Extending the applications of circular dichroism in structure elucidation: aqueous environment breaks the symmetry of tartrate dianion†

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Electronic circular dichroism and quantum mechanical studies show that in aqueous solution tartrate dianions are non-symmetrically hydrated and their expected C_2 symmetry is reduced to C_1 while preserving the conformation of the carbon skeleton. Our results indicate that inclusion of explicit solvent (water) molecules in quantum mechanical calculations is instrumental in detailed studies on molecular structure in solution. Moreover, the presented combined experimental and theoretical approach is a unique demonstration of the capability of ECD spectroscopy to detect subtle structural changes of molecules in solution. In addition to the n-π* Cotton effect at *ca.* 212 nm, the CD spectra of (*R*,*R*)-tartrates in aqueous solution reveal the presence of a Cotton effect at *ca.* 193 nm which is, at least partly, the result of n-σ* excitation.

Introduction

Circular dichroism (CD), either electronic or vibrational, is among the most important spectroscopic methods for studying structures, *i.e.* absolute configuration and/or conformation of chiral molecules.[1] A standard procedure currently adopted for correlation of the CD spectra with structure employs calculation of a number of low energy structures and confrontation of their calculated CD spectra with the experimental one. This procedure leads to the determination of the absolute configuration or conformation (or sometimes both[2]) in a non-empirical manner. Whereas absolute configuration determination is a straightforward process of distinguishing between mirror-image structures and their CD spectra, the conformational analysis may be more complex, in particular if several low-energy conformers in equilibrium are involved. The conformers usually originate from changes of conformation of the carbon skeleton of a molecule and the CD spectra, both calculated and experimental, are due to the average Boltzmann contributions of individual conformers. The confrontation procedure proved to be very effective, for example in analyzing the gross secondary structures of proteins or other polymers.[3] Recently we demonstrated that the CD spectra of *cis*-5,6-dihydroxy-1,3-cyclohexadienes are sensitive to the hydrogen bonding pattern involving the hydroxy groups, bringing about changes in population of helical diene conformers and consequently in the sign and magnitude of the diene π–π* Cotton effect.[4] Tartaric acid and its derivatives represent a class of acyclic chiral diols of great significance in stereochemistry, and rich history, marked by the discoveries of Pasteur[5] (discovery of enantiomers) and Bijvoet[6] (assignment of absolute configuration). These compounds are extensively used in syntheses[7] and for resolution of racemic amines.[8] Moreover, salts of tartaric acid exhibit piezoelectric or ferroelectrics or non-linear optical properties, with diverse applications.

It is now well established that tartaric acid and its salts prefer the extended (*trans*) conformation of the carbon chain, both in the solid state and in solution.[9] Vibrational CD (VCD) studies of dimethyl tartrate also indicate a planar conformation of the carbon chain.[10] On the other hand, surprisingly little is known about the solvent effects on (*R*,*R*)-tartaric acid and its salts, even though studies of Haynes *et al.*[11] have shown that the tartrate dianion is on the top of the list of the anions that have the highest percentage of hydrates (68%). This is in a striking contrast to the hydrogen tartrate salts in which the percentage of hydrates drops to 37%. Therefore we set out to study, both quantum mechanically and experimentally, the effect of water molecules on molecular and electronic structure of tartrate dianion in solution. Such combined computational and experimental approach has already proven effective in elucidation of molecular shapes[12] and interactions,[13] reactivity in the ground[14] and excited states,[15] as well as interpretation of electronic circular dichroism spectra.[16,17] We will demonstrate here, on the basis of CD measurements and DFT computations, that the expected C_2 symmetry of tartaric acid breaks upon formation of a dianion in water solution (Fig. 1).

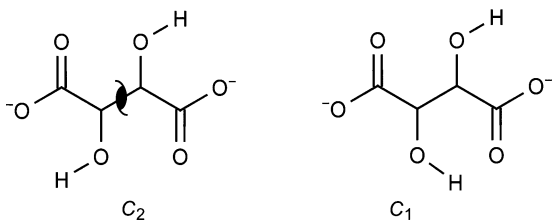

Fig. 1 Divalent (*R*,*R*)-tartrate anion of C_2 and C_1 symmetry.

