two basis sets in vacuum shows that the structure optimized by 6-31G(d,p) presents shorter bond lengths with respect to that calculated by LanL2DZ, with less ample bond angles. For what concerns the solvent interaction, the structure calculated by 6-31G(d,p) basis sets does not show significant changes about distances and bonds involving the copper ion, while the presence in ethanol and water lead to changes in the structure optimized by LanL2DZ. Regarding the geometrical features related to the carbon atoms coordinate by $Cu^+$, C28, C26, C3 and C2, and the atoms of the phenol and resorcinol fragments, C16 and C4, no substantial changes are observed both for what concerns the basis set and for the interactions with solvents or in vacuum. The interaction of resveratrol with $Cu^+$ leads to change in structure, as observed by the increasing of the C28-C26 bond length and especially from the change of the dihedral angles. The dihedral angle defined by C28, C26, C3, and C2 in the complex becomes about $-10°$ when calculated by 6-31G(d,p), while is $-25°$ for the structure optimized in vacuum by LanL2DZ, and *ca.* 2° for the structure optimized by this latter basis set, in water and in ethanol. For what concerns the phenol and resorcinol groups, in the Cu-complex they are no longer coplanar, the dihedral angle is about 160°.

**Table 1.** Geometrical features of trans-resveratrol. We report the distances C28-C26, C26-C3, and C3-C2, in Å, and the dihedral angles for C28-C26-C3-C2, and for C16-C28-C26-C4, in degrees. The structures have been optimized by B3LYP/6-31G(d,p) and B3LYP/LanL2DZ for the molecule in vacuum.

| | | C28-C26 (Å) | C26-C3 (Å) | C3-C2 (Å) | C28-C26-C3-C2 (degrees) | C16-C28-C26-C4 (degrees) |
|---|---|---|---|---|---|---|
| In vacuum | 6-31G(d,p) | 1.35 | 1.47 | 1.41 | 0 | 180 |
| | LanL2DZ | 1.35 | 1.46 | 1.41 | 0 | 180 |

Dissociation energies of the [Resv]$Cu^+$ complex in vacuum have been calculated by using the 6-31G(d,p) and LanL2DZ basis sets (Table 3). For both basis sets the energy is negative, corresponding to a more stable complex, if compared with the energy of resveratrol - $Cu^+$ system separated by infinite distance. The 6-31G(d,p) overestimates the

**Table 2.** Geometrical features of the [Resv]$Cu^+$ complex. We report the distance between Cu and the four adjacent carbon atoms, C28, C26, C3, and C2, in Å, and the related bond angles, in degrees. We also report the distances C28-C26, C26-C3, and C3-C2, and the dihedral angles for C28-C26-C3-C2 and for C16-C28-C26-C4. The structures have been optimized by B3LYP/6-31G(d,p) and B3LYP/LanL2DZ for the molecule in vacuum, in water and in ethanol.

| | | Cu-C28 (Å) | Cu-C26 (Å) | Cu-C3 (Å) | Cu-C2 (Å) | C28-Cu-C26 (degrees) | C26-Cu-C3 (degrees) | C3-Cu-C2 (degrees) |
|---|---|---|---|---|---|---|---|---|
| In vacuum | 6-31G(d,p) | 2.15 | 2.02 | 2.09 | 2.05 | 38.8 | 42.4 | 41.0 |
| | LanL2DZ | 2.70 | 2.24 | 2.26 | 2.29 | 30.9 | 38.8 | 37.0 |
| In water | 6-31G(d,p) | 2.15 | 2.01 | 2.10 | 2.12 | 38.8 | 42.3 | 39.8 |
| | LanL2DZ | 2.20 | 2.14 | 2.92 | 3.61 | 37.6 | 29.2 | 22.0 |
| In ethanol | 6-31G(d,p) | 2.15 | 2.01 | 2.10 | 2.11 | 38.7 | 42.3 | 39.9 |
| | LanL2DZ | 2.20 | 2.14 | 2.92 | 3.60 | 37.6 | 29.2 | 22.0 |
| | | C28-C26 (Å) | C26-C3 (Å) | C3-C2 (Å) | | C28-C26-C3-C2 (degrees) | | C16-C28-C26-C4 (degrees) |
| In vacuum | 6-31G(d,p) | 1.39 | 1.49 | 1.45 | | -12.6 | | -163.6 |
| | LanL2DZ | 1.39 | 1.50 | 1.44 | | -25.9 | | -152.5 |
| In water | 6-31G(d,p) | 1.39 | 1.49 | 1.44 | | -10.3 | | -162.8 |
| | LanL2DZ | 1.40 | 1.47 | 1.42 | | 2.1 | | -166.2 |
| In ethanol | 6-31G(d,p) | 1.38 | 1.49 | 1.44 | | -10.3 | | -163.6 |
| | LanL2DZ | 1.40 | 1.47 | 1.42 | | 2.3 | | -166.1 |

