

ON THE LIMITED PRECISION OF TRANSFER OF MOLECULAR OPTICAL ACTIVITY TENSORS

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Dedicated to Dr. Zdeněk Havlas on the occasion of his 60th birthday.

Transfer of molecular property tensors (force field, dipole derivatives, polarizabilities, etc.) from smaller fragments to bigger molecules is powerful tool to calculate molecular vibrational spectra. However, we found serious accuracy limits for valinomycin (*Phys. Chem. Chem. Phys.* **2010**, *12*, 11021), where the transfer of the Raman optical activity tensors (ROA) had to be avoided. Therefore, in this study, the individual polarizable group model is analyzed for a model water dimer, and the corrections stemming from mutual group polarizations neglected in the transfer are estimated ab initio. The electric dipole polarizability was found more local and less sensitive to the interaction of distant molecular parts than the optical activity tensors (G' , A), which can partially explain the error observed during the transfer. In the second part of the study, tensor derivatives are transferred from smaller fragments to model valinomycin and insulin molecules, and the resultant tensor derivatives and ROA spectra compared to benchmark computations. The results confirmed that the error is caused by mutual polarization of molecular parts, more significant in insulin than in valinomycin, and could only partially be improved by increased size of the fragments.

Keywords: Ab initio calculations; Raman spectroscopy; Peptides; Optical activity; Tensor transfer.

Current chemistry possesses many techniques that can be used to analyze molecular structure. One of them is the chiral spectroscopy that explores different interaction of left and right circularly polarized light components with non-symmetric molecules, i.e. those without symmetry plane or a center¹. Traditionally, optical rotatory dispersion or circular dichroism was used to determine absolute configuration based on electronic transitions. Later, optical activity of vibrational transitions appeared more convenient for many applications, as the vibrational bands are energetically more re-

solved, and only electronic ground states need to be calculated to interpret the spectra².

In particular, the Raman optical activity (ROA), first observed in 1973³, appears very useful for biological applications, as it allows for studying molecules in the physiological aqueous environment, and the spectra can be recorded for a wide range of fundamental transitions. The technique can be applied to small molecules⁴⁻⁶, as well as to peptides^{7,8}, proteins, nucleic acids, and even viruses^{9,10}. The inhomogeneous band broadening in the spectra reflects molecular flexibility¹¹. A decomposition of experimental spectra into calculated subspectra of model dipeptides provided similar conformational ratios as NMR¹².

Routinely, the spectra can be calculated within the harmonic approximation directly by available quantum-chemical programs, such as Dalton¹³⁻¹⁵, Turbomole (local version)¹⁶⁻¹⁸, or Gaussian^{19,20}. These analytical implementations of the coupled-perturbed techniques^{19,21} speeded up calculation of the optical activity tensors²² A and G' , so that about the same computational effort is required for ROA as for an unpolarized Raman spectrum simulation⁸. Large proteins were simulated directly using an extensive parallelization of the computer code¹⁷.

Nevertheless, there are serious restrictions of the direct ab initio approach, as it is still very computationally demanding and lower accuracy (restricted basis set, approximation level) must be anticipated for larger systems. One way how to overcome the computational cost of the quantum-chemical methods is the Cartesian coordinate tensor transfer (CCT)²³. It was successfully applied for simulation of vibrational circular dichroism (VCD) of peptides²⁴ and nucleic acids²⁵. The computational times were reduced dramatically, and the accuracy of the IR and VCD spectra was about the same as for a direct calculation. However, for valinomycin ROA tensors, we found that the accuracy deteriorated more, and the transfer had to be avoided⁸. This indicates that the polarizability tensor (A , G') derivatives are not as local as the properties needed for VCD (force field, electric and magnetic dipole derivatives). By other words, the polarizability derivatives do not depend only on the closest neighborhood of the differentiated atom.

Therefore, in this work, we discuss the origin of the non-locality, and estimate the accuracy numerically on model examples. It appears that mutual polarization of different molecular parts is more important for ROA than for the unpolarized Raman scattering. Thus ROA is more sensitive to a tertiary molecular structure than VCD, which contradicts a popular believe among the ROA community. Another interesting observation is that

the simple polarization model²⁶ (not utilizing the A and G' tensors at all) works surprisingly well for simulation of the spectra of larger molecules.

So far, the CCT technique was used relatively rarely for ROA, although successful applications already include small molecules^{14,27}, β -peptides²⁸, model oligopeptides²⁹, and even unfolded proteins³⁰. Nevertheless, accuracy of the simulations is limited by many factors, including the harmonic limit³¹. Also noise in the experimental spectra often complicates the interpretations based on the computations. Therefore, we find it necessary to test the method not only against the experimental data, but also against exact computational benchmarks.

