Circular Dichroism as a Probe of Chiral Solvent Structure around Chiral Molecules

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Molecular dynamics simulations have been used to study solvent effects on the circular dichroism (CD) of the n–π* carbonyl transition in camphor and 9,10-dibromocamphor. It is found that achiral solvents may contribute as much as 10–20% of the CD intensity; this arises because the camphors induce solvation structure that is chiral even when the solvent molecules themselves are achiral. The magnitude of the solvent effect is found to depend strongly upon the nature of both the solute and the solvent. This has implications for enhancing the enantiomeric selectivity of chiral syntheses.

One of the current driving forces in synthetic organic chemistry is the desire to make enantiomerically pure molecules, preferably by asymmetric synthetic routes. Although such chemistry invariably takes place in solution, and different solvents are known to affect reaction rates and mechanisms, little or no attention has been given to the effect of the solvent on the enantiomeric purity of the product. Conversely, there has been considerable speculation that the lifetimes of drugs *in vivo* are extended if the water about the molecule is structured so that it looks like bulk water.[1,2] Undoubtedly one of the major reasons for the lack of any substantial information about the significance of solvent structure is the difficulty of probing that structure. In the course of studying violations of the well-known octant rule for the circular dichroism (CD) of carbonyl compounds,[3] we found that the observed CD was sensitive to solvent structure. For the case of β-axial adamantanones,[4] the β substituent forces an asymmetry in the distribution of solvent molecules about the carbonyl chromophore by creating a 'solvent hole' from which solvent molecules are excluded. It was postulated that the asymmetric solvent distribution makes a net contribution to the observed CD. This suggested that CD spectroscopy coupled with molecular dynamics simulations and calculations of the solvent contribution to the CD could be used as a combined experimental and theoretical probe of solvent structure about molecules.

The work reported here is the first stage in such a study, and uses computer simulations to investigate the distribution of achiral solvent molecules about a chiral solute molecule. The purpose of these simulations is to establish that the solvation shell is chiral, even though the solvent molecules themselves are achiral, and to demonstrate that this chiral solvation shell does have an observable effect on the CD spectrum. CD spectroscopy can then be used as an experimental probe to quantify the chirality of the solvent distribution. Since the mechanisms giving rise to the CD of the n–π* transition of the carbonyl chromophore are well understood, we have chosen to use the CD of this transition to investigate the solvent chirality. In this paper we present computer simulations of the solvent contribution to the CD of (+)-camphor and 9,10-dibromo-(+)-camphor when dissolved in simple (*i.e.* spherical) solvents; to a first approximation, therefore, the results of this work apply to solvents such as methane and carbon tetrachloride. One advantage of this simplified model of the solvent is that, being spherical, the solvent molecules cannot make an intrinsic contribution to the carbonyl CD; thus any solvent contribution to the CD must arise from the way the solvent is distributed around the solute. These systems have also been simulated at different temperatures as experiments[4] indicate different temperature dependence for the CD spectrum in different solvents. Work is in progress using more realistic solvent molecules in the simulations and comparing these with temperature-dependent measurements of the CD using the same solvents and solutes.

A brief summary of the theory of the CD of the n–π* transition of carbonyls is given in the next section. This is followed by the details of the simulations, and of the calculations of the solvent contribution to the CD.

CD of the n–π* *Transition of Carbonyls*

The octant rule of Moffit *et al.*[5] for the CD of the n–π* transition of carbonyls has proved to be the most successful of all empirical CD sector rules. In its original form Moffit's octant rule stated that component parts of a molecule contributed to the total CD according to the product $-xyz$, where (x,y,z) is a position vector in the right-handed coordinate system defined with the z-axis along the C=O bond, the y axis in the carbonyl plane and the origin centred on the nodal surface of the orbitals involved in the n–π* transition (*cf.* Fig. 1). The xz and yz reflection planes are thus defined by the approximate C_{2v} symmetry of the carbonyl part of the system, and the third plane by the orbitals involved in the transition. A perturbation theory analysis of the CD induced into the n–π* transition of an achiral carbonyl chromophore by a chiral environment enabled Hohn and Weigang[6] to give a theoretical justification of the octant rule. This was the first use of what we shall call the Independent Systems/Perturbation approach (see *e.g.* refs. 3, 7 and 8 for further details). An alternative formalism, which is somewhat less suited to the symmetry analysis approach of ref. 7, is provided by the work of Buckingham and Stiles.[9] Our previous work on carbonyls showed that unless there were strongly polar or charged groups the octant rule was the dominant contribution to the CD. Thus, in this work we expect eqn. (1) to account for the CD of the entire system (*i.e.* molecule + solvent). The assumptions leading to the derivation of eqn. (1) have been discussed previously in some detail[3] and so the equation is simply quoted as shown

