Gibbs energies of transfer of chiral anions across the interface water|chiral organic solvent determined with the help of three-phase electrodes

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For the first time the differences in free energies have been experimentally determined for the solvation of two enantiomeric ions in two enantiomeric solvents. Three-phase electrodes consisting of a droplet of a solution of decamethylferrocene in a chiral solvent (D- and L-2-octanol) attached to a graphite electrode and immersed in an aqueous solution containing chiral anions, allow the measurement of these data for the transfer of the enantiomeric ions across the water|chiral solvent interface. In all studied combinations the Gibbs energy to transfer an L-ion from water to the L-solvent was equal to the Gibbs energy of transfer of the D-ion from water to the D-solvent, and the same was found for the transfer of a L-ion from water to the D-solvent and for the D-ion from water to the L-solvent. In all cases, the combinations D-anion/D-solvent and L-anion/L-solvent have smaller standard Gibbs energies than the combinations D-anion/L-solvent and L-anion/D-solvent. This can be explained by less favourable interactions between an anion and a solvent molecule in the latter cases.

Introduction

The interactions between chiral molecules or ions play a key role in biochemical systems. Therefore, the quantification of such interactions is important and appropriate methods have to be developed. Here we describe experiments aimed at determining the Gibbs energies of transfer of chiral ions from the achiral environment water to a chiral solvent. Fig. 1 depicts the possibilities to transfer a D- and L-ion from an aqueous solution to a D- and L-solvent. Because of the mirror symmetry of D- and L-forms of molecules, one must expect the Gibbs energy to transfer an L-ion from water to an L-solvent to be equal to the Gibbs energy of transfer of the D-ion from water to the D-solvent. The same should hold true for the L-ion from water to the D-solvent and for the D-ion from water to the L-solvent. To assess the role of the chiral centres in the interaction, one has to determine the differences in Gibbs energies between the couples D-ion/D-solvent and D-ion/L-solvent, and between the couples L-ion/D-solvent and L-ion/L-solvent. These data could not be determined until now because of a lack of appropriate techniques. In the standard 4-electrode technique[1] to study the ion transfer at the interface of immiscible liquids it is impossible to use solvents like octanol and no reports about the use of chiral solvents have been published so far. The reason that such solvents cannot be used in 4-electrode measurements is that they need electrolytes in the aqueous and in the

$\Delta G^{\theta,w\rightarrow D-liq}_{D-ion}$

$\Delta G^{\theta,w\rightarrow D-liq}_{L-ion}$

D-ion

D-liquid

water phase

chiral organic phase

$\Delta G^{\theta,w\rightarrow L-liq}_{D-ion}$

L-ion

L-liquid

$\Delta G^{\theta,w\rightarrow L-liq}_{L-ion}$
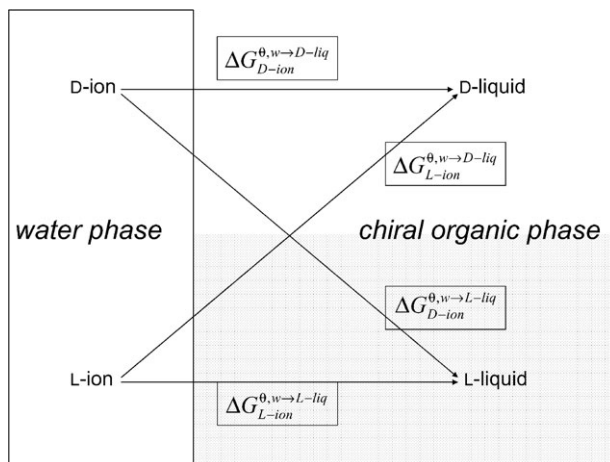
Fig. 1 Scheme of the possible processes of transfer of chiral ions across the water|chiral organic solvent interface and the associated standard Gibbs energies.