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† Electronic supplementary information (ESI) available: Tables S1 to S5 and Fig. S1–S5 presenting results of quantum mechanical calculations on (*R*,*R*)-tartrate dianion: (i) isolated, interacting with (ii) one water molecule, (iii) two water molecules, (iv) three water molecules, (v) 50 water molecules. Tables S6–S9 present the results of TD-DFT calculations on the electronic excitations. See DOI: 10.1039/c0nj00072h

Methods

CD spectra were recorded with a JASCO J810 instrument in a 0.1 cm cell at room temperature, using water solutions of the tartrates at concentrations 10^{-4} mol dm^{-1}.

Computational details: Full geometry optimizations at the level of density functional theory with B3LYP/6-31 + G(d) method for molecular (*R*,*R*)-tartrate anion were performed for the following systems: (i) isolated, (ii) interacting with one, (iii) two, (iv) three water molecules. For the systems (i)–(iii) the systematic search for potential energy minima was performed. For the system (v) 50 + 108 water molecules—tartrate surrounded by 50 + 108 explicit water molecules three layer ONIOM approach was utilized,[18] where the tartrate was treated at the level of B3LYP/6-31 + G(d),[19,20] the surrounding 50 water molecules constituting medium layer at the level of HF/STO-3G,[21] while the remaining 108 water molecules were treated with universal force field (UFF).[22] The role of 108 water molecules of the outermost layer was limited to providing a mechanical embedding for the inner part (tartrate with 50 water molecules). Initial geometries for quantum mechanical calculations were obtained from molecular dynamics simulations (293 K, 1 μs) for which intermolecular interactions were accounted for with OLPS-AA force field.[23] In the molecular dynamics calculations periodic boundary conditions were imposed and TINKER program was utilized.[24] It must be mentioned that in our calculations we tested situations were (a) the tartrate anion itself and its complex with surrounding water molecules exhibited C_2 symmetry, (b) only the tartrate anion had C_2 symmetry, while the surrounding water molecules were free to move without symmetry constrains imposed, and (c) neither tartrate alone nor its complex with the water had C_2 symmetry. Finally, we undertook quantum mechanical dynamic simulations using Born–Oppenheimer molecular dynamics model for the (*R*,*R*)-tartrate interacting with five explicit water molecules. Such a model was a result of a compromise between limited computer resources and the attempt to model the key interactions of tartrate anion with water molecules. Five water molecules seemed to constitute the first solvation sphere in the molecular dynamics calculations. All DFT calculations were performed with Gaussian03[25] including UV/CD computations employing the TD-DFT (time dependent density functional theory) approach with B3LYP hybrid functional and 6-31 + G(d) basis set. The rotational strength calculations were carried out in both the velocity and the length formalisms, resulting in very similar values. The calculated CD spectra in $\Delta\varepsilon$ units were simulated by overlapping Gaussian functions according to the formula:

$$\Delta\varepsilon(E) = \frac{1}{2.297 \times 10^{-39}} \frac{1}{\sqrt{2\pi}\sigma} \sum_{i=1}^{N} \Delta E_i R_i \exp\left[-\left(\frac{E - \Delta E_i}{2\sigma}\right)^2\right] \quad (1)$$

where ΔE_i and R_i are the excitation energies and rotatory strengths for the transition i, respectively, while σ is an empirical parameter, representing the width of the band at 1/e height. On the referee's suggestion we also perfomed a check on basis set quality calculating CD spectra on the basis of the results obtained at aug-cc-pVTZ basis set.

CSD searches were done with the version 5.27 (November 2005 + one update), using ConQuest version 1.8.

Results and discussion

It is widely believed that for carboxylic acids and their anions the n-π* transition is the only one accessible in the UV and CD spectra down to 185 nm.[26] In this study we carried out CD measurements down to 185 nm for a series of water soluble (*R*,*R*)-tartaric acid mono- and divalent salts (Table 1).

