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## Molecular modeling of poly(ethylene oxide) model cofactors; 1,3,6-tri-O-galloyl- $\beta$ -D-glucose and corilagin

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**Abstract** The most stable structures of two poly(ethylene oxide) (PEO) model cofactors,  $\beta$ -1-O-galloyl-3,6-(*R*)-hexahydroxydiphenoyl-D-glucose (corilagin) and 1,3,6-tri-O-galloyl- $\beta$ -D-glucose (TGG), are calculated using molecular modeling and PM3 semiempirical molecular orbital theories. The theoretical PM3 structures agree with interpreted structures from experimental NMR; the glucopyranose ring of corilagin has a boat and TGG a chair conformation, for which the heats of formation, torsion angles, distances, van der Waals surface, and the infrared spectra are calculated.

**Keywords** Corilagin · Papermaking · Cofactor · TGG · Molecular orbital theory

### Introduction

This work uses molecular modeling and PM3 semiempirical calculations to study cofactors, used in the pulp and paper industry to enhance the efficiency of a flocculating agent poly(ethylene oxide) (PEO), and to study the bonding between these cofactors and the polymer. Theoretical calculations of molecular properties are accurate and reliable and of practical value in papermaking chemistry, where experimental data are lacking or where experimental procedures fail to explain specific aspects of polymer bonding. A high molecular weight non-ionic PEO, used in newsprint production, has as cofactor a phenolic resin, such as a phenol–formaldehyde resin

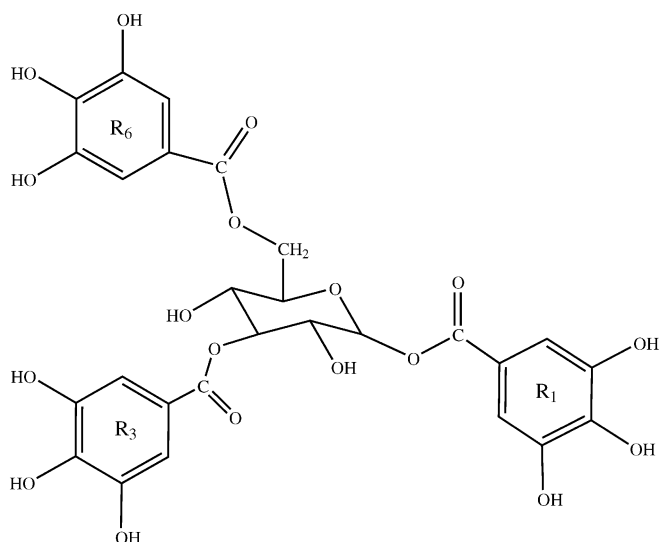
(PFR), a modified phenolic resin (MPR), or a sulfonated kraft lignin (SKL). The PEO and the cofactor form a complex, which flocculates cellulose fibres, fines and fillers, and is a drainage aid; higher drainage gives increased production and improved profits. Many mechanisms describe the interaction chemistry of PEO with cofactors, fibres, fines and fillers, including a polymer network (Lindström) [1], complex bridging (Pelton) [2], association induced polymer bridging (van de Ven) [3], asymmetric polymer bridging (van de Ven) [4], and temperature induced flocculation. Englezos [5] Lindström [1] and Pelton [2] postulate a hydrogen bond between the ether oxygen of the PEO and a phenolic hydrogen of the cofactor resin, supplemented by hydrophobic interactions between ethylene and aromatic rings (Cong) [6].

To simplify the calculations, 1,3,6-tri-O-galloyl- $\beta$ -D-glucose (TGG) (Fig. 1a) and corilagin (Fig. 1b) are used as model cofactors; they are non-polymerized small molecules, and contain the phenolic groups characteristic of real polymeric phenolic cofactors. TGG is a sugar ring esterified three times by gallic acid. In TGG there is no bond between the galloyl rings, giving a flexible structure, which parallels the polymeric phenolic resins used in papermaking. Haslam et al. [7] have studied this molecule by NMR, and from the  $^1\text{H}$  and  $^{13}\text{C}$  frequencies, and the two-dimensional long-range heteronuclear shift correlation, defined the positions of esterification of the D-glucopyranose ring by gallic acid. Corilagin, a form of tannic acid, [8] an ellagitannin, has been widely studied. [9, 10, 11, 12, 13, 14, 15, 16] Yoshida and Okuda [13] published the  $^{13}\text{C}$  nuclear magnetic resonance spectra of corilagin and geraniin in acetone-D<sub>6</sub>. The assignments of the signals of the glucose moiety of corilagin reflected a perturbed boat conformation of the glucopyranose ring. Corilagin as a model cofactor for the PEO has rings 3 and 6 joined, and therefore is less flexible than TGG. Haslam et al. [7] reported the distribution coefficients of 1,3,6-tri-O-galloyl- $\beta$ -D-glucose (TGG) and corilagin between octane-1-ol and water ( $K_{\text{oct}/\text{H}_2\text{O}}$ ) at 293 K as 1.5 and 0.1 respectively. Tanaka et al. [17] interpreted this result as related to the greater rigidity of corilagin com-