$$R_{\mathrm{n}-\pi^*} = \mathrm{Im}\left\{\sum_{\mathrm{c}} r_{\mathrm{c}}^{-4} 12 K^{\mathrm{pol}}_{\mathrm{mom}}[5\alpha_{zz}xyz + \alpha_{zx}y(5x^2 - 1) + \alpha_{zy}x(5y^2 - 1)]\right\} \quad (1)$$

where the summation is over the chromophores {C} of the system (see below), excluding the carbonyl itself. Im denotes the imaginary part of the expression; $K^{\mathrm{pol}}_{\mathrm{mom}}$ is a parameter that depends only on the carbonyl chromophore, and so we shall take it as a transferable constant; α_{zu}, $u = (x,y,z)$, is the *zu*-

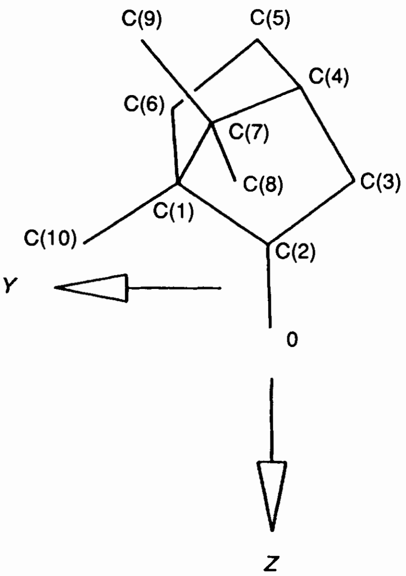

Fig. 1 The coordinate system and numbering of the carbons used within this work for camphor and its derivatives. The x axis points up from the page, so that the bridging carbon is in the $+x$ hemisphere.

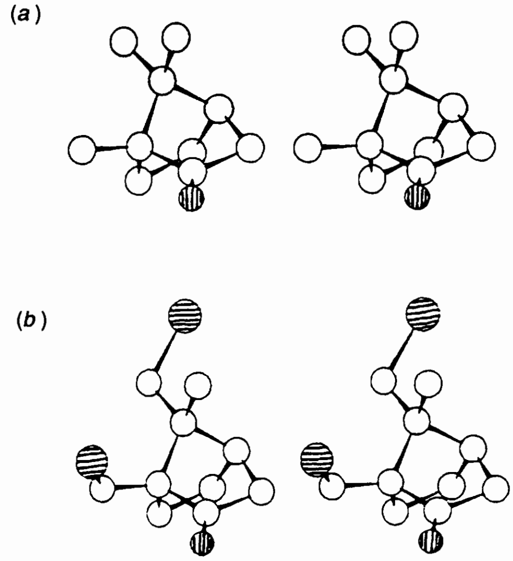

Fig. 2 Stereoscopic views of the conformations of (*a*) (+)-camphor and (*b*) 9,10-dibromo-(+)-camphor used in this work. Vertical lines indicate the oxygen atom, while horizontal lines indicate the bromine atoms.

component of the polarizability of C; r_c is the distance between the C origin and that of the carbonyl; and (x,y,z) is the unit vector along the line from the origin of the carbonyl to that of C in the coordinate system as defined by Fig. 1. The most problematic part of implementing eqn. (1) is defining the polarizability of the non-exchanging chromophoric units of the system. However, since the molecules studied here are saturated, except for the carbonyl group, either bond polarizabilities or polarizabilities of groups such as CH_2 units[10,11] may be used. This will be discussed further in the Results section.