Unlike (*R*,*R*)-tartaric acid,[9] its C_2 symmetry esters,[9] and *O*,*O*-dialkyl ether derivatives,[28] which show only a single negative n-π* Cotton effect at around 210–215 nm, mono- and disalts of (*R*,*R*)-tartaric acid display two negative Cotton effects, one at 210–213 nm and the other at around 193 nm (Table 1). Relative intensities of these two Cotton effects depend on the tartrate salt composition. Addition of base (NaOH) to tartaric acid solution (Fig. 2) results in gradual appearance of additional, short wavelength negative CD band.[29]

The intensity of the second CD band increases until two equivalents of the base are added. As a consequence, reverse relation of the intensities of the two CD bands is observed for mono- and disalts of (*R*,*R*)-tartaric acid. This observation is general, independent of the nature of the cation used (Table 1). No further change of the CD spectrum is observed on addition of an excess of sodium hydroxide. Likewise, acidification of (*R*,*R*)-tartaric acid solution with hydrochloric acid to pH 2 does not change the shape of the CD band. It should be noted that short wavelength Cotton effect is absent in anions of α-hydroxy monocarboxylic acids. From these data we conclude that the presence of an additional n-π* type Cotton effect at around 193 nm is due to doubly ionized tartrate species in aqueous solution. Compared to non-ionized carboxylate group the excitation energy of the carboxylate anion is increased, resulting in a blue shift of the corresponding Cotton effect.

Quantum mechanical calculations were carried out to help elucidate experimental findings. Before calculating CD spectra we assessed the effects of aqueous solution in a series of

Table 1 CD maxima of mono- and divalent salts of tartaric acids in water solution

Cation	Monovalent salt $\Delta\varepsilon$ [a]/nm	Divalent salt $\Delta\varepsilon$ [a]/nm
Li^+	−4.0 (213)	−2.4 (211)
	−1.3 (193)	−4.1 (193)
Na^+	−3.1 (211)[b]	−2.5 (210)[b]
	−2.7 (194)	−4.2 (193)
K^+	−3.4 (213)[b]	−2.1 (210)[b]
	−1.7 (199)	−3.3 (193)
Rb^+	−3.7 (212)	−2.7 (212)
	−1.8 (194)	−4.0 (193)
NH_4^+	−2.1 (213)	−2.6 (211)
	−1.3 (193)	−4.1 (193)
Na^+, K^+	—	−2.6 (211)
		−4.1 (193)
Ca^{2+}	—	−1.4 (210)
		−2.8 (193)
Mg^{2+}	—	−1.5 (210)
		−3.2 (193)

[a] $\Delta\varepsilon$ in L mol^{-1} cm^{-1}. [b] Data from ref. 27.

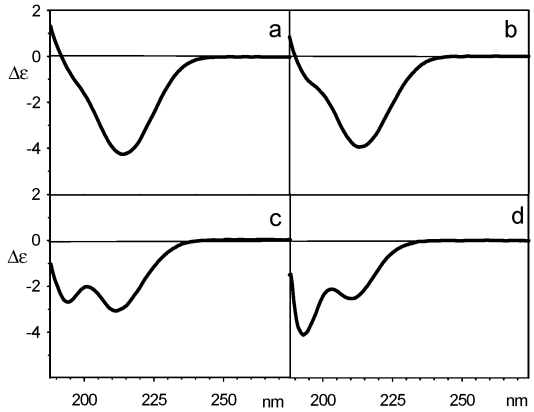

Fig. 2 CD spectra of (*R*,*R*)-tartaric acid in water solution (a), and with 0.5 (b), 1.0 (c), 2.0 (d) molar equivalents of sodium hydroxide added.