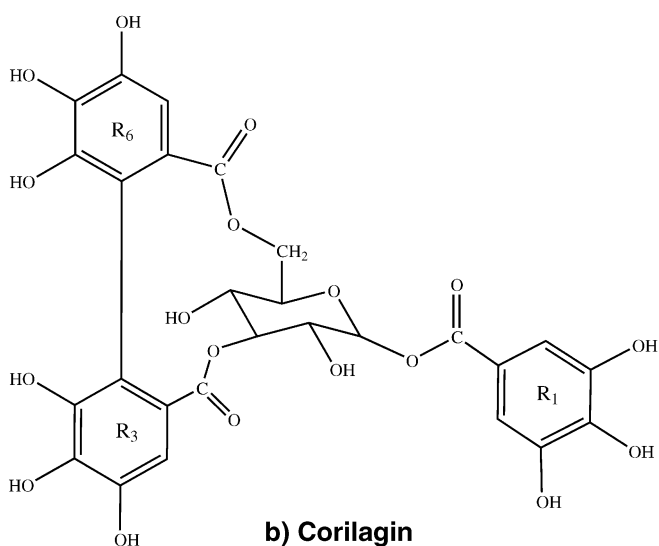
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a) TGG



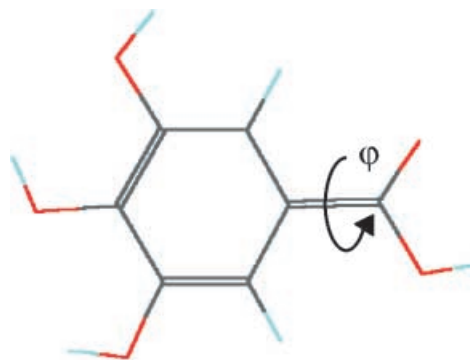
b) Corilagin

**Fig. 1** Molecular structure of **a** TGG (1,3,6-tri-O-galloyl- $\beta$ -D-glucose), **b** corilagin (R1, R3, and R6 designate rings 1, 3, and 6 respectively)

pared to TGG. The Merck Index [18] refers to corilagin under the tannic acid name; the structure in the Merck Index is 1,3,6-tri-O-galloyl- $\beta$ -D-glucose.

### Conformational analysis

The molecular mechanics and PM3 semiempirical calculations were performed using a Silicon Graphics workstation Cerius<sup>2</sup> software (Molecular Simulation Inc.). Molecular mechanics used the Dreiding force field (DFF) [19] which, in the energy minimization procedure, includes bond stretching, valence angle bending, torsional twisting, out of plane torsions, non-bonding interactions, van der Waals (vdW) forces, hydrogen bonding



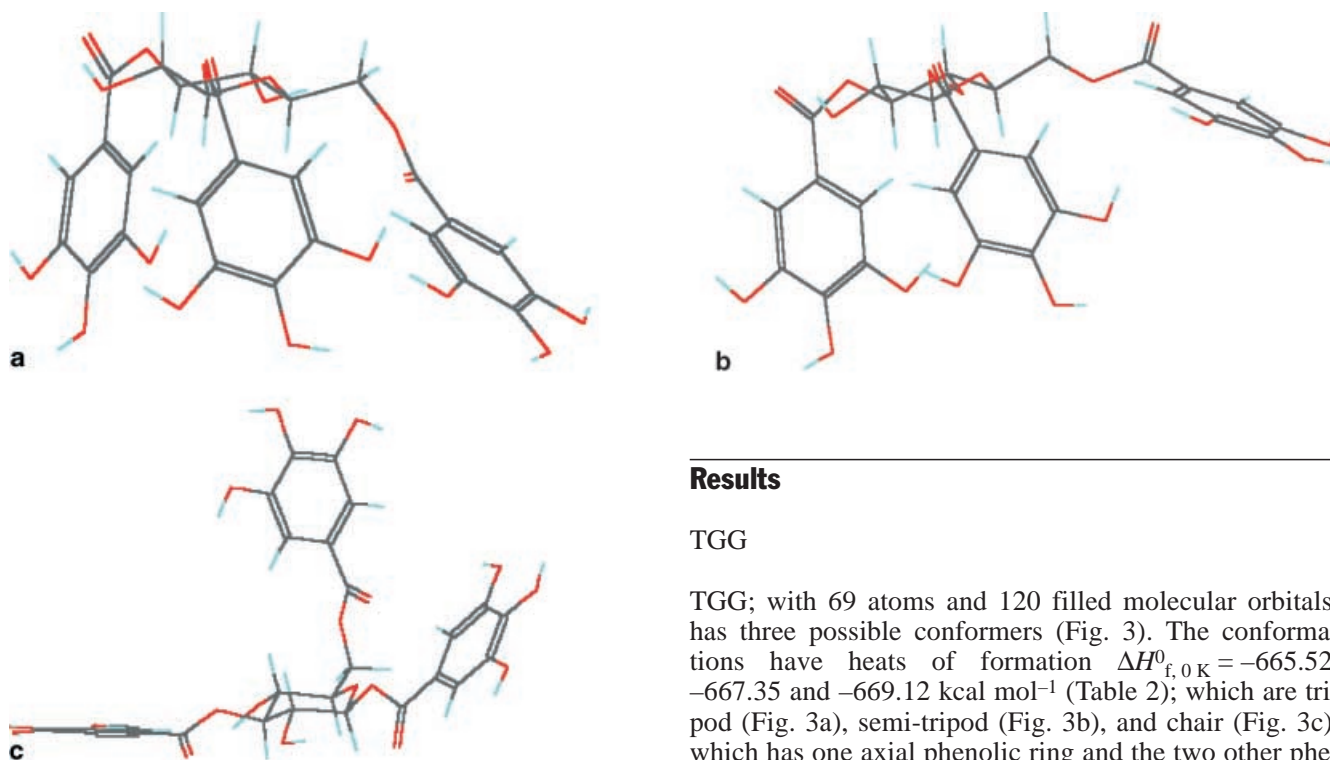
**Fig. 2** Molecular structure of gallic acid (calculated with PM3) where  $\phi$  is the angle of rotation