organic phase, and no electrolytes have been found for solvents like octanol allowing a polarisation of the water|organic interface. We have chosen the anions of three D- and L-amino acids and of D- and L-2-chloropropionic acid because they are simple systems typical of chiral molecules in biological systems. As solvents we have chosen D- and L-2-octanol because *n*-octanol is a standard solvent used to measure partition coefficients and quantify the lipophilicities of compounds.[2]

The experimental methodology

The determination of the differences in Gibbs energies of transfer of ionic enantiomers across water|chiral solvent interfaces is not trivial because, as it will be shown here, they are in the range of some kJ mol^{-1} only. In 2000, we introduced a new technique to determine Gibbs energies of ion transfer using a three-phase electrode and employing a 3-electrode potentiostat.[3] This approach has been used for the determination of transfer data of various anions[3–13] and cations[12,13] across the water|nitrobenzene,[3–7,11–13] water|*n*-octanol,[8,10,11] water|1,2-dichloroethane,[3] water|nitrophenyl-octyl ether,[11] water|D- and water|L-menthol interfaces.[9] The three-phase electrode experiments[14] make use of a working electrode modified by a droplet of an organic solution of a lipophilic neutral electroactive compound. The modified electrode, a counter and a reference electrode are immersed in the aqueous solution of a salt as in common 3-electrode voltammetric experiments. Provided that the neutral electroactive compound in the organic phase undergoes a 1-electron oxidation under anodic polarization, an anion transfer from water to the organic phase may accompany the oxidation. Generally, two ways of ion transfer are possible, either the transfer of the electrochemically produced cations from the organic phase to water, or the transfer of the anions from water toward the organic phase. What happens depends on the standard Gibbs energies of transfer of both pretenders. If the solvation of the electrochemically generated cations in the organic phase is stronger than the hydration of the anions present initially in the aqueous phase, then the transfer of the anions across the liquid|liquid interface will occur. In that case, one can determine the value of the standard Gibbs energy of transfer of the anions across the water|organic solvent interface.[3,11] By attaching a single droplet of a *chiral organic solvent* containing the electroactive compound decamethylferrocene to the surface of a paraffin impregnated graphite electrode, and immersing the modified electrode in an aqueous solution containing *chiral* anions, it is possible to measure the desired data. Fig. 2 depicts the situation at the three-phase electrode with an immobilized droplet of a chiral solvent. By applying an appropriate potential difference between the working and the reference electrode in such a set-up, dmfc is reversibly oxidized in a 1-electron step to dmfc^{+} in both chiral 2-octanol solvents. This electron transfer at the graphite|D- or graphite|L-2-octanol interface
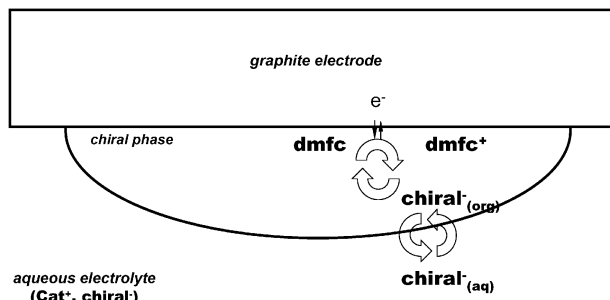
Fig. 2 Scheme of a three-phase electrode with an immobilized droplet of a chiral solvent containing decamethylferrocene. The electrode is immersed in a solution of a salt with chiral anions.