calculations with divalent (*R*,*R*)-tartrate anion surrounded by the increasing number of explicit water molecules. The isolated divalent (*R*,*R*)-tartrate anion shows preference towards the C_2 symmetric structure (see Table 2), where hydroxy groups serve as hydrogen bond donors for their closest carboxylic oxygen atoms.[30] The structure of the isolated tartrate dianion of C_1 symmetry is higher in energy by about 3.2 kcal mol^{-1} and has a tendency to converge to the C_2 symmetric structure. However, in the presence of water molecules the energetic preferences are reversed. In the case where many (50) water molecules surround tartrate dianion (see Fig. 3) the system with C_2 tartrate is energetically disfavored with respect to the C_1 tartrate by over 5 kcal mol^{-1}. In such a case ONIOM calculations indicate that the C_2 tartrate dianion itself is of 3.9 kcal mol^{-1} lower in energy, but the interactions with the surrounding water molecules are of about 9.2 kcal mol^{-1} less stabilizing than for the dianion of C_1 symmetry. It is worth mentioning that these calculations needed over 1000 optimization steps to obtain geometry convergence, and that the tartrate dianion with C_2 symmetry was converging towards the C_1 conformer when symmetry imposed restraints were released.

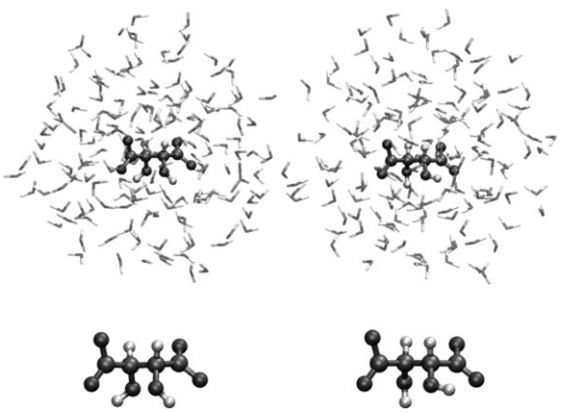

Fig. 3 Even though C_2 symmetric structure (left) of the isolated (*R*,*R*)-tartrate is energetically favored by *ca.* 4 kcal mol^{-1}, the asymmetric solvation by water molecules favors the C_1 structure of the (*R*,*R*)-tartrate (right), so that the solvated system with C_1 symmetry is favored by *ca.* 5 kcal mol^{-1}.

Table 2 Relative energies in kcal mol^{-1} for the isolated divalent (*R*,*R*)-tartarate dianion and for the dianion interacting with the water molecules (data for the lowest energy structures)

(*R*,*R*)-tartrate	C_2 symmetry	C_1 symmetry
isolated[a]	0.0	3.2
+1 water[b]	5.1	4.3
+2 water[b]	5.6	4.5
+3 water	0.8	0.0
+50/108 water[c]	5.2	0.0

[a] For the C_1 symmetry structure one HOCC torsion angle was frozen at the value obtained for the system with three water molecules. [b] Structures where water molecules were involved in interactions with the hydroxy groups. [c] 50/108 water means that in quantum mechanical calculations explicit 50 water molecules were surrounding the tartrate dianion, while additional explicit 108 water molecules constituted a mechanical embedding treated at molecular mechanics level. The system with C_2 symmetry imposed on the whole tartrate/water complex was still of higher energy.

When one or two water molecules interact with (*R*,*R*)-tartrate, the lowest energy structures are the ones where water molecules interact with negatively charged carboxylic groups only (see ESI†). However, among the structures where water molecules are involved in interactions with the hydroxy groups the C_2 symmetry tartrate dianion is disfavored by about 1 kcal mol^{-1}. It should be noted that the sum of intra and inter molecular hydrogen bonds is the same for each system studied. Similarly, in the case where three explicit water molecules are considered, the C_1 symmetry structure of the tartrate is about 1 kcal mol^{-1} more stable then the C_2 symmetric one (in this case the C_1 structure is the global minimum). The common feature of all the C_1 symmetry structures of hydrated (*R*,*R*)-tartrates is the formation of one strong(er) intramolecular hydrogen bond between the carboxyl oxygen and the α-hydroxy group. Upon formation of one such bond, the other OH group is more likely to be involved in an intermolecular hydrogen bonding.