and Coulombic energy (CE) interactions. The charges of the various atoms were recalculated every 50 iterations using a charge equilibration method ( $Q_{Eq}$  charged 1.1) that depends directly on the geometry of the conformation and the electronegativities of the constituent atoms. Energy minimization used the Smart Minimizer, which is a combination of methods, starting with the Steepest Descent Method, followed by the ABNR and Quasi Newton methods, and ending with the accurate Truncated Newton Method. Energy minimization is terminated when the root-mean square (rms) force is less than  $1.000 \text{ cal mol}^{-1} \text{ \AA}^{-1}$ . The semiempirical PM3 calculations used Cerius<sup>2</sup>\_3.5/MOPAC 6/PM3 version 6.00. [20, 21] The heat of formation ( $\Delta H_{f,0K}^0$ ) of cyclopentadiene was calculated and agreed with previous calculations and experiment,  $31.9 \text{ kcal mol}^{-1}$ , [22] when PM3 includes the electrostatic potential (ESP), establishing the accuracy of the method. The structure of methyl  $\beta$ -D-glucose was used to build TGG and corilagin by the Tree Branch Method. [23] In TGG and corilagin the total charge was zero, with a spin ground state of spin zero to start the calculation. The Tree Branch Method [23] replaces the three hydrogens, located on the methyl group of the methyl  $\beta$ -D-Glucose, with gallic acid. The calculated conformers ensure that even close energy conformers are located by this method, unlike standard minimizations, which generate most stable conformations. Rotational barriers were calculated every  $5^\circ$  around the ester group of each conformer.

### Method of validation

The PM3 semiempirical method [20, 21] has been shown to be predictive for small molecules because the PM3 results parallel experiment. Testing this on the small molecule gallic acid (Fig. 2) established that PM3 would be reliable for larger molecules such as TGG and corilagin.

The initial structures calculated for gallic acid by the Molecular Modeling Dreiding Force Field were flat, with a torsion angle  $\phi=0^\circ$ ; they were used as input for the semiempirical calculations (see Table 1).

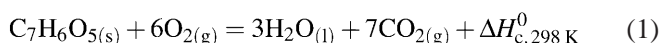


**Fig. 3** Side views of the three most stable PM3 calculated conformations of TGG: **a** tripod; **b** semi-tripod; **c** chair

**Table 1** Semiempirical results for gallic acid

Semiempirical method	$\Delta H_{f,0\text{K}}^0$ (kcal mol <sup>-1</sup> )	$\phi$ (°)
PM3	-198.04	+5.0

The predicted PM3 structure heat of formation was shown to fit experiment using the experimental values of the heat of formation  $\Delta H_{f,298\text{K}}^0$  calculated from



Substituting the heats of formation, gives

$$\Delta H_{f,298\text{K}}^0 + 6(0.0) = 3(-68.32) + 7(-94.05) + \Delta H_{c,298\text{K}}^0 \quad (2)$$

The heat of combustion  $\Delta H_{c,298\text{K}}^0$  was 621.3 kcal mol<sup>-1</sup> [24] and 633.7 [25] giving  $\Delta H_{f,298\text{K}}^0 = -242.0$  or  $-229.6$  kcal mol<sup>-1</sup> respectively. To these experimental results,  $\Delta H_{s,298\text{K}}^0$  (sublimation) was added using the value for *p*-hydroxy benzoic acid (*p*-HBA), a similar structure, giving 27.75 kcal mol<sup>-1</sup>. [26] Because of the difference in structure between *p*-HBA and gallic acid,  $\Delta H_{s,298\text{K}}^0$  (sublimation) of gallic acid would be expected to be greater than 27.75 kcal mol<sup>-1</sup>. Therefore the experimental  $\Delta H_{f,298\text{K}}^0$  of gallic acid should be close to  $-214.2$  or  $-201.8$  kcal mol<sup>-1</sup>. PM3 gave a  $\Delta H_{f,0\text{K}}^0$  of  $-198.04$  kcal mol<sup>-1</sup>. Gaussian 98 STO 3-21G calculations on gallic acid gave a torsion angle  $\phi$  of 0°, and a flat conformation.