is coupled to a simultaneous transfer of chiral anions across the water|D- or water|L-2-octanol interface. The overall reaction at the three-phase electrode is as follows:

$$\text{dmfc}_{(\text{chiral 2-octanol})} + X^-_{(\text{aq})} \rightarrow \text{dmfc}^+_{(\text{chiral-2-octanol})} + X^-_{(\text{chiral-2-octanol})} + e^- \tag{I}$$
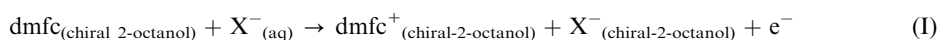
where X^- is the transferable chiral anion. If there are no kinetic constraints either for the electron or the ion transfer, the thermodynamic treatment of reaction (I) leads to the following form of the Nernst equation:[3,11]

$$E_c^{\ominus\prime} = E^{\ominus}_{\text{dmfc}^+_{(\text{org})}|\text{dmfc}_{(\text{org})}} - \frac{\Delta_W^{\text{org}} G^{\ominus}_{X^-}}{zF} - \frac{RT}{F}\ln\left(c_{X^-_{(\text{aq})}}\right) + \frac{RT}{F}\ln\left(\frac{c_{\text{dmfc}_{(\text{org})}}}{2}\right) \tag{1}$$

In eqn. (1) $E_c^{\ominus\prime}$ is the formal potential of the system portraying the coupled electron/ion transfer, $E^{\ominus}_{\text{dmfc}^+_{(\text{org})}|\text{dmfc}_{(\text{org})}}$ is the standard redox potential of dmfc/dmfc$^+$ in the organic phase (*i.e.*, D- or L-2-octanol), $\Delta_W^{\text{org}} G^{\ominus}_{X^-}$ is the standard Gibbs energy of transfer of the chiral anions X^- from water to the chiral 2-octanol, $c_{\text{dmfc}_{(\text{org})}}$ is the initial concentration of dmfc in the organic phase, $c_{X^-_{(\text{aq})}}$ is the concentration of the chiral anions in the aqueous phase, while R, T, F and z are the gas constant, absolute temperature, Faraday constant and ionic charge, respectively. Eqn. (1) allows determination of the values of $\Delta_W^{\text{org}} G^{\ominus}_{X^-}$ by measuring the formal redox potentials in the above discussed systems. As an indicator whether the entire reaction is electrochemically reversible one can use the dependence of the formal potential of the electrochemical system on the concentration of the anions in the aqueous phase. A slope of the dependence $E_c^{\ominus\prime}/\log\left(c_{X^-_{(W)}}\right)$ of about -60 mV, and stable voltammograms during consecutive cycling, are strong indications that the studied system behaves as described by reaction (I).

Experimental

Decamethylferrocene (dmfc) and 2-chloropropionic acid were products of ACRÖS, Germany; all the amino acids were products of BACHEM, Germany, while D- and L-2-octanol and all the other chemicals were purchased from Sigma–Aldrich, Germany. The square-wave and cyclic voltammetric experiments were performed with the aid of a conventional 3-electrode potentiostat (AUTOLAB PGSTAT 10, Eco-Chemie, Utrecht, Netherlands). An Ag/AgCl (sat. NaCl) served as reference electrode, while a Pt wire was the counter electrode. The working electrode was a paraffin impregnated graphite electrode (PIGE) with a radius of 2 mm. The procedure for preparing the PIGE is described elsewhere.[14,15] A droplet of 0.05 mol L^{-1} solution of dmfc dissolved in an organic solvent (D- or L-2-octanol) with a volume of 1 μL was attached to the surface of the working (PIGE) electrode and thereafter immersed in an aqueous electrolyte solution that contained one of the chiral forms of the investigated anions. The pH of the aqueous solution of the chiral amino acid anions of phenylalanine and lysine was 13 (1 mol L^{-1} NaOH), while pH of 9.80 (0.5 mol L^{-1} borax buffer) and 4.75 (1 mol L^{-1} acetate buffer) were explored for studying the transfer of chiral anions of tyrosine and 2-chloropropionate, respectively. The peak potentials of the redox reaction of dmfc
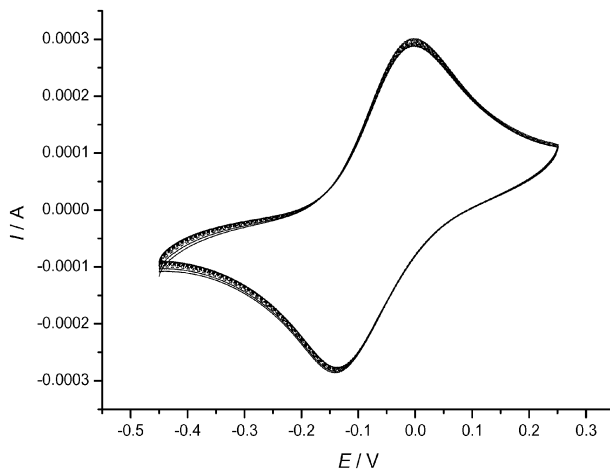
coupled to the transfer of the chiral anions were determined by square-wave voltammetry (SWV).[16] Typical parameters for square-wave voltammetric measurements were: SW frequency $f = 10$ Hz, SW amplitude $E_{sw} = 50$ mV, and scan increment $dE = 1$ mV. In all cases additional measurements were performed with cyclic voltammetry at different scan rates (from 20 mV s^{-1} to 400 mV s^{-1}) in order to check the electrochemical reversibility of the system by measuring the anodic to cathodic peak separation and the peak current ratio, while the overall stability of the measurements was checked in repeated cycles (at least 10). In square-wave voltammetry the forward to backward peak current ratio is 1.0, the peak potential separation is 8 mV and the half-width is 140 mV at a frequency of 10 Hz. Concentration dependencies have been measured for all chiral anions in order to ensure that the entire system behaves according to reaction (I) and eqn. (1). The polarimetric measurements for determining the rotation angles of the solutions of the chiral anions were performed with the aid of a Perkin–Elmer 241 Polarimeter (Na 589) in order to check the stability of the compounds in the solutions.