Simulation Method

Algorithm.—Constant temperature/constant pressure molecular dynamics simulations (MD) were used to study the behaviour of camphor and 9,10-dibromocamphor in simple solvents; both solutes were treated as rigid molecules. Equations of motion were integrated using the leap-frog quaternion algorithm for the solute, and the Verlet algorithm for the solvent, while constant temperature and pressure were maintained by kinetic energy and volume rescaling, respectively.[12] Interactions were truncated when the site–site separation exceeded half the length of the simulation box, and the usual isotropic estimates of the long-range contributions to the pressure and energy were used to correct for this.[12] A time step of 5 fs was used throughout, which kept energy fluctuations to about 0.01% of NkT in constant energy/constant volume simulations. Thermodynamic properties of the pure liquid calculated from this program were in complete agreement with published values for a Lennard–Jones fluid.[13]

The simulations were started from a face-centred cubic array of 108 solvent molecules, with periodic boundary conditions being used to mimic the infinite system. A single solute molecule was then placed at the centre of the simulation box, and those solvent molecules that overlapped with it were removed. Typically, this left about 100 solvent molecules, the actual number depending on the conditions being used. The system was found to have equilibrated after 10 ps whereupon a further 400 or 800 ps was simulated for analysis; such long analysis times were needed because the calculated CD strength was very noisy. A 400 ps simulation took about 3 h on an AMDAHL 5870 computer.

Average thermodynamic and structural properties were calculated by analysing every tenth configuration, and standard deviations were estimated by comparing successive 50 ps segments of the trajectories.

Potentials.—All methyl and methylene groups in the solute molecules were modelled using the united atom approximation, which treats such groups as single spherical sites. The sp^2 carbon, the O and any Br atoms were modelled explicitly. This resulted in an 11-site model for camphor, and a 13-site model for dibromocamphor. A single spherical site was used for the solvent molecules. All site–site interactions were described by Lennard–Jones potentials with most parameters being taken either from the work of Jorgensen *et al.*[14] or from the CHARMm force field. The only exception was CCl_4, for which we modified existing gas phase parameters to reproduce the density and enthalpy of the liquid at 298 K and 1 atm. Potential parameters are listed in Table 1.

The molecular mechanics program CHEMMIN was used to find the stable conformers of both camphor and dibromocamphor, and these geometries were then used to define the rigid solute molecule in the simulations. For camphor this gave a unique conformation. However, for dibromocamphor there were several different conformations with nearly the same energy, differing only in the orientation of the CH_2Br groups. Since this paper is meant to illustrate how chiral solvent structure can be induced, we have chosen just one of the conformations as a representative example. The conformations used for camphor and 9,10-dibromocamphor are depicted in Fig. 2.

Systems and Conditions.—The combination of two solutes with two different solvents gives four distinct combinations to be examined. In addition, since we were interested in seeing whether it was possible to observe a significant temperature shift in the CD, we have simulated each of these systems at reduced temperatures ($T^* = kT/\varepsilon$, where k is Boltzmann's constant and ε is the Lennard–Jones energy parameter) of 0.7 and 0.9; these correspond to temperatures of 104 K and 133 K for the CH_4-like system, and 385 K and 495 K for the CCl_4-like system. In all cases the reduced pressure ($P^* = P\sigma^3/\varepsilon$) was kept to 0.2 (about 7 Mpa for CH_4 and 10 MPa for CCl_4); pressures of this magnitude are needed to ensure that volume fluctuations

Table 1 Lennard–Jones parameters for atoms and groups

	Solutes					Solvents	
Parameter	C (sp^3)	C (sp^2)	H	O	Br	CH_4	CCl_4
ε/k/K	81.0	81.0	0.0	80.0	161.0	148.0	550.0
σ/Å	3.91	3.91	—	2.85	3.88	3.73	5.25

during a simulation do not take the system into a two-phase region, but are still small enough to ensure that the liquid properties are very similar to those at atmospheric pressure.

Results

Solvent-induced CD.—The spherical solvent molecules used in this work lead to substantial simplifications in eqn. (1). Given the single-site model for the solvent, a chromophore is most sensibly identified with the solvent molecule itself and, being a symmetric top, the *zx* and *zy* components of its polarizability must vanish. Each chromophore is therefore characterized by the same isotropic polarizability α, and eqn. (1) simplifies to eqn. (2). Thus the magnitude of the solvent-induced CD

$$R_{\text{solvent}} = 12K^{\text{pol}}_{\text{mom}}\alpha\left(\sum_{c}\frac{xyz}{r^4}\right) \tag{2}$$

depends on a property of the carbonyl chromophore, $K^{\text{pol}}_{\text{mom}}$, a property of the solvent molecule, α, and a geometric factor that describes the solvent structure. This last term is just a projection of the solvent pair distribution about the carbonyl group $g(\mathbf{r})$ [eqn. (3)] and as such it is readily calculated from the simulations; values for G_{solvent} are listed in Table 2.