## Results

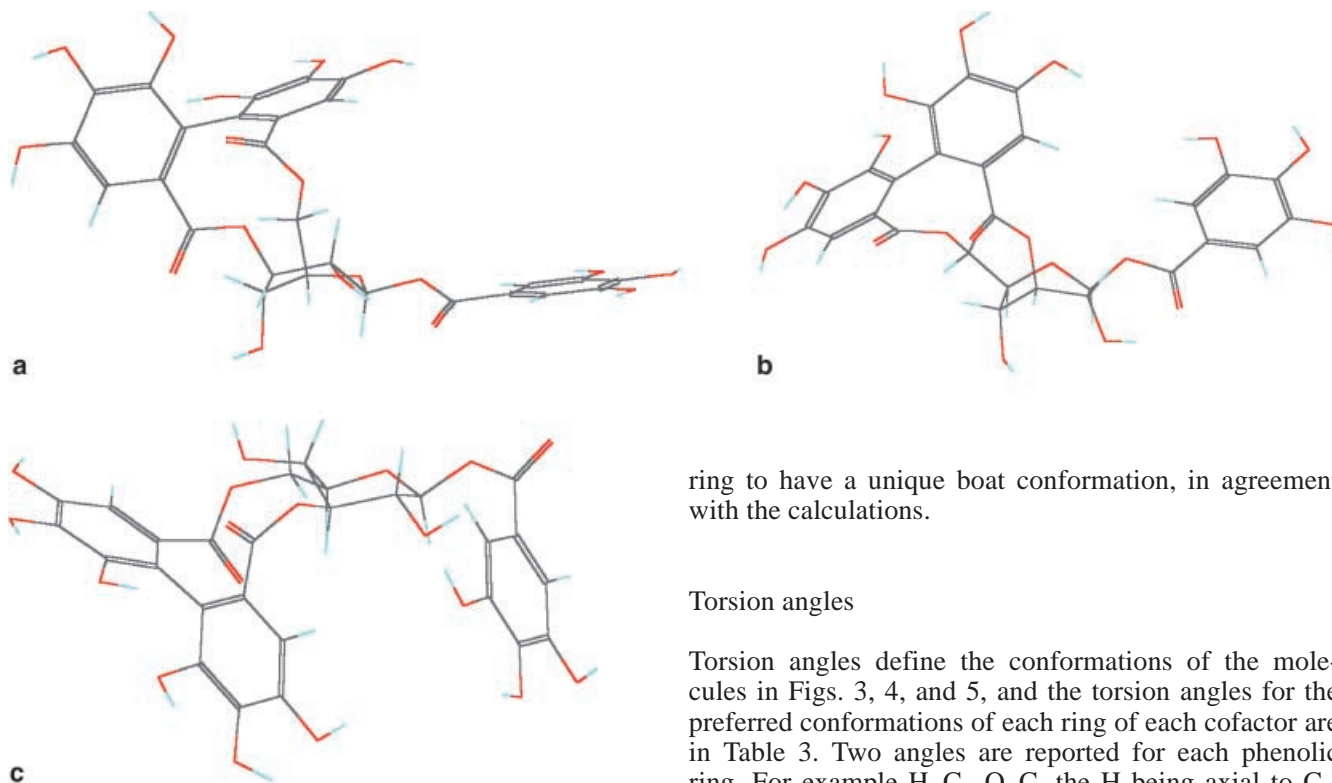
### TGG

TGG; with 69 atoms and 120 filled molecular orbitals, has three possible conformers (Fig. 3). The conformations have heats of formation  $\Delta H_{f,0\text{K}}^0 = -665.52$ ,  $-667.35$  and  $-669.12$  kcal mol<sup>-1</sup> (Table 2); which are tripod (Fig. 3a), semi-tripod (Fig. 3b), and chair (Fig. 3c), which has one axial phenolic ring and the two other phenolic rings, in the sugar plane and perpendicular to the plane. These are nearly equivalent structures where the maximum difference in  $\Delta H_{f,0\text{K}}^0$  is 3.60 kcal mol<sup>-1</sup>, and the probabilities of the conformations are 90, 10 and 1% respectively.

### Corilagin

Corilagin (Fig. 4), with 67 atoms and 119 filled molecular orbitals, has two joined phenolic rings (R3–R6), giving three conformations: boat (Fig. 4a), skew-boat (Fig. 4b), and chair (Fig. 4c) with final heats of formation of  $-645.61$ ,  $-629.09$ , and  $-623.57$  kcal mol<sup>-1</sup>. The R3–R6 C–C bond between the two phenolic rings makes corilagin less flexible than TGG, giving a higher energy of formation. The difference in the final heat of formation between the boat and skew-boat corilagin conformers (16.52 kcal mol<sup>-1</sup>) shows that corilagin has a boat conformation (Table 2). The chair conformation ( $\Delta H_{f,0\text{K}}^0 = -623.57$  kcal mol<sup>-1</sup>) will be the least stable. Possible additional conformers were considered with the C–C bond between the phenolic rings (R1–R3) (Fig. 5a) and (R1–R6) (Fig. 5b) which gave higher energies  $-598.96$ , and  $-626.66$  kcal mol<sup>-1</sup> (Table 2). These conformers are therefore unlikely.