Results and discussion

Fig. 3 depicts square-wave voltammograms of dmfc oxidation in the respective chiral octanol coupled to the transfer of anions of D-phenylalanine from water to D-2-octanol and to L-2-octanol, and the square-wave voltammograms of dmfc oxidation in the respective chiral octanol coupled to
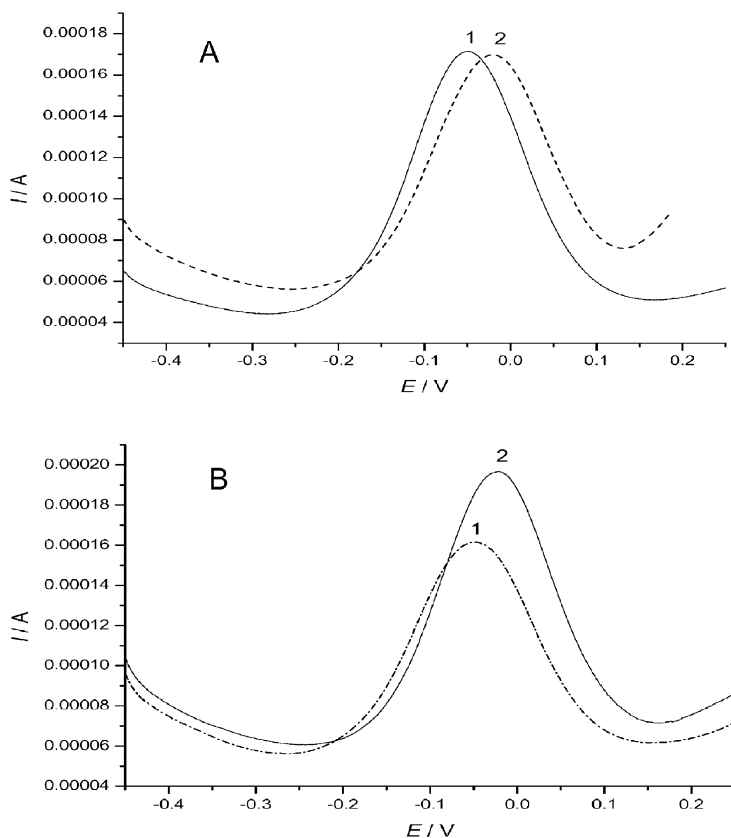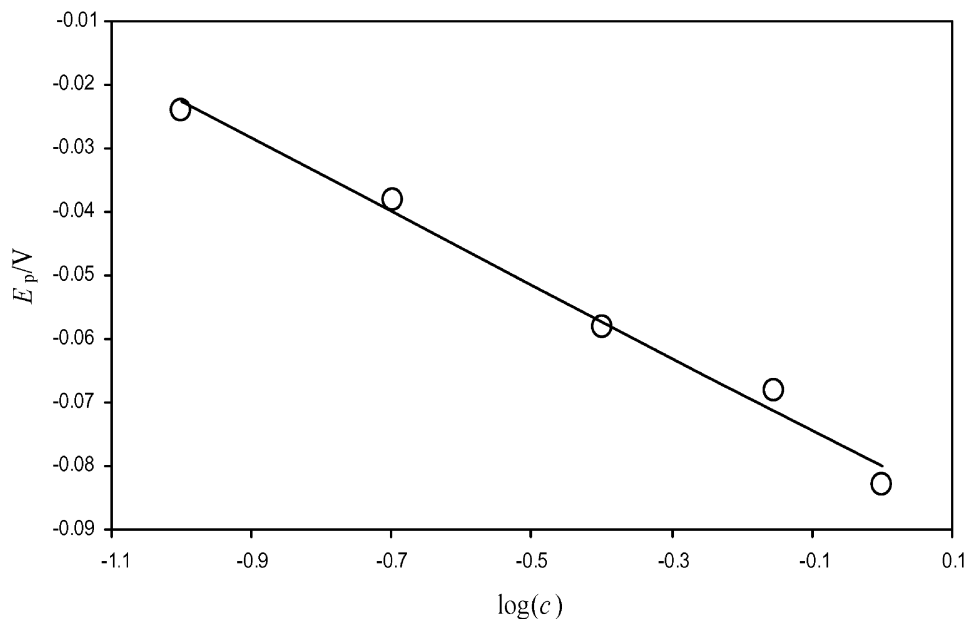