$$\sum_{c}\frac{xyz}{r^4} = \int\frac{xyz}{r^4}\,g(\mathbf{r})\,\mathrm{d}\mathbf{r} = G_{\text{solvent}} \tag{3}$$

The choice of α is not obvious for the model solvents considered here. However we expect α to be closely correlated with the choice of σ and ε. This is because dispersion forces vary as α^2/r^6, and so the polarizability for Lennard–Jones molecules may be expected to scale as $\varepsilon^{\frac{1}{2}}\sigma^3$. Since $K^{\text{pol}}_{\text{mom}}$ is the same for all carbonyl groups, it is convenient to define the product of $\varepsilon^{\frac{1}{2}}\sigma^3$ with G_{solvent} as a reduced solvent-induced CD intensity, R^*, as in eqn. (4). R^* is a direct measure of the solvent's role in inducing CD. It should therefore provide a convenient means of quantifying the variations in solvent-induced CD that occur between different solvents and for different thermodynamic conditions. Values for R^* are listed in Table 2.

$$\begin{aligned} R^* &= \sqrt{\varepsilon}\,\sigma^3 G_{\text{solvent}} \\ &\propto \frac{R_{\text{solvent}}}{12K^{\text{pol}}_{\text{mom}}} \end{aligned} \tag{4}$$

The first thing to note from Table 2 is that the solvent-induced CD is (statistically) non-vanishing; although there are relatively large standard deviations associated with the values given in Table 2, *t*-tests indicate that they are all significantly greater than zero. For an achiral solvent distribution the product *xyz* must vanish, and so the fact that it does not vanish provides clear evidence that the camphors are inducing a chiral distribution in the solvent.

However, to say that the values are statistically significant does not necessarily mean that they will be experimentally significant, and so we have also estimated the intramolecular contribution to the carbonyl CD using the same method as for the solvent: based on the geometry and Lennard–Jones parameters used for the camphors. These intrinsic CD values are the intensity one would expect to see in a gas phase experiment, and are listed in Table 2 as $R^*_{\text{intrinsic}}$. Comparison of R^* and $R^*_{\text{intrinsic}}$ reveals that the solvent effect is substantial, amounting to 5–10% of the intrinsic intensity for camphor, and 10–20% for dibromocamphor. One might expect that by choosing more complex solvents it should be possible to enhance the structuring of the solvent around the solute, and maybe even to control this solvent contribution.

The trends revealed in Table 2 are readily interpreted in terms of packing effects in the solvent, and confirm earlier conjectures.[3] With the smaller solvent, solvent molecules will approach more closely to the carbonyl group, and will pack more tightly around it. As a consequence, the smaller solvent gives rise to a larger r^{-4} factor, and hence G_{solvent} is significantly larger in CH_4 than in CCl_4 solvents. On the other hand, the CCl_4 has a much larger polarizability, and this suffices to make the net solvent-induced CD larger in CCl_4 than in CH_4.

The sign of the solvent-induced CD can also be understood in terms of solvent structure around the CH_3 and CH_2Br side groups. These groups lead to inefficient packing of the solvent molecules, and so create a deficiency of solvent in the octant containing them. This may also be viewed as a surplus of solvent in the adjacent octants, and so it will be these neighbouring octants that will dominate the solvent-induced CD. The two bridging side chains are unlikely to have much effect in camphor and dibromocamphor, since they lie close to the carbonyl *zx* reflection plane, and are fairly distant from the CO group. The remaining side chain lies in a negative octant (*i.e.* the product *xyz* is negative), and so should induce a positive solvent contribution arising from solvent molecules in the adjacent octants, as observed.

These considerations are quite general. If a substituent on a molecule does generate an asymmetry in the solvent packing, then it will induce a solvent contribution to the CD that opposes its own intrinsic contribution. In this context, therefore, it is interesting to note that for the camphors, the net effect of the solvent actually reinforces the intrinsic CD. This arises because the intrinsic CD of these camphors is dominated by the contribution from the two methylene groups that are β to the CO group. However, these groups are well shielded from the solvent by the bridging and side methyl groups, and so have little effect on the solvent structure. Thus different chiral centres are responsible for the intrinsic and solvent-induced CD. This raises the interesting possibility that by using different solvents it may be possible either to amplify or nullify the chirality of a specific centre, and thereby to 'tune in' to specific chiral centres.