dissociation energy if compared with LanL2DZ by a factor 2 (Fig. 2). In this preliminary work, possible errors due to basis set superposition were not considered.

**Table 3.** Dissociation energy, in kJ/mol, of the [Resv]$Cu^+$ complex in vacuum, calculated by B3LYP/6-31G(d,p) and B3LYP/LanL2DZ.

| | Dissociation energy (kJ/mol) |
|---|---|
| 6-31G(d,p) | −522.4 |
| LanL2DZ | −269.7 |

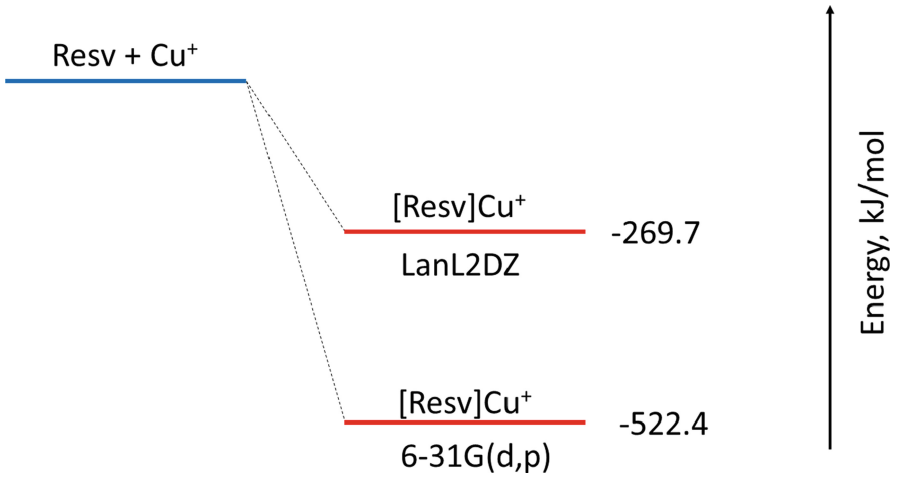


**Fig. 2.** Dissociation energies of Resv[Cu]$^+$ calculated by LanL2DZ and 6-31G(d,p) basis sets.

The solvation energy was calculated both for the complex in water and in ethanol, by using the two basis sets applied so far (Table 4). Solvated complexes calculated by LanL2DZ are more stable by about 50 kJ/mol with respect to the 6-31G(d,p) counterpart. For both basis sets, [Resv]Cu$^+$ in water is more stable than in ethanol by 8–9 kJ/mol (Fig. 3).

**Table 4.** Solvation energies of the [Resv]Cu$^+$ complex in water and in ethanol, calculated by B3LYP/6-31G(d,p) and B3LYP/LanL2DZ

| | | Solvation energy (kJ/mol) |
|---|---|---|
| In water | 6-31G(d,p) | −225.5 |
| | LanL2DZ | −263.9 |
| In ethanol | 6-31G(d,p) | −217.5 |
| | LanL2DZ | −254.3 |

We report a description of the IR spectrum of [Resv]Cu$^+$ in vacuum obtained by our calculations (Fig. 4). Low intensity peaks, at wavenumbers no higher than 400 cm$^{-1}$ are attributed to modes involving the ethylene group, especially hindered rotations, bending and stretching motions. An intense peak is found at *ca.* 450 cm$^{-1}$, mainly due to the motion out of the plane of the hydrogens in the resorcinol fragment: H7, H9, H11, and H13 (Fig. 5a). Motions out of the plane of the hydrogen atoms of the molecule, together with carbons in the resorcinol fragment, determine a peak of small intensity at *ca.* 850 cm$^{-1}$. At 1200 cm$^{-1}$, there are at least four intense peaks related to motions of the hydrogen atoms in the plane of the phenol and resorcinol rings (Fig. 5b). A vibrational mode related to the motion in the plane of the hydrogens of the phenol fragment correspond to a moderately intense peak at 1350 cm$^{-1}$. Five peaks at wave numbers between