NMR interpretations of TGG predicted a single chair conformation. [11] The present theoretical results give three conformers. The NMR results average out the three conformers to a single conformer on the NMR time scale. The three conformers, calculated with the Tree Branch Method, ensure that even close energy conformers are found in the calculation. Nuclear magnetic resonance [11, 13] of corilagin showed the glucopyranose



**Fig. 4** The three PM3 calculated conformations of corilagin: **a** boat, the most stable; **b** skew-boat; **c** chair

**Table 2** Heat of formation ( $\Delta H_{f,0K}^0$ )

Molecule	Conformers	$\Delta H_{f,0K}^0$ (kcal mol <sup>-1</sup> )
TGG	Chair	-665.52
TGG	Semi-tripod	-667.35
TGG	Tripod	-669.12
Corilagin	Boat	-645.61
Corilagin	Skew-boat	-629.09
Corilagin	Chair	-623.57
R1R3	Skew-boat	-598.96
R1R6	Skew-boat	-626.66

The names of the molecules in full are:

**TGG:** C<sub>27</sub>H<sub>24</sub>O<sub>18</sub>  
1,3,6-Tri-O-galloyl-β-D-glucose, or 1,3,6-tri-O-galloyl-β-D-glucopyranose

**Corilagin:** C<sub>27</sub>H<sub>22</sub>O<sub>18</sub>  
β-1-O-Galloyl-3,6-(R)-hexahydroxydiphenoyl-D-glucose [14]  
or

β-D-Glucopyranose, cyclic 3,6-[(1R)-4,4',5,5',6,6'-Hexahydroxy-1,1'-biphenyl]-2,2'-dicarboxylate] 1-(3,4,5-trihydroxybenzoate)

**R1R3:** C<sub>27</sub>H<sub>22</sub>O<sub>18</sub>  
β-D-Glucopyranose, cyclic 1,3-[4,4',5,5',6,6'-Hexahydroxy[1,1'-biphenyl]-2,2'-dicarboxylate] 6-(3,4,5-trihydroxybenzoate)

**R1R6:** C<sub>27</sub>H<sub>22</sub>O<sub>18</sub>  
β-D-Glucopyranose, cyclic 1,6-[4,4',5,5',6,6'-Hexahydroxy[1,1'-biphenyl]-2,2'-dicarboxylate] 3-(3,4,5-trihydroxybenzoate)  
where the shorthand names are used in the text.

ring to have a unique boat conformation, in agreement with the calculations.

### Torsion angles

Torsion angles define the conformations of the molecules in Figs. 3, 4, and 5, and the torsion angles for the preferred conformations of each ring of each cofactor are in Table 3. Two angles are reported for each phenolic ring. For example H-C<sub>x</sub>-O-C, the H being axial to C<sub>2</sub>, C<sub>23</sub> and C<sub>43</sub> or C<sub>44</sub> of the glucopyranose ring (Fig. 6a); and O=C-C=C-, between the ester carbonyl group and the C=C bond of the phenolic ring of the cofactor. There are two C=C bonds, the C<sub>a</sub>=C<sub>b</sub> and C<sub>a</sub>=C<sub>c</sub>, where *a*, *b*, *c* are 6, 7, and 17 for ring 1 of corilagin (Fig. 6a) and an angle ±<180° is found. [27] Figure 6a shows the atom numbering, not included in Figs. 3, 4, and 5 because it would make the conformations difficult to read: structures in Figs. 3, 4, and 5 are shown as in Fig. 6b.

### Distances between phenolic rings

The distances between the phenolic rings in Table 4 are the distances between the carbons *para* to the carboxylic sugar linkage, Fig. 6a. These distances define a cavity for the interactions of TGG and corilagin with PEO.

Figure 7 shows the van der Waals surface of TGG using the DFF force field as a dotted surface, to coincide with the total charge density calculated by the semiempirical PM3 method as a solid surface. Therefore the MM van der Waals surface can be used to interpret cavity and molecular sizes.

### Infrared

The infrared vibrational frequencies of the most stable conformers of TGG (tripod) and corilagin (boat) were calculated using PM3 MOPAC 6.00 (Figs. 8 and 9).

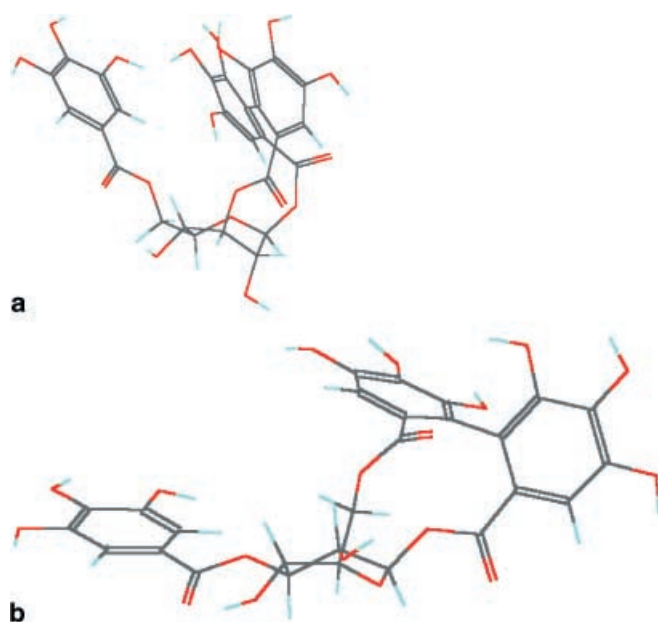
The infrared spectra, from 1900 cm<sup>-1</sup> to 4000 cm<sup>-1</sup>, were analyzed to show the differences between the IR of the two molecules. Table 5 shows the stretching bands