Temperature Dependence.—The intrinsic CD is related to the electronic properties of a stable molecule, and as such should be essentially independent of temperature. On the other hand, solvent structure can be quite sensitive to changes in temperature, and so one might expect the solvent contribution to the CD to change with temperature. There is some experimental evidence for this,[4] and our own preliminary experimental measurements on camphor derivatives in various solvents

Table 2 Contributions to the carbonyl n–π* CD[a]

	T^{*b}	Camphor		Dibromocamphor	
		CH_4	CCl_4	CH_4	CCl_4
$G_{\text{solvent}}/10^4$ Å^4	0.7	1.22 ± 0.15	0.359 ± 0.060	1.040 ± 0.128	0.321 ± 0.044
	0.9	1.25 ± 0.20	0.340 ± 0.080	0.865 ± 0.149	0.137 ± 0.058
R^*	0.7	0.153 ± 0.019	0.244 ± 0.041	0.131 ± 0.016	0.218 ± 0.030
	0.9	0.158 ± 0.025	0.231 ± 0.054	0.109 ± 0.019	0.093 ± 0.040
$R^*_{\text{intrinsic}}$		2.242		0.984	

[a] Uncertainties quoted are the standard deviation. [b] The temperature is related to the reduced temperature, T^*, according to $T = T^*\varepsilon/k$, where ε is given in Table 1 and k is Boltzmann's constant.

indicate that the CD intensity varies by about 2–3% of the total intensity over a temperature range of about 40 °C.

The results in Table 2 do give some support for a temperature dependence in the solvent-induced CD, but it is clear that accurate calculations from MD simulations will be very difficult. For our systems the solvent provides 5–20% of the total CD intensity. Thus, a variation of 2–3% in the total intensity corresponds to changes of about 20% in the solvent contribution. Unfortunately, this is about the level of the statistical uncertainty in our calculations, despite using reasonably lengthy simulations. We have, however, found one system in which the temperature variation is large enough to be seen clearly: a *t*-test indicates that the change for dibromocamphor in CCl_4 is significant at the 5% level. We conclude that a combined experimental/simulation study could be useful in understanding the temperature variation, but that the solute and solvent would have to be carefully chosen to maximize the extent of the variation.

Chiral Solvent Structure.—It is worth considering the structure of the solvent more closely in order to identify the mechanisms by which its chirality is manifested. The standard method of examining solvent structure is in terms of radial distribution functions (RDF's) such as the radial distribution of solvent about the centre of the CO bond, g_{CO}. The difficulty with such an approach is that it involves a spherical average of the solvent density, and so is not designed to pick up the angular variations that give rise to the chiral properties. Another approach that has proved useful for other systems is to consider the full pair distribution, $g(r,\Omega)$, where Ω denotes the relative orientation of the solute and solvent molecules, and to decompose this into its *r*-dependent spherical harmonic contributions;[15] however the chiral distributions will then be of high order, and so are difficult to calculate accurately: for example with the CO-solvent distribution, the only term of less than fourth order to have a chiral contribution is g_{221}.

We have therefore developed a method of analysis designed to probe the asymmetry of the solvent distribution by using appropriate point-symmetry projections. As the average distribution of solvent about a solute molecule adopts the symmetry of the solute,[16] it is possible to calculate symmetry adapted RDFs from $g_{CO}(r,\Omega)$. The unperturbed CO chromophore has C_{2v} symmetry, and so we have adopted the representations of the C_{2v} point group as a basis for calculating this decomposition of $g_{CO}(r,\Omega)$.† Two of these symmetry-adapted RDFs are particularly relevant for this work: the totally symmetric A_1 component of the distribution, g_{A1}, is just the normal RDF, g_{CO}, and measures the local density of the solvent around the CO group; the A_2 component, g_{A2}, indicates the extent to which the symmetry of the two reflection planes has been broken and thus quantifies the chiral part of the distribution. Note that since eqn. (1) predicts an octant rule for the CD but the C_{2v} point group only distinguished between *xy* quadrants, we have found it convenient to analyse solvent in the positive and negative *z* hemispheres separately (*n.b.* positive *z* points away from the camphor along the CO bond—see Fig. 1); these will be denoted by an additional subscript, *e.g.* g_{A2+} is the contribution to g_{A2} arising from solvent in the positive *z* hemisphere. Symmetry-adapted distribution functions for the various solute/solvent systems are depicted in Fig. 3.