Fig. 3 (A) Square-wave voltammograms of dmfc oxidation in the respective chiral octanol coupled to the transfer of anions of D-phenylalanine from water to D-2-octanol (curve 1), and from water to L-2-octanol (curve 2). (B) Square-wave voltammograms of dmfc oxidation in the respective chiral octanol coupled to the transfer of anions of L-phenylalanine from water to L-2-octanol (curve 1) and from water to D-2-octanol (curve 2). For conditions see Experimental section.

Fig. 4 Multiple scan cyclic voltammograms (2nd to 10th cycle) of dmfc oxidation in L-2-octanol coupled to the transfer of L-2-chloropropionate anions from water to L-2-octanol. Scan rate: 200 mV s^{-1}.

the transfer of anions of L-phenylalanine from water to L-2-octanol and to D-2-octanol. Distinct differences in the peak potentials can be determined. The standard deviation of peak potentials in repeated experiments was 1–3 mV only, which is equivalent to Gibbs energies of transfer of 0.1 to 0.3 kJ mol^{-1}. The slight mismatch of peak currents is due to small deviations in the droplet size in each experiment. These differences are without effect on the peak potentials. Fig. 4 shows the 2nd to 10th cycle of cyclic voltammograms of dmfc oxidation in L-2-octanol coupled to the transfer of L-2-chloropropionate anions from water to L-2-octanol. These curves illustrate the chemical reversibility of the system. The same stability was observed in all other cases of anion transfer reported in this paper. Fig. 5 depicts a typical plot of peak potentials of square-wave voltammograms of dmfc oxidation in L-2-octanol coupled to the transfer of L-2-chloropropionate anions from water to L-2-octanol *versus* concentration of L-2-chloropropionate in the aqueous phase. Clearly, the system follows the concentration dependence described with eqn. (1). From the peak potentials of the square-wave voltammograms the standard Gibbs energies of ion transfer have been calculated according to that equation. For this purpose the following standard potential of dmfc in the two chiral octanols was used: −0.317 V *vs* Ag/AgCl. The estimated standard Gibbs energies of transfer from water to D- or L-2-octanol of all chiral monoanionic forms considered