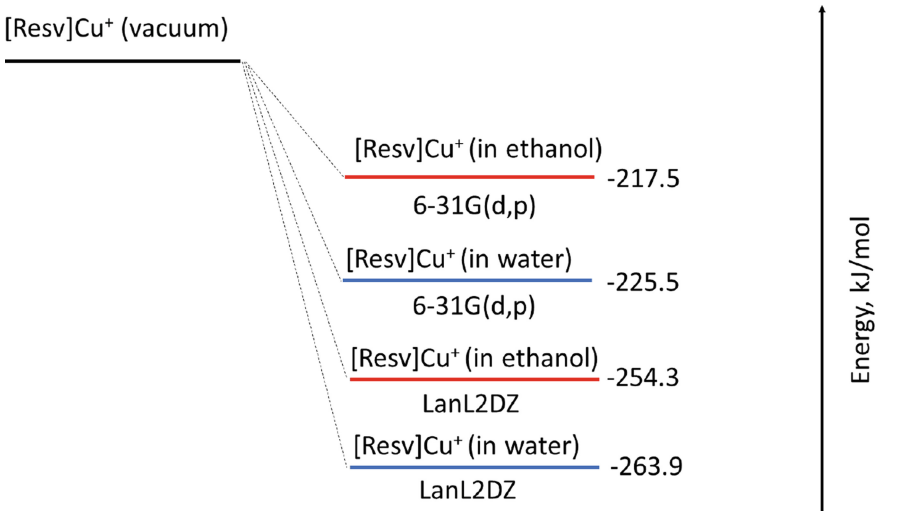


**Fig. 3.** Solvation energies (not in scale) of Resv[Cu]$^+$ in water and in ethanol, calculated by 6-31G(d,p) and LanL2DZ basis sets.

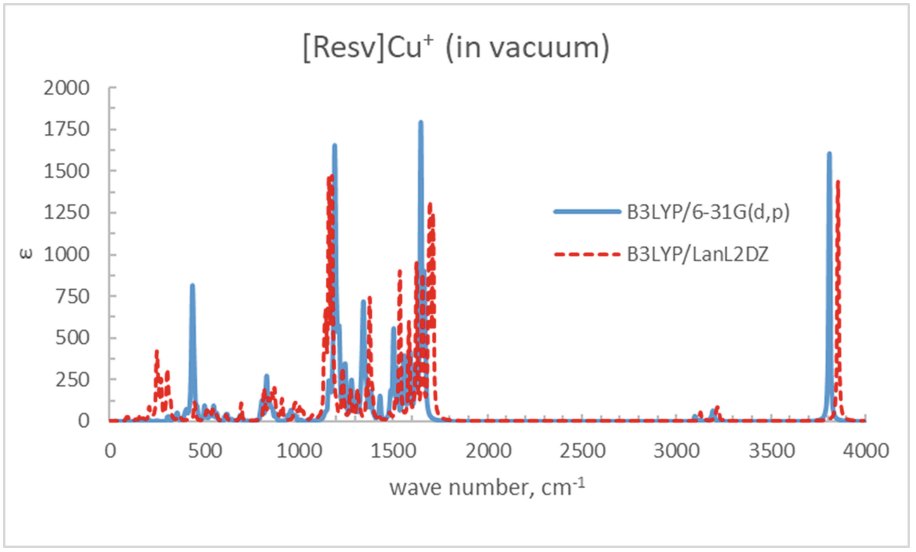


**Fig. 4.** IR spectra of [Resv]Cu$^+$ in vacuum calculated by B3LYP/6-31G(d,p) and B3LYP/LanL2DZ.

1500 and 1600 cm$^{-1}$ correspond to vibrations in the plane of the two aromatics rings. At 1650 cm$^{-1}$, two very intense peaks correspond to bending and stretching motions in the plane involving separately the atoms of the resorcinol group and those of the phenol group. The highest in energy peaks are found at *ca.* 3800 cm$^{-1}$ and are assigned to the