To clarify the relationship between the solvent structure and induced CD we have also calculated the radial dependence of the induced CD (RCD); this is achieved by averaging the product xyz/r^{-4} over all the solvent molecules found in a thin shell of radius *r* that is centred on the CO bond, and gives a measure of how the different regions of the solvent contribute to the induced CD. As with the solvent distribution functions, it is convenient to analyse the positive and negative *z* hemispheres separately; these functions are also depicted in Fig. 3.

There are several points to note for Fig. 3. Firstly, it is apparent that there is a strong correlation between g_{A2} and the RCD. For $z > 0$ this is a positive correlation, with the position and sign of the peaks coinciding, while for $z < 0$ it is a negative correlation. As discussed above, the positive and negative correlations arise from the superposition of an octant rule for the CD on the C_{2v} symmetry.

From the symmetry adapted RDFs it is apparent that most of the chiral solvent-structure appears in the $z < 0$ region. This is not surprising, since the camphor molecule is in the negative *z* hemisphere (see Fig. 1), and so the first solvation shell in this region is strongly affected by the geometry of the camphor. However, there is also significant structure in the positive *z* hemisphere. In methane, this extends over more than 6 Å from the centre of the carbonyl bond, and so probably indicates that there is some secondary solvation structure. It is worth noting that for any substitution reactions involving camphors, the reactants would have to penetrate through these solvation shells. Thus a well defined solvent structure is likely to predispose the substituents to approach from directions in which the solvent is more mobile, and may therefore enhance the selectivity of the reaction; for chiral solvent-distributions this would affect the enantiomeric selectivity.

Much of the behaviour of the curves depicted in Fig. 3 can again be interpreted in terms of solvent packing around the solute. Most of the camphor and dibromocamphor lies in the region of negative *z* (the only exception is the O atom), and so we expect a very close relationship between solute shape and solvent structure for $z < 0$. For example, g_{A1-} shows that the solvent has very restricted access to the CO group at short distances and very little solvent gets within 6 Å of the CO bond,

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† For C_{2v} symmetry these may be obtained by calculating the solvent distribution in each of the *xy* quadrants, and then adding and subtracting these in the manner specified by the symmetry tables. For example, g_{A1} is just $g_{x,y} + g_{x,-y} + g_{-x,-y} + g_{-x,y}$, and g_{A2} is $g_{xy} - g_{x,-y} + g_{-x,-y} - g_{-x,y}$. Usually these would be normalized by a factor of 1/4, but that has been omitted in this work to enable us to identify g_{A1} with g_{CO}.