in this study are given in Table 1. As can be seen from the data in Table 1, within the experimental error of peak potential measurements, in all cases the $\Delta_W^{org} G_{X^-}^{\ominus}$ values for the transfer of the D-ion to D-2-octanol are the same as the $\Delta_W^{org} G_{X^-}^{\ominus}$ values of transfer of the L-ion to L-2-octanol. The same holds true for the transfer of D-ions to L-2-octanol and for L-ions to D-2-octanol (*cf*. Fig. 6). This kind of symmetry of the results was expected; however, initial experiments gave very different results. It took some time to detect that these, obviously wrong, results, were due to racemization reactions. Racemization could be detected in these cases by polarimetric measurements. Racemization and epimerization of amino acids are very slow processes at room temperature or below, and at around pH 7. Under these conditions amino acids have half life times in the ka (kilo years) range, which is utilized for age determinations of foraminifers, shells, bones, *etc*.[17] The racemization is strongly dependent on pH, and it is assumed that the racemization occurs *via* abstraction of the α-proton by OH$^-$. The rate constant for the proton abstraction is supposed to increase in the raw cationic, zwitterionic, anionic form, because of increasing electron-withdrawing and resonance stabilizing capacities of the substituents attached to the α-carbon atom.[18] Rather rapid racemizations have been observed in the case of both enantiomers of the amino acid leucine. Significant changes in the rotation angle were observed within the first few hours after dissolving an enantiomer of leucine in 1 M NaOH. The racemization processes of the other studied amino acids were much slower, *i.e.*, changes in the rotation angles were observable only after a period of one day or more. In order to prevent the undesirable racemization, the electrochemical measurements were performed immediately after
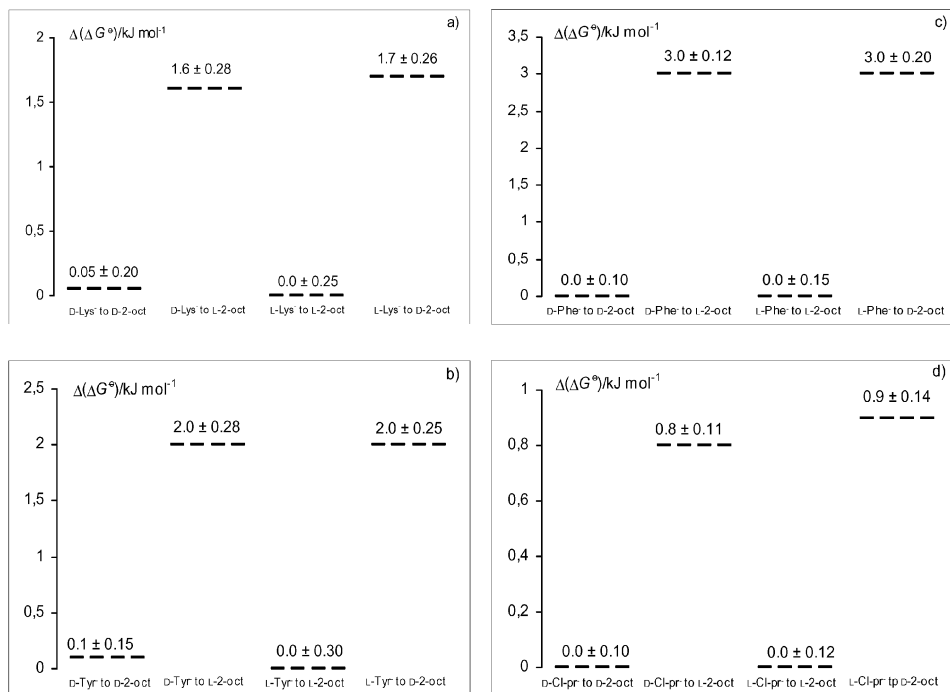
Fig. 5 Peak potentials of square-wave voltammograms of dmfc oxidation in L-2-octanol coupled to the transfer of L-2-chloropropionate from water to L-2-octanol *versus* concentration of L-2-chloropropionate in the aqueous phase.