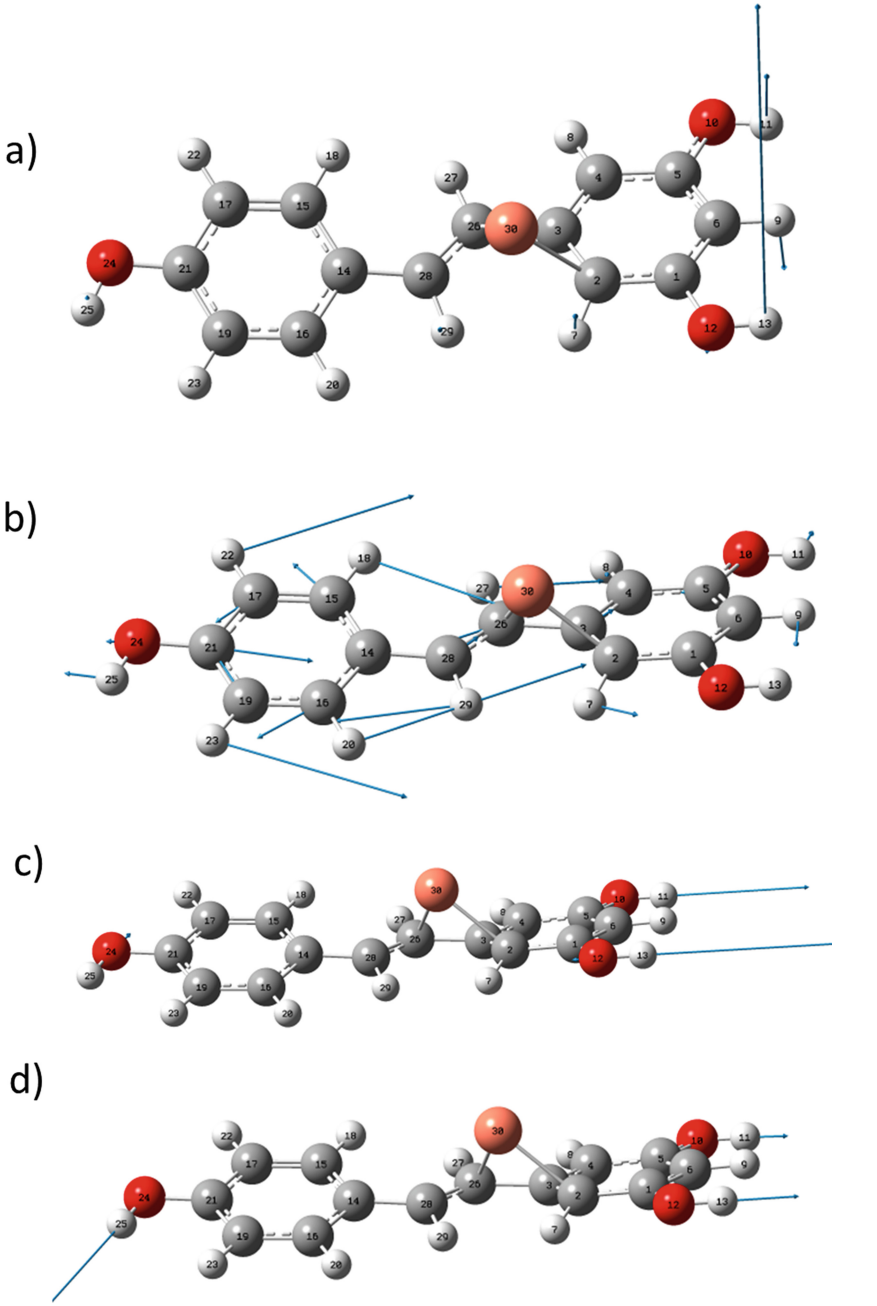


**Fig. 5.** Vector displacement (blue arrows) of four normal modes at a) 450 $cm^{-1}$, b) 1200 $cm^{-1}$, c) and d) 1800 $cm^{-1}$. (Color figure online)