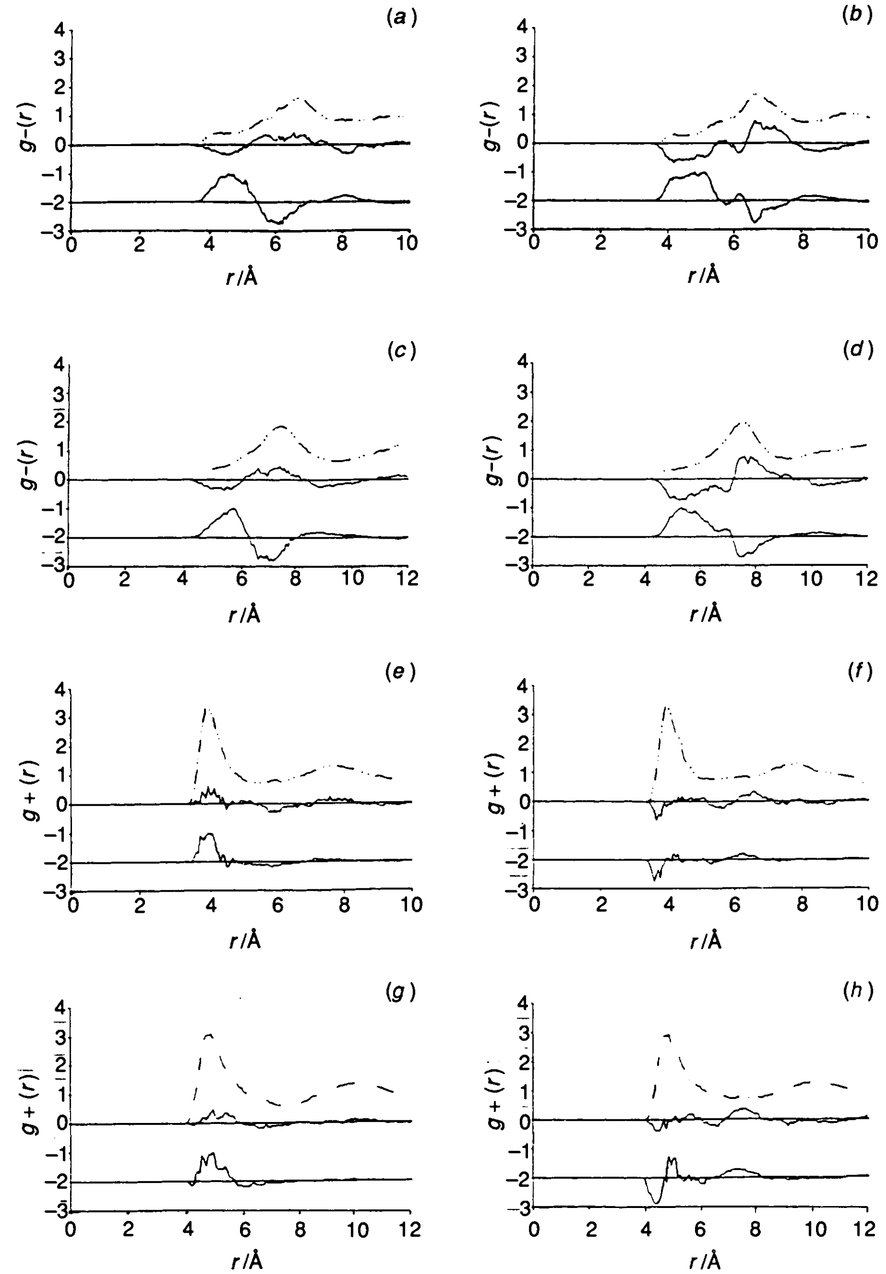

Fig. 3 Symmetry-adapted radial distribution functions describing the distribution of solvent around the carbonyl group, and the Radial contribution to the CD (RCD) arising from solvent in: (*a*) the $-z$ hemisphere for camphor/CH_4; (*b*) the $-z$-hemisphere for dibromocamphor/CH_4; (*c*) the $-z$ hemisphere for camphor/CCl_4; (*d*) the $-z$ hemisphere for dibromocamphor/CCl_4; (*e*) the $+z$ hemisphere for camphor/CH_4; (*f*) the $+z$ hemisphere for dibromocamphor/CH_4; (*g*) the $+z$ hemisphere for camphor/CCl_4; (*h*) the $+z$ hemisphere for dibromocamphor/CCl_4. The curves are as follows: — · · —, g_{A1}; ——(upper), g_{A2}; —— (lower), RCD. The RCD has been shifted down 2 units and normalized to its highest peak, while the height of g_{A2} has been doubled for clarity.

yet from the RCD it is clear that this small amount of solvent contributes strongly to the induced CD. The precise relationship between solute shape and solvent structure is very complicated, and it is not easy to associate any particular feature of g_{A2} or the RCD directly to the solute molecule. We have therefore confined our attention to the differences between the camphor and dibromocamphor systems, since any changes can be associated directly with the Br atoms. In both solvents the major difference is an extra positive contribution giving a peak in the RCD for dibromocamphor (at about 6.1 Å in CH_4 and 6.9 Å in CCl_4). This is associated with solvent packing around the C(8), C(9) and C(10) groups. In camphor these methyl groups form a convenient 'pocket' in which solvent molecules can sit, such that a CH_4 molecule in this 'pocket' would be 6.2 Å from the CO bond or a CCl_4 molecule would be 6.9 Å away. Further, this 'pocket' lies in the $(-x,-y,-z)$ octant and so gives rise to a negative R^* contribution. In the dibromocamphor conformation that we have used, this 'pocket' is largely obscured by the Br bonded to C(10). Thus in dibromocamphor there is a net loss of solvent from a negative octant which results in a more positive contribution to the RCD at this distance.

Solvent in the positive *z* region (*i.e.* pointing out from the solute along the CO bond) behaves quite differently from that in the negative region. The symmetric distribution g_{A1+} indicates that the first solvation shell is well defined, and there is some evidence of a second solvation shell although the chiral structure does not appear to extend into the second shell.