preparing the fresh solutions of the amino acids in basic media. For the applicability of the three-phase electrode measurements it is of utmost importance to perform parallel experiments to control the stability of the chiral ions towards racemization. Especially in strongly alkaline solutions there is the danger of rather rapid racemization reactions. In our previous communication on the transfer of the anions of D- and L-tryptophan from water to D- and L-menthol an asymmetry of Gibbs transfer energies was observed.[9] In the course of the experiments reported here, we have made the observation that a precipitate forms at the liquid|liquid interface with these solvents. It is rather difficult to detect these precipitates in the experiments with the three-phase microdroplet modified electrodes. However, by simple shaking of the organic phase together with the aqueous solution, it was obvious that a precipitation of tryptophan occurs at the water|D- and water|L-menthol interfaces. A similar precipitation of tryptophan was observed at the water|D-2-octanol and water|L-2-octanol interfaces. Therefore no reliable data could be obtained for the anion of tryptophan.

Table 1 Standard Gibbs energies of transfer of the chiral anions from water to D-2-octanol ($\Delta_W^{D\text{-}2\text{-}oct}G_{X^-}^{\ominus}$), from water to L-2-octanol ($\Delta_w^{L\text{-}2\text{-}oct}G_{X^-}^{\ominus}$), and from D-2-octanol to L-2-octanol ($\Delta_{D\text{-}2\text{-}oct}^{L\text{-}2\text{-}oct}G_{X^-}^{\ominus}$) The values are estimated by using the value of the standard redox potential of dmfc/dmfc$^+$ in *n*-octanol from ref. 8

Monoanion of:	$\Delta_W^{D\text{-}2\text{-}oct}G_{X^-}^{\ominus}$/kJ mol^{-1}	$\Delta_w^{L\text{-}2\text{-}oct}G_{X^-}^{\ominus}$/kJ mol^{-1}	$\Delta_{D\text{-}2\text{-}oct}^{L\text{-}2\text{-}oct}G_{X^-}^{\ominus}$/kJ mol^{-1}
D-Lysine	30.80	32.45	1.65
L-Lysine	32.40	30.70	−1.70
D-Tyrosine	27.80	29.90	2.10
L-Tyrosine	29.80	27.70	−2.10
D-Phenylalanine	25.80	28.90	3.10
L-Phenylalanine	28.95	25.85	−3.10
D-2-Cl-propionic acid	22.60	23.40	0.80
L-2-Cl-propionic acid	23.50	22.65	−0.85

Fig. 6 Diagrams showing the differences in the standard Gibbs energies of transfer of the studied chiral anions. The symbols Lys$^-$, Phe$^-$, Tyr$^-$, and Cl-propionate$^-$ denote the monoanionic forms of lysine, phenylalanine, tyrosine and 2-chloropropionic acid, respectively, while the symbol 2-oct stands for 2-octanol.

Conclusions

To the best of our knowledge this is the first report of the differences of Gibbs energies of solvation of chiral ions in chiral solvents. There are no calorimetric studies of these systems, probably because of the low solubilities of salts in chiral solvents like D- and L-2-octanol. Given that the differences in Gibbs energies are rather small this will make it even more difficult to obtain similar data by calorimetry.