Below, we provide an introduction to the Barron formulation of the polarizability theory of isolated chromophores in a time-dependent electromagnetic field, and derive expressions for polarizability tensors for an ensemble of molecules. Then individual terms contributing to the electric dipole–electric dipole (α), electric dipole–magnetic dipole (G') and electric dipole–electric quadrupole (A) polarizability are evaluated using the coupled-perturbed approach on a water dimer, which provides a feeling for their importance. Finally, the accuracy of ROA spectral simulations is analyzed with the aid of more realistic valinomycin and insulin models.

THEORY

We need to investigate a system of individual chromophores/molecules in a laser electromagnetic field²². Schematically, the situation is outlined in Fig. 1, where the laser field is, for example, represented by the intensity E_0 . In addition to this external field, individual chromophores (positioned at r_i) sense the field from the neighboring ones, e.g. the radiation coming from the induced dipoles μ_j .

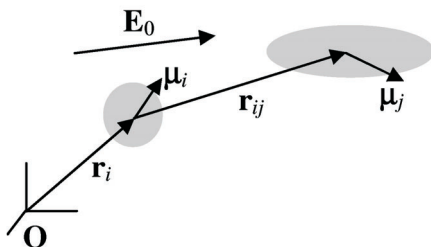


FIG. 1

In a system of many chromophores/molecules, each one (i) senses not only the external laser field (E_0), but also contributions coming from the other ones, e.g. from induced dipoles μ_j ($j \neq i$)

More completely, we consider a system of independent chromophores, each with a dipole (μ_i), magnetic dipole (\mathbf{m}_i), quadrupole (Θ_i), in the laser field (light) described by electric field \mathbf{E}_0 , its gradient $\nabla\mathbf{E}_0$, and magnetic field \mathbf{B}_0 . For ROA^{12,32}, we are interested in the polarizability α of the whole system and the optical activity tensors \mathbf{G}' and \mathbf{A} , defined as²²

$$\alpha_{\alpha\beta} = \frac{\partial \mu_\alpha}{\partial E_{0\beta}} \quad (1a)$$

$$G'_{\alpha\beta} = -\omega \frac{\partial m_\beta}{\partial \dot{E}_{0\alpha}} \quad (1b)$$

$$A_{\alpha,\beta\gamma} = \frac{\partial \Theta_{\beta\gamma}}{\partial E_{0\alpha}}. \quad (1c)$$

It is very important to realize the origin dependence of the variables. We express tensor properties of each chromophore at a coordinate system having origin at the chromophore position. On the other hand, properties of the whole system are evaluated at common origin. The total moments can be thus obtained as

$$\mu_\alpha = \sum_i \mu_{i,\alpha} \quad (2a)$$

$$m_\beta = \sum_i m_{i,\beta} + \frac{1}{2} \sum_i \epsilon_{\beta\gamma\delta} r_{i,\gamma} \dot{\mu}_{i,\delta} \quad (2b)$$

$$\Theta_{\alpha\beta} = \sum_i \Theta_{i,\alpha\beta} + \frac{3}{2} \sum_i (r_{i,\alpha} \mu_{i,\beta} + r_{i,\beta} \mu_{i,\alpha}) - \delta_{\alpha\beta} \sum_i r_{i,\gamma} \mu_{i,\gamma}. \quad (2c)$$

We can expand the induced parts as

$$\mu_{i,\alpha} = \alpha_{i,\alpha\beta} E_{i,\beta} + \frac{1}{3} A_{i\alpha,\beta\gamma} \nabla E_{i,\beta\gamma} + \frac{1}{\omega} G'_{i\alpha\beta} \dot{B}_{i,\beta} + \dots \quad (3a)$$

$$\Theta_{i,\beta\gamma} = A_{i\alpha,\beta\gamma} E_{i,\alpha} + \dots \quad (3b)$$

$$m_{i,\beta} = -\frac{1}{\omega} G'_{i\alpha,\beta} \dot{E}_{i,\alpha} + \dots \quad (3c)$$

The intensities experienced by each group are sums of the laser and surrounding chromophores' fields,

$$E_{i,\alpha} \cong E_{0,\alpha} + \sum_{j \neq i} T_{ij,\alpha\beta} \mu_{j,\beta} - \frac{1}{3} \sum_{j \neq i} t_{ij,\alpha\beta\gamma} \Theta_{j,\beta\gamma} \quad (4a)$$

$$\nabla E_{i,\alpha\beta} \cong \nabla E_{0,\alpha\beta} + \sum_{j \neq i} t_{ij,\alpha\beta\gamma} \mu_{j,\gamma} \quad (4b)$$

$$B_{i,\alpha} \cong B_{0,\alpha} + \frac{1}{c^2} \sum_{j \neq i} T_{ij,\alpha\beta} m_{j,\beta} \quad (4c)$$

where

$$T_{ij,\alpha\beta} = \frac{1}{4\pi\epsilon_0} \frac{3r_{ij,\alpha}r_{ij,\beta} - \delta_{\alpha\beta}r_{ij}^2}{r_{ij}^5},$$

$$t_{ij,\alpha\beta\gamma} = \nabla_{i\gamma} t_{