**Table 3** PM3 torsion angles for the different conformations of TGG and corilagin

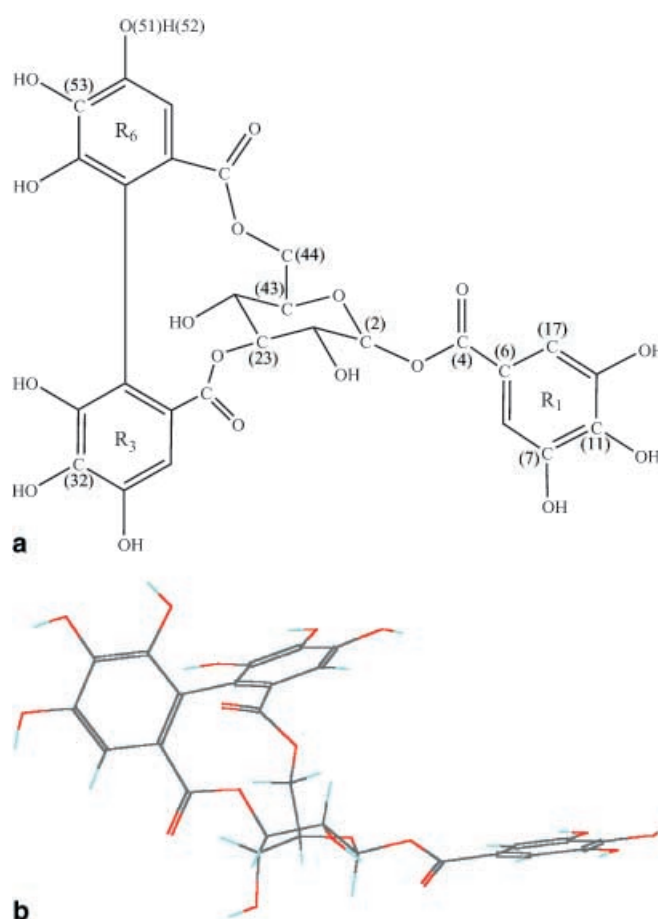
Molecule	Conformation	Ring-1	Ring-3	Ring-6
		H-C <sub>2</sub> -O-C: O=C-C=C-	H-C <sub>23</sub> -O-C: O=C-C=C-	H-C-C-O: O=C-C=C-
TGG	Chair	-14.6°: -22.9°	-30.3°: -31.7°	+176.7°: -29.7°
TGG	Semi-tripod	+18.5°: +59.5°	+8.3°: -71.2°	-46.4°: -44.1°
TGG	Tripod	+26.2°: +65.8°	-4.7°: +70.3°	+26.0°: -36.0°
Corilagin	Boat	-44.7°: +25.1°	-39.4°: -13.4°	-171.2°: +49.7°
Corilagin	Skew-boat	-60.5°: -10.0°	-43.9°: -45.4°	+144.0°: +32.0°
Corilagin	Chair	+22.9°: +82.8°	-22.4°: +84.9°	+69.0°: +48.1°
R1R3	Skew-boat	+131.3°: -61.9°	+57.2°: -12.3°	+166.3°: -1.0°
R1R6	Skew-boat	+37.8°: +5.2°	-56.7°: -22.2°	-174.3°: -46.9°

**Table 4** Distances between phenolic rings in TGG and corilagin

Molecule	Conformation of the glucopyranose ring	Distances between rings (Å)		
		R3-R6 *C <sub>32</sub> to C <sub>53</sub> **C <sub>32</sub> to C <sub>54</sub>	R1-R3 C <sub>11</sub> to C <sub>32</sub>	R1-R6 *C <sub>11</sub> to C <sub>53</sub> **C <sub>11</sub> to C <sub>54</sub>
Corilagin*	Boat	5.8	14.1	9.7
TGG**	Chair	11.4	13.7	10.3
TGG**	Semi-tripod	12.3	8.2	6.6
TGG**	Tripod	9.4	8.6	8.4

**Fig. 5** Two hypothetical PM3 calculated structures of corilagin: **a** R1R3, skew-boat; **b** R1R6, skew-boat

localized on the different functional groups; C=O, CH (sugar), CH of CH<sub>2</sub>, and the CH and OH on the galloyl rings. There are two CH vibrational frequencies per ring for the TGG and one CH vibration on ring 3 and 6 for corilagin because the rings are joined. There are three OH vibrational frequencies per ring in both molecules from the three OH groups per ring believed H-bonded to the PEO. [1, 2] Also, the carbonyl bands are at different frequencies for the two molecules.