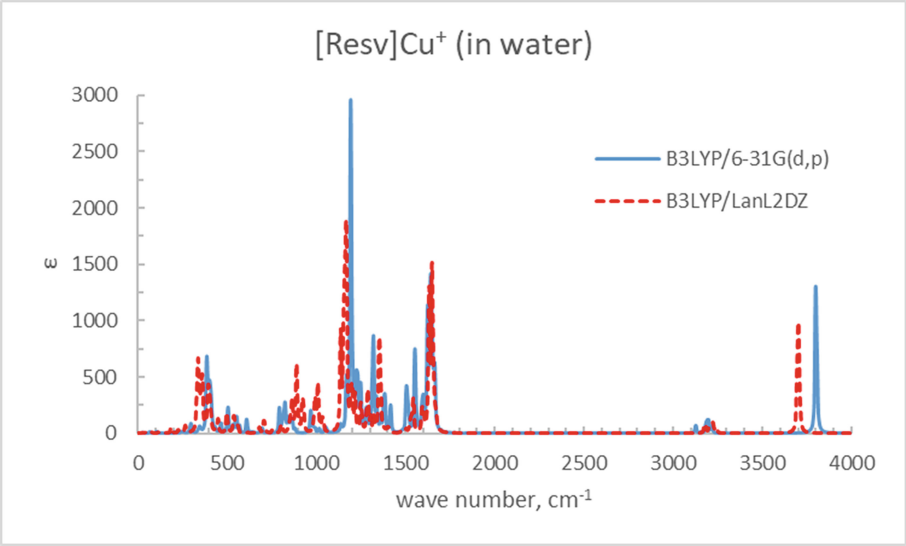


**Fig. 6.** IR spectra of [Resv]$Cu^+$ in water calculated by B3LYP/6-31G(d,p) and B3LYP/LanL2DZ.

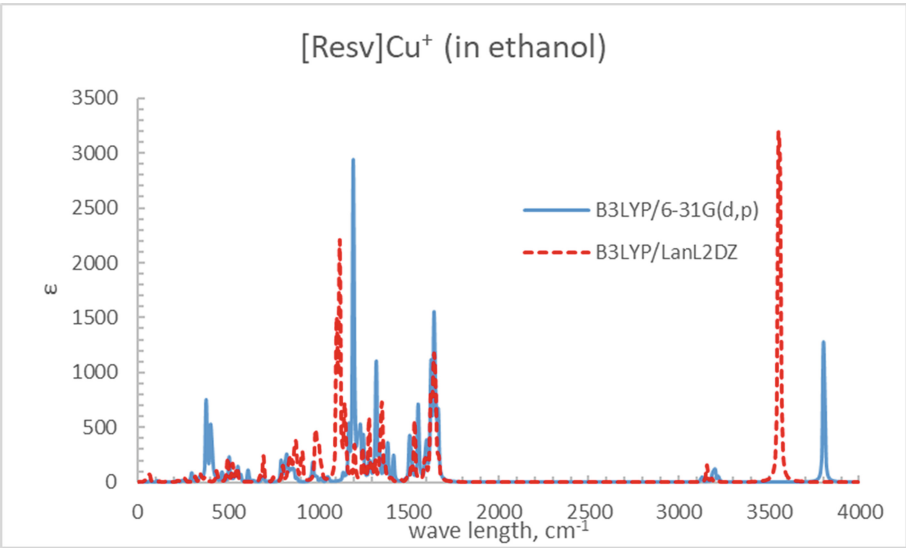


**Fig. 7.** IR spectra of [Resv]$Cu^+$ in ethanol calculated by B3LYP/6-31G(d,p) and B3LYP/LanL2DZ.

bond stretching involving O10-H11, O12-H13, and O24-H25 (Figs. 5c and 5d). Experimentally, IRMPD spectroscopy revealed important features of the [Resv]$Cu^+$ complex in the wave number range between 1100–1300 and 1500–1600 $cm^{-1}$, and a peak at 3628 $cm^1$ that corresponds to the OH vibrations region. Comparison of the spectra calculated by 6-31G(d,p) and LanL2DZ shows a substantial agreement between these two basis sets. The largest differences are found at low energies, in correspondence of the vibrations out of plane. Signals corresponding to the OH stretching, at *ca.* 3800 $cm^{-1}$ are calculated with about 50 $cm^{-1}$ of discrepancy. Effect of water as a solvent does not substantially change the spectrum, except the wave number region under 500 $cm^{-1}$, where the two basis sets give more similar spectra, and the intense peak found at 500 $cm^{-1}$ by 6-31G(d,p) basis set is not found in this case (Fig. 6). Effect of ethanol does not modify the spectrum, with respect to water, while differences between the spectrum calculated by the two basis sets are more marked (Fig. 7). The most evident difference is also in this case found at high wave numbers, where the peak attributed to the OH stretching is determined at *ca.* 3600$cm^{-1}$ by LanL2DZ and at *ca.* 3800 $cm^{-1}$ by 6-31G(d,p).

## 4 Conclusions

A preliminary study has been performed on the *trans*-Resveratrol - Cu(I) complex in vacuum, in water, and in ethanol, by DFT method using the B3LYP functional combined with 6-31G(d,p) and LanL2DZ basis sets. Optimization by 6-31G(d,p) leads to structures with copper roughly equidistant to the four adjacent carbon, *ca.