The differences in standard Gibbs energies of ion transfer suggest that the anions probably form diastereomeric complexes with one solvent molecule. If the anions where to be housed in a sphere of solvent molecules without such kind of specific interaction, *i.e.*, if the anions would see only a randomized solvation sphere, the differences would be negligible. Fig. 7 shows intuitively drawn complexes between D- and L-2-octanol and D- and L-anions of amino acids. Obviously, one has to assume one strong hydrogen bond between the OH-group of octanol and the COO$^-$-group of the amino acid anion. The hexyl group of octanol is itself rather large and at room temperature it will need even more space due to its rotation, so that the NH$_2$ group is more repelled in the D/L and L/D than in the D/D and L/L combinations, making the latter two arrangements energetically slightly more favourable. The experimentally determined energetic differences between the D/D and L/L pairs on one side and the D/L and L/D on the other side are in the range of typical van-der-Waals' forces. The steric differences may be responsible for the different van-der-Waals' interactions between the anions and solvent molecules.

Future efforts must be focussed on molecular dynamic calculations of interaction energies of chiral anions with chiral solvent molecules. It is hoped that the experimental data reported here may serve for comparison with theoretical data.

Stereoselective interactions between chiral molecules have tremendous importance both for analytical and synthetic separations. Chiral phases are used in chromatography to separate enantiomers,[19] and chiral reagents are used in electrophoretic separations.[20] However, the
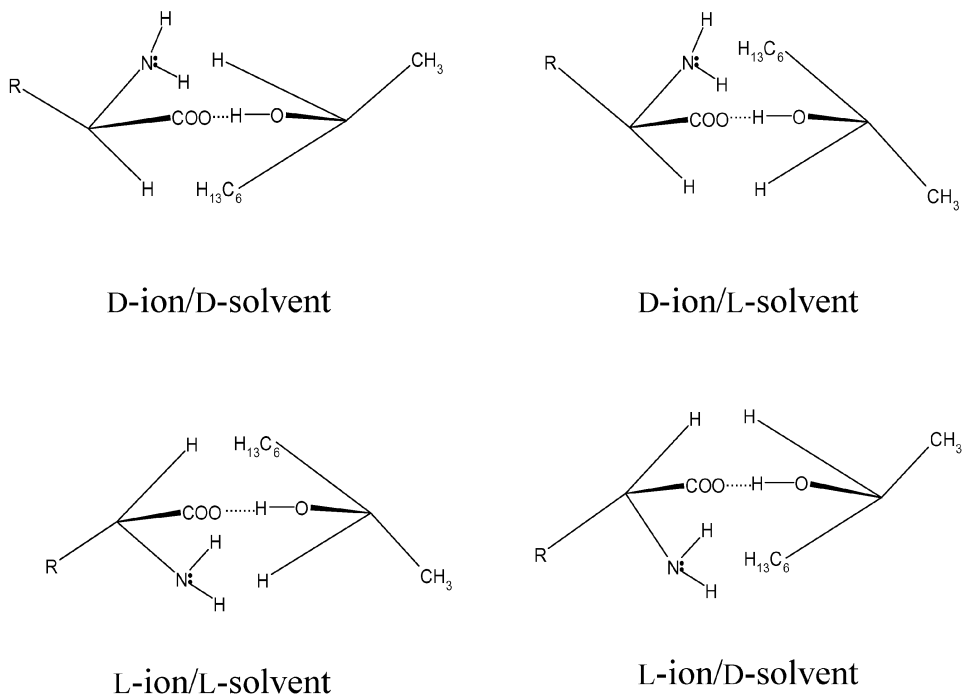
Fig. 7 Interactions of chiral anions of amino acids with the chiral solvents D- and L-2-octanol.

conditions for both techniques are much more complicated than for simple solvation experiments. Thus it is believed that the data produced in transfer experiments using three-phase electrodes may find an easier theoretical explanation than data derived from interactions with chirally derivatized solid surfaces, or data from electrophoretic measurements, *i.e.*, with the involvement of a strong electric field and under dynamic conditions.

Acknowledgements

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