**Fig. 6** Atom numbering for corilagin: **a** planar diagrammatic structure; **b** side view, 3D conformation

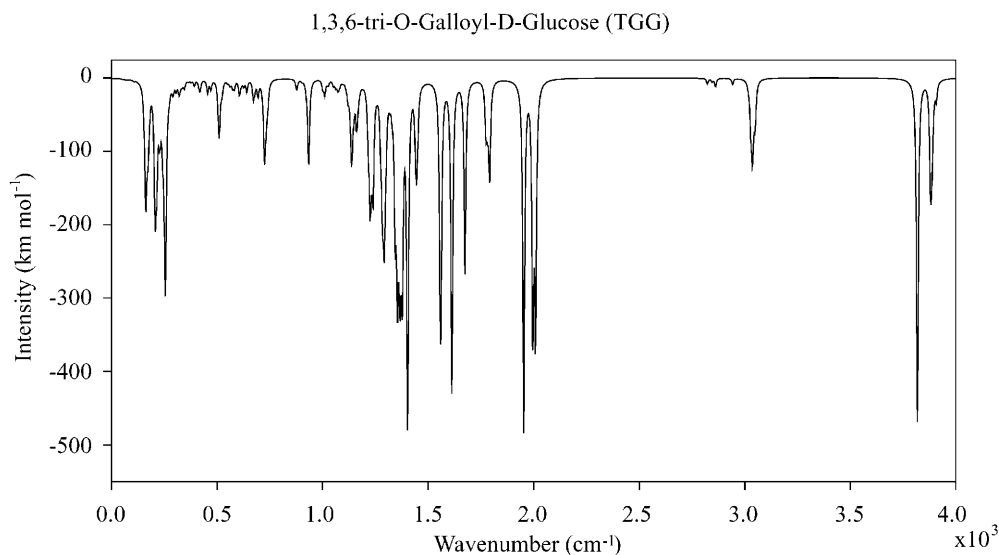


**Fig. 7** van der Waals surface of TGG (*dotted surface*), calculated by molecular modeling using DFF force field, coincides with the total charge density (*solid surface*) calculated by the semiempirical PM3 method

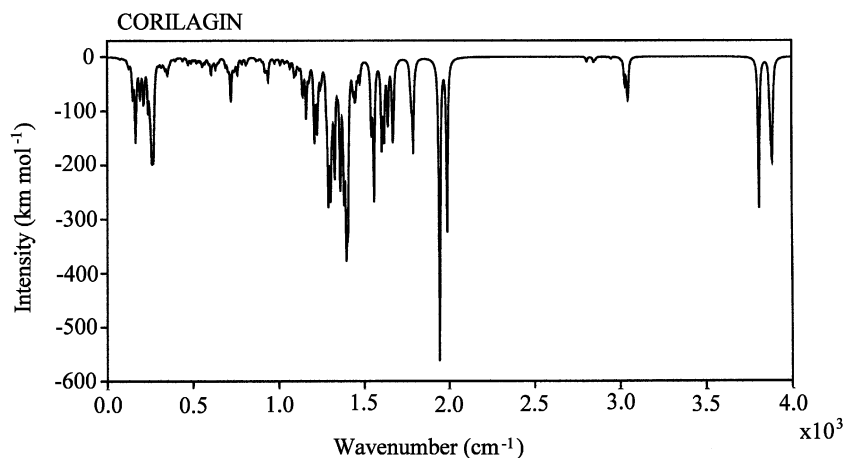
TGG and corilagin are not commercially available, and therefore an IR analysis was performed on tannic acid, which contains similar functional groups (Fig. 10). Note that the experimental wavenumber scale is inversed compared to theoretical spectrum (Figs. 8 and 9). The experimental tannic acid carbonyl bands are at  $1707\text{ cm}^{-1}$ , in agreement with Krilov et al. [28] on gallic acid, and below the theoretical values from PM3. The OH of the galloyl rings of tannic acid centred at approximately  $3370\text{ cm}^{-1}$  ( $3200\text{--}3500\text{ cm}^{-1}$  [28]) are also below the theoretical values of  $3818.08\text{--}3889.59\text{ cm}^{-1}$ , and show absorption peaks caused by OH stretching vibrations on top of a broad spectral feature. Consequently the tannic acid and TGG/corilagin are expected to have similar IR spectra, and the theoretical spectra can be interpreted remembering the downward frequency shift.

The ratio between the theoretical and experimental frequencies is identical for TGG and corilagin, and is 1.15 for the carbonyl band and 1.15 for the OH band of the galloyl rings. However, the theoretical vibrational frequencies for CH of the galloyl rings ( $3024.11\text{--}3050.42\text{ cm}^{-1}$ ) are located within the experimental range,  $3000\text{--}3100\text{ cm}^{-1}$ . The region from  $400$  to  $1650\text{ cm}^{-1}$  of