The direct trajectory calculations were carried out at the DFT level, which was determined by compromise of computational costs and accuracy. In these calculations, BOMD (Born–Oppenheimer molecular dynamics) method implemented in the Gaussian03 package[25] was employed. This method uses a fifth-order polynomial fitted to the energy, gradient, and Hessian at each time step.[31] BOMD treats the motion of the nuclei classically with Newton's equations. Due to computational restrictions, it was possible to sample only 10 initial conditions for starting the trajectories. In all of the trajectories one hydroxy group formed intramolecular hydrogen bonding to its nearest carboxylic oxygen atom while the OH group was oriented so that it was forming hydrogen bond either with the surrounding water molecule or the first OH group. More importantly, in one of the trajectories we detected that the change of the orientation of the hydroxy group in a direction allowing both OH groups to form intramolecular hydrogen bonds with the nearest carboxylic oxygen atoms resulted after *ca.* 600 steps in the rotation of the first OH group so that it broke intramolecular hydrogen bonding with the carboxylic oxygen atom and formed hydrogen bonding interaction with the surrounding water molecule. As a

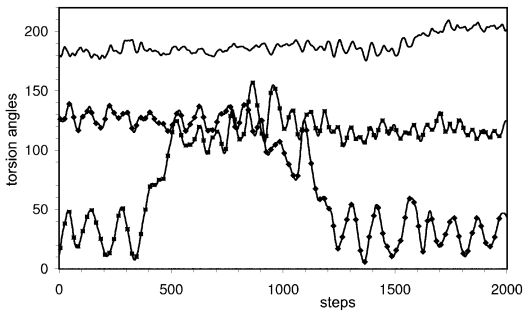

Fig. 4 Calculated changes in torsion angles in tartaric acid molecule: carbon backbone (black line), and H–O–C2–C3 (square and diamond lines).

result (*R*,*R*)-tartrate anion assumed an approximate C_2 symmetry and almost immediately hydroxy groups were rearranged to obtain C_1 symmetry. It is noteworthy that the tartrate carbon chain remained nearly flat during entire trajectory calculations. (Fig. 4)

The results of structural calculations are further augmented by crystallographic data of tartrate salts. Cambridge Structural Database contains data for 61 crystals having (*R*,*R*)-tartrates in their structures, for which the atomic coordinates are available. If multiple entries are omitted this number reduces to 52. Because of the presence of multiple asymmetric units in some of the crystal structures the number of observations increases to 65. Fig. 5 graphically presents a scattergram with the values of HOC2C3 torsion angles on the X and Y axes. Only the hits on the diagonal, that is 15.4%, correspond to the (*R*,*R*)-tartrate structures that exhibit C_2 or nearly C_2 symmetry. In particular even divalent tartrates of the first group cations which may seem to be predisposed towards having C_2 symmetry often lacks it. Only dirubidium and dicesium salts show C_2 symmetry, while the well-known dipotassium and disodium salts do not. Interestingly, the isomorphic dirubidium and dicesium tartrate crystals are anhydrous, while disodium and dipotassium tartrates are hydrated. This is an additional evidence that even in the crystals of (*R*,*R*) tartaric acid salts with simple monovalent cations the conformations of the tartrates (*i.e.* the rotamers of the hydroxy groups) are dependent on the presence of water molecules in the crystal lattice, while the conformation of the carbon chain remains planar.

Recent results on the simulated CD spectra based on quantum mechanical calculations have proven that explicit solvent molecules play key role for obtaining results comparable to the experimental measurements.[32,33] Our results also showed that aqueous solution significantly affects the structure of (*R*,*R*)-tartrate dianion. The calculated spectra of the two key structures of (*R*,*R*)-tartrate dianion in complex with three water molecules are shown in Fig. 6. As it is clearly visible the calculated CD spectra for (*R*,*R*)-tartrate dianion in the structure with C_1 symmetry correspond very well to the experimental results. In the case of the C_1 symmetry conformer, the simulated CD spectrum shows two negative peaks, at 215 and 193 nm, while for the conformer with C_2 symmetry only one negative peak is present. In the case of the C_1 symmetry structure the lower energy Cotton effect is apparently due to the overlapping two transitions which are calculated to appear