* 2 Å; this structure is quite similar both in vacuum, in water, and in ethanol. Structures optimized by LanL2DZ present a higher bond length between copper and the adjacent atoms. Differences are observed between the structure in vacuum and in solvents. Comparison of the structures of *trans*-resveratrol and [Resv]$Cu^+$ shows that most of differences between the two basis sets are observed in the features related to $Cu^+$, both in vacuum and when solvent interactions are considered. On the contrary, choice of the basis sets does not affect the geometry optimization of the resveratrol molecule. The effect of $Cu^+$ to resveratrol determines lose of coplanarity between phenol and resorcinol groups. It can be observed for the two basis sets, both in vacuum and in solvents.

Infrared spectra were calculated by using both the basis sets. The spectra of the complex in vacuum are compared with experimental data, showing a substantial qualitative agreement. Both calculated spectra are in agreement, with differences that concern especially the peaks at the highest wave numbers, corresponding to the OH stretching modes. Such differences increase when the complex is in water and in ethanol.

The remarkable differences in the geometrical features related to $Cu^+$ and the atoms of resveratrol closest to this metal ion, as well as the huge differences in energy, especially for the dissociation energy, suggest that future works must be addressed to the assessment of functionals and basis sets that could correctly predict energy and structural properties of this copper complex. Investigations will be extended to complexes with other trace elements.

**Acknowledgements.** The authors thank the Dipartimento di Ingegneria Civile ed Ambientale of Università degli Studi di Perugia for allocated computing time within the project "Dipartimenti di Eccellenza 2018–2022". N.F.-L. acknowledges the Fondo Ricerca di Base 2021

(RICBASE2021FAGINAS) of Dipartimento di Chimica, Biologia e Biotecnologie of Università degli Studi di Perugia for financial support. The authors acknowledge the Italian Ministry for Education, University and Research (MIUR) for financial support through Scientific Independence of young Researchers SIR 2014 (RBSI14U3VF) and (RBSI144EUA).