**Fig. 8** Theoretical infrared spectrum of TGG (tripod)



**Fig. 9** Theoretical infrared spectrum of corilagin (boat)



**Table 5** Theoretical infrared vibrational frequencies of TGG and corilagin

Molecule	Vibrational frequencies (cm <sup>-1</sup> ); stretching bands				
	-C=O (of ester)	-C-H (of glucose)	-CH (of CH <sub>2</sub> )	-CH (of phenolic ring)	-OH (of phenolic ring)
TGG (Tripod) $\Delta H_{f,0K}^0 = -669.12$ kcal mol <sup>-1</sup>	R1 <sup>a</sup> : 2008.51  R3: 1995.71  R6: 1952.70	C1 <sup>b</sup> : 2787.01  C2: 2861.61  C3: 2822.37  C4: 2844.65  C5: 2825.63	2942.58 (Asymmetric)  3016.95 (Symmetric)	R1 <sup>a,c</sup> : 3028.33 3050.42  R3 <sup>c</sup> : 3035.71 3047.36  R6 <sup>c</sup> : 3035.61 3040.04	R1 <sup>a,d</sup> : 3818.08 3881.09 3881.96  R3 <sup>d</sup> : 3878.02 3884.12 3887.79  R6 <sup>d</sup> : 3878.70 3881.47 3887.98
Corilagin (Boat) $\Delta H_{f,0K}^0 = -645.61$ kcal mol <sup>-1</sup>	R1 <sup>a</sup> & R3: 1941.81  R1 <sup>a</sup> & R3: 1942.71  R6: 1986.62	C1 <sup>b</sup> : 2774.57  C2: 2843.67  C3: 2803.74  C4: 2823.16  C5: 2854.78	2946.20 (Asymmetric)  3003.96 (Symmetric)	R1 <sup>a,c</sup> : 3038.56 3043.80  R3 <sup>c</sup> : 3024.11  R6 <sup>c</sup> : 3045.29	R1 <sup>a,d</sup> : 3882.45 3883.33 3889.59  R3 <sup>d</sup> : 3878.19 3885.16 3885.89  R6 <sup>d</sup> : 3870.21 3876.66 3883.94

<sup>a</sup> Galloyl ring attached to carbon 1 of glucose

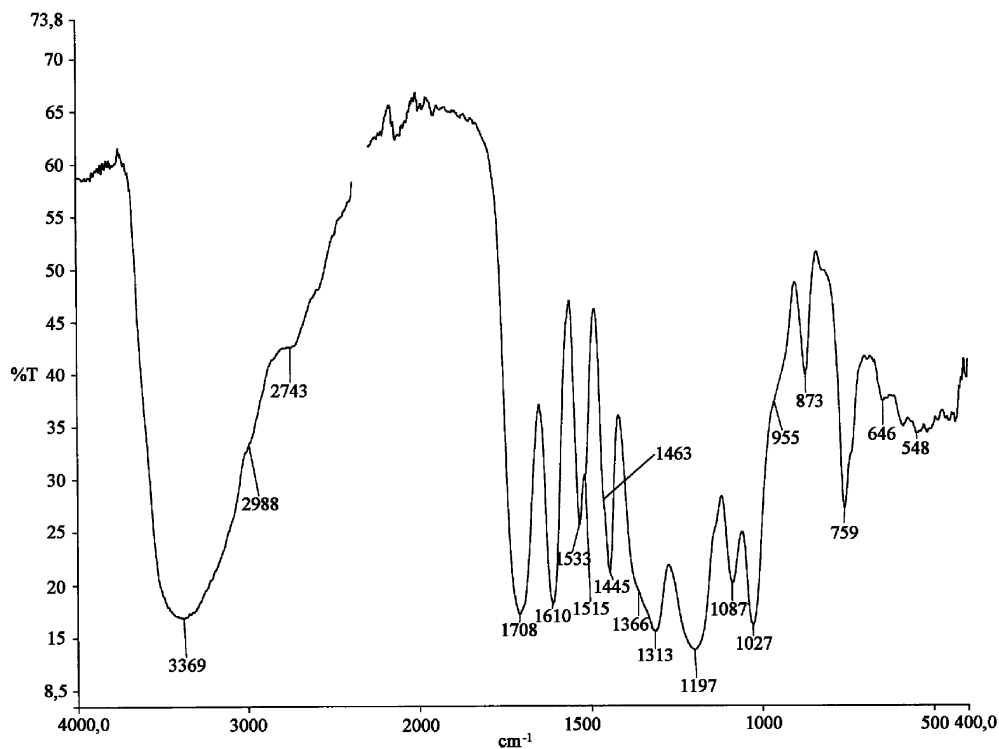
<sup>b</sup> Carbon 1 of glucose

<sup>c</sup> Two CH per ring

<sup>d</sup> Three OH per ring

<sup>e</sup> One CH per ring

**Fig. 10** Experimental infrared spectrum of tannic acid



the experimental spectrum is not discussed, because this region contains no frequencies characteristic of bonds interesting to our work.

## Conclusions

The calculation of 1,3,6-tri-O-galloyl- $\beta$ -D-glucose (TGG), a model cofactor for PEO, using molecular mechanics and PM3 semiempirical molecular orbital theories, suggests three possible conformations for TGG; tripod, semi-tripod, and chair ( $\Delta H_{f,0K}^0 = -669.12$ ,  $-667.35$ , and  $-665.52$  kcal mol $^{-1}$ ). The three theoretical structures should average out to the single conformer observed in the NMR time scale. [11] The conformation of the glucopyranose ring of corilagin, a form of tannic acid, is a boat conformation, with  $\Delta H_{f,0K}^0 = -645.61$  kcal mol $^{-1}$ , in agreement with the NMR structure. [11, 13] The conformers R1R3 and R1R6, having skew-boat conformations, do not occur because of unfavorably high energies,  $-598.96$  and  $-626.66$  kcal mol $^{-1}$ . From the van der Waals surface of the most stable TGG conformer (tripod), the cavity available for PEO interaction calculated by molecular modeling (DFF) fits the PM3 total charge density. The size of the cavity is large enough to contain a segment of the PEO molecule. Similarly, corilagin can interact with PEO where the cavity ranges from 5.8 to 14.1 Å.

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