For camphor, the RCD reveals a positive peak followed by a negative peak, but the first peak is much sharper and occurs at

Table 3 Radical density of solvent in the $+z$ octants at $T^* = 0.7$

			Octant densities[a] ($+z$)			
Solvent	Solute	r/Å	(x,y)	$(-x,y)$	$(-x,-y)$	$(x,-y)$
CH_4	Camphor	3.9	3.84	2.41	3.66	3.84
		5.9	0.82	1.04	0.49	0.58
	Dibromocamphor	3.6	0.56	0.55	0.98	2.32
		4.2	2.04	2.22	3.14	2.81
		6.3	1.51	0.91	0.50	0.64
CCl_4	Camphor	4.9	3.02	2.16	3.33	3.22
		6.0	1.00	1.40	1.05	0.78
	Dibromocamphor	4.4	1.11	1.00	1.85	2.78
		5.0	1.89	2.08	3.20	2.75
		7.3	1.28	0.83	0.55	0.44

[a] Densities have been normalized so that the bulk density corresponds to a value of 1.

shorter distances than for negative z, while the second peak is much broader. This behaviour is probably associated with the C(6) methylene group; although C(6) is in the $(-x,y,-z)$ octant [located at (−1.9, 1.3, −1.1) Å], its van der Waals radius extends into the middle of the corresponding $+z$ octant, and so it will hinder solvent access to the CO bond from this direction. Thus we may expect an asymmetry in the radius of the solvation shell, with the peak in solvent density being further out in the $(-x,y,z)$ octant than in the other three $+z$ octants. Consequently there will be a mismatch in the RCD arising from the positive and negative octants that results in the observed oscillation. Further, we note that solvent structure tends to become less distinct as one moves away from the solute, and so it is not surprising that the second peak in the RCD should be much broader than the first. Detailed calculations of the solvent density in each octant confirm this picture (Table 3). For $+z$, the substitution of the Br appears to have quite a large effect. There is now a large negative peak in the RCD at shorter distances than for camphor, followed by a smaller positive peak coincident with that of camphor, and then another positive peak about half a solvent radius further out. In this case the effect of the C(6) group is effectively balanced by the Br bonded to C(10). The Br is about the same size as the methylene group and is nearly at the image position [(2.2, 2.4, 1.0) Å] so that for short distances these two effects cancel each other out; however, the Br is a bit further from the CO bond than is C(6) which allows closer approach of the solvent in the (x,y,z) octant at sufficiently large distances; it is this that leads to the positive peak in the RCD for dibromocamphor at 6 Å (CH_4) and 7.5 Å (CCl_4) (see Table 3).

The cancellation of the C(6) and Br at small distances means that more subtle influences from the rest of the molecule can be seen at small solvent–CO separations than was the case for camphor. The only other group to impinge upon the $+z$ hemisphere is C(3) [located at (−0.4, −1.2, −1.4) Å], which causes a deficiency of solvent in the $(-x,-y,z)$ octant. Thus, the RCD is dominated by the negative contribution from the adjacent $(-x,-y,-z)$ octant. In CCl_4 there is then a small mismatch in the size of the solvation shells in these two structures (as explained for camphor, above) which results in the subsequent positive peak. For CH_4, however, the size of the solvent is much closer to that of the C(3) group; hence the mismatch in solvent structure is less significant, and the positive peak at 4.2 Å all but vanishes. The assignment of the RCD to these octants is again confirmed by Table 3.

Conclusion

In this work we have presented computer simulations of camphor and 9,10-dibromocamphor in simple solvents designed to model CH_4 and CCl_4. It was shown that the chiral solute molecule does induce a chiral distribution of the solvent around the solute even though the solvent itself is achiral. This allowed the achiral solvents to contribute significantly to the circular dichroism (CD) spectrum of the camphors. Detailed calculations for the solvent-induced intensity of the CD of the n–π* carbonyl transition show that solvent structure can be responsible for as much as 10–20% of the observed CD intensity. Even for simple solvents, the magnitude of this effect is strongly related to the nature of the solvent.

A detailed analysis of the solvent structure has been carried out. The first solvation shell shows a very intricate chiral structure that can be related back directly to the conformation of the camphor and dibromocamphor. It was found that the solvent structure and intrinsic contributions to the carbonyl CD were sensitive to different parts of the solute molecule; in particular the intrinsic CD is dominated by the C(4) and C(6) groups (Fig. 2) whereas the solvent-induced CD was dominated by the CH_3 and CH_2Br side groups. This suggests that solvents could be used to 'tune into' different chiral centres on a molecule.

It is anticipated that these observations will not be limited to circular dichroism, but may also be expected for other chiral phenomena. In particular, the path by which two reactants approach is solvent mediated and should be sensitive to solvent structure, and an understanding of this may have implications for enantiomeric selectivity in chiral syntheses.

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