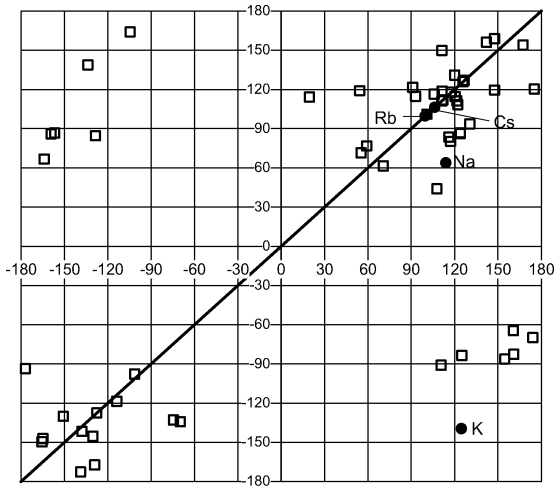

Fig. 5 Scatter plot showing the distribution of H–O–C2–C3 torsional angles in divalent chiral tartrates

at 227 nm and 206 nm. These two excitations merge together into one broader peak whose minimum is at about 216 nm. The experimentally measured long-wavelength Cotton effect appears for divalent (*R*,*R*)-tartrate salts in aqueous solution at 210–212 nm (see Table 1), which corresponds quite well to the calculated value. In the case of the short wavelength Cotton effect both calculated and experimentally measured $\Delta\varepsilon$ are negative (−4.0 at *ca.* 193 nm).

Fig. 7 presents selected molecular orbitals involved in the excitations observed as Cotton effects in the CD spectra. According to our quantum mechanical calculations the peak observed at longer wavelength (*ca.* 210 nm) is the result of two excitations in which mainly orbitals HOMO−1 and LUMO, as well as HOMO and LUMO+1 are involved. HOMO and HOMO−1 orbitals, as expected, correspond to lone electron

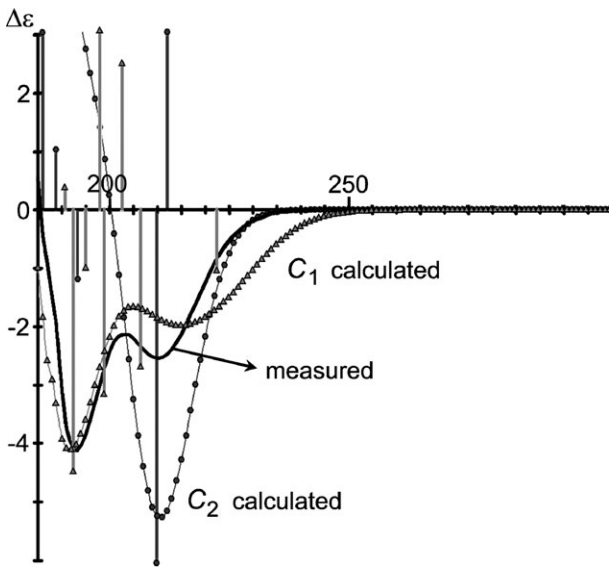

Fig. 6 Comparison of experimental CD spectra of divalent (*R*,*R*)-tartrate in aqueous solution (plain line) and calculated CD spectra of (*R*,*R*)-tartrate dianion in C_1 (triangles) and C_2 (circles) symmetry structures. Vertical bars represent rotational strengths of the contributing transitions.