## References

1. Ghanim, H., et al.: An antiinflammatory and reactive oxygen species suppressive effects of an extract of polygonum cuspidatum containing resveratrol. J. Clin. Ebdocrinol. Metab. **95**(9), E1–E8 (2010)
2. Renaud, S., de Lorgeril, M.: Wine, alcohol, platelets, and the French paradox for coronary heart disease. Lancet **339**(8808), 1523–1526 (1992)
3. Penumathsa, S., Maulik, N.: Resveratrol: a promising agent in promoting cardioprotection against coronary heart disease. Can. J. Physiol Pharmacol. **87**, 275 (2009)
4. Park, S.J., et al.: Resveratrol ameliorates aging-related metabolic phenotypes by inhibiting cAMP phosphodiesterase. Cell **148**, 421 (2012)
5. Ragonese, F., et al.: Resveratrol depolarizes the membrane potential in human granulosa cells and promotes mitochondrial biogenesis. Fertil. Steril. **115**, 1063–1073 (2021)
6. Dionigi, L., et al.: Focus on the use of resveratrol as an adjuvant in glioblastoma therapy. Curr. Pharm. Des. **26**(18), 2102–2108 (2020)
7. Iannitti, R.G., et al.: Resveratrol supported on magnesium DiHydroxide (Resv@MDH) represents an oral formulation of resveratrol with better gastric absorption and bioavailability respect to pure resveratrol. Front. Nutr. **7**, 570047 (2020)
8. Iuga, C., Alvarez-Idaboy, J.R., Russo, N.: Antioxidant activity of trans-resveratrol toward hydroxyl and hydroperoxyl radicals: a quantum chemical and computational kinetics study. J. Org. Chem. **77**(8), 3868–3877 (2012)
9. Mazzone, G., Malaj, N., Russo, N., Toscano, M.: Density functional study of the antioxidant activity of some recently synthesized resveratrol analogues. Food Chem. **141**, 2017–2024 (2013)
10. Benayahoum, A., Amira-Guebailia, H., Houache, O.: A DFT method for the study of the antioxidant action mechanism of resveratrol derivatives. J. Mol. Model. **19**, 2285–2298 (2013)
11. Benayahoum, A., Amira-Guebailia, H., Houache, O.: Homolytic and heterolytic O-H bond cleavage in trans-resveratrol and some phenantrene analogs: a theoretical study. Comp. Theor. Chem. **1037**, 1–9 (2014)
12. Tellone, E., et al.: Molecular interactions of hemoglobin with resveratrol: potential protective antioxidant role and metabolic adaptations of the erythrocyte. Biol. Chem. **395**, 347–354 (2014)
13. Frau, J., Muñoz, F., Glossman-Mitnik, D.: A molecular electron density theory study of the chemical reactivity of cis- and trans-resveratrol. Molecules **21**(12), 1650 (2016)
14. Frau, J., Muñoz, F., Glossman-Mitnik, D.: Application of DFT concepts to the study of the chemical reactivity of some resveratrol derivatives through the assessment of the validity of the "Koopmans in DFT" (KID) procedure. J. Theor. Comp. Chem. **16**, 1750006 (2017)
15. Wang, F., Chatterjee, S.: Dominant carbons in *trans*- and *cis*-resveratrol isomerization. J. Phys. Chem B **121**(18), 4745–4755 (2017)
16. Kores, K., Lešnik, S., Bren, U., Janežič, D., Konc, J.: Discovery of novel potential human targets of resveratrol by inverse molecular docking. J. Chem. Inf. Model. **59**(5), 2467–2478 (2019)
17. Nakajima, M., Adachi, Y., Nemoto, T.: Computation-guided asymmetric total syntheses of resveratrol dimers. Nature Comm. **13**, 152 (2022)

18. Tamboli, V., Defant, A., Mancini, I., Tosi, P.: A study of resveratrol-copper complexes by electrospray ionization mass spectrometry and density functional theory calculations. Rapid Commun. Mass Spectrum. **25**, 526–532 (2011)
19. Chiavarino, B., Crestoni, M.E., Fornarini, S., Taioli, S., Mancini, I., Tosi, P.: Infrared spectroscopy of copper-resveratrol complexes: a joint experimental and theoretical study. J. Chem. Phys. **137**, 024307 (2012)
20. Tamboli, V., Re, N., Coletti, C., Defant, A., Mancini, I., Tosi, P.: A joint experimental and theoretical investigation on the oxidative coupling of resveratrol induced by copper and iron ions. Int. J. Mass Spectrom. **319–320**, 55–63 (2012)
21. Frisch, M.J.: Gaussian 09, Revision A.02. Gaussian, Inc., Wallingford CT (2016)
22. Yang, Y., Weaver, M.N., Merz, K.M., Jr.: Assessment of the "6-31-G** + LANL2DZ" mixed basis set coupled with density functional theory method and the effective core potential: prediction of heats of formation and ionization potentials for first-row-transition-metal complexes. J. Phys. Chem. A **113**(36), 9843–9851 (2009)
23. Klamt, A., Moya, C., Palomar, J.: A comprehensive comparison of the IEFPCM and SS(V)PE continuum solvation methods with the COSMO approach. J. Comp. Theory Comput. **11**(9), 4220–4225 (2015)