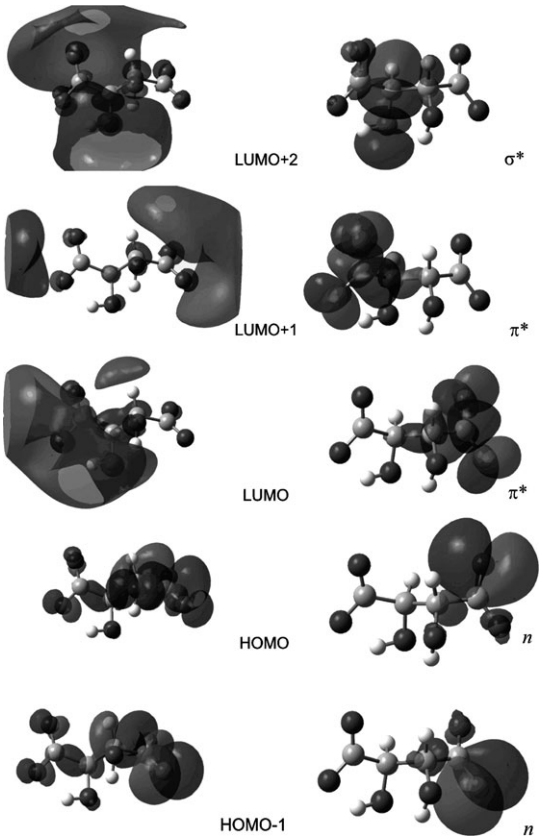

Fig. 7 Graphical representation of canonical (left) and natural localized (right) orbitals[34] involved in the transitions observed in the CD spectra of divalent (*R*,*R*)-tartrates.

pairs of carboxylic oxygen atoms. It is also clearly visible that unoccupied orbitals are highly delocalized. The inspection of population analyses for LUMO and LUMO + 1 orbitals indicate π* character. Thus, both transitions responsible for the longer wavelength Cotton effect in the CD spectra of divalent (*R*,*R*)-tartrate anion are of the n-π* character.

The results of quantum mechanical calculations also show that the short-wavelength transition (at *ca.* 193 nm) results mainly from an excitation between HOMO−1 and LUMO + 2. Our results seem to indicate that σ antibonding orbital along the βC–O(H) bond might be partially involved in the short wavelength excitation observed in the CD spectra of tartrate dianions. Thus, the shorter wavelength transition might be of n-σ* character. It is worth mentioning that n(2p)-σ*(3s) transitions were suggested as responsible for the longest-wavelength Cotton effects of chiral alcohols having no other chromophoric group.[35] Moreover, the recent study showed that π–σ* excited states play important role in photodissociation of heteroaromatic molecules occurring at the wavelengths below 230 nm.[36]

Returning now to the case of non-ionized (*R*,*R*)-tartaric acid, based on our earlier studies,[37] we selected two lowest energy structures that are stabilized by intramolecular hydrogen bonds between the hydroxy groups and their proximal carboxylic oxygen atoms (Fig. 8). One of these structures is of C_2 while the other of C_1 symmetry. The structure of C_2 symmetry has been previously used for VCD computational

Fig. 8 Lowest energy structures of isolated molecules of (*R*,*R*)-tartaric acid. The conformer of C_2 symmetry corresponds to the potential energy global minimum, while the structure of C_1 symmetry is of 1.1 kcal mol^{-1} higher energy.

studies.[38] The calculated spectra for (*R*,*R*)-tartaric acid, superimposed on the experimental one, are presented in Fig. 9. As is clearly visible, the spectrum calculated for the lowest energy structure of C_2 symmetry exhibits features almost identical with the one obtained experimentally which is in line with the earlier findings.[38] The negative peak dominating the CD spectrum of (*R*,*R*)-tartaric acid is the result of an excitation from the HOMO to the LUMO orbitals (see Fig. 10), so it has n-π* character. In the case of the C_1 symmetry structure, the calculated CD spectrum has a completely different character, showing a positive peak at 216 nm and a negative peak at about 185 nm.

Conclusions

It has recently been shown, on the basis of Raman and NMR measurements, that solvation may lead to symmetry breaking in achiral nitrate,[39] triiodide,[40] and phthalate anions.[41] We have shown here that CD spectroscopy, in combination with quantum chemical calculations, is capable to differentiate between C_2 and C_1 symmetry structures of chiral tartrate ions and that fully ionized tartrate anion in water solution breaks its C_2 symmetry favored for the isolated molecular ion. Thus tartrate anion in aqueous solution gives rise to two negative

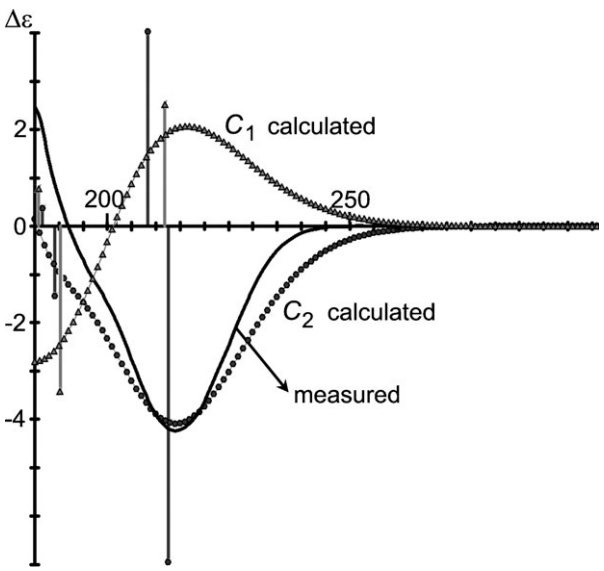

Fig. 9 Comparison of experimental CD spectra of (*R*,*R*)-tartric acid in aqueous solution (plain line) and of calculated CD spectra of (*R*,*R*)-tartaric acid in C_1 (triangles) and C_2 (circles) symmetry structures. Vertical bars represent rotational strengths of the contributing transitions.

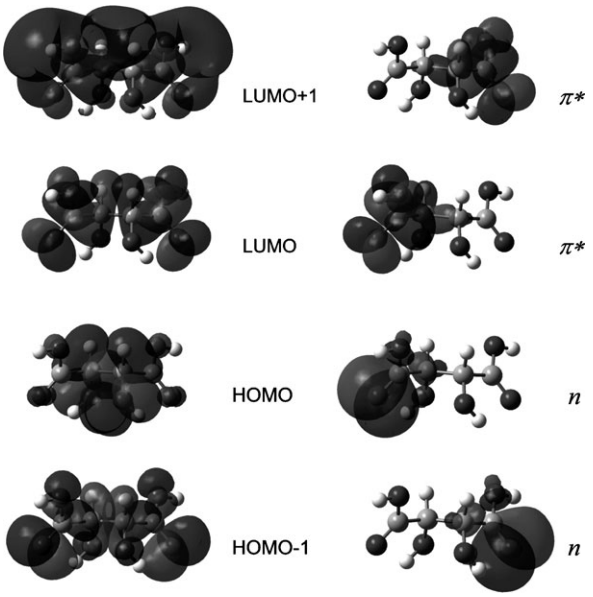

Fig. 10 Graphical representation of canonical (left) and natural localized (right) orbitals[34] involved in the transitions observed in the CD spectra of (*R*,*R*)-tartaric acid.

Cotton effects, with the shorter-wavelength band more intense. The lower energy Cotton effect is apparently due to the n-π* transition in the carboxylate ion. Orbital localization procedure seems to indicate that the higher energy Cotton effect might be partly due to the n-σ* excitation. The accepting σ* orbital corresponds to the βC–O(H) bond in which hydroxy group is involved in an intramolecular hydrogen bond with its proximal carboxylate oxygen atom.

Aqueous solvent force the divalent (*R*,*R*)-tartrate molecule to break its C_2 symmetry that is energetically favored for the isolated molecule. In C_1 symmetry dianion one of the hydroxy groups is bound to form an intramolecular hydrogen bond with the proximal carboxylic oxygen atom while the other hydroxy group is more free to rotate and more likely to be involved in intermolecular hydrogen bonds. Thus, it appears that symmetry breaking due to the interactions with surrounding water molecules is a feature likely to be observed also for other dicarboxylic anions possessing multiple hydroxy groups in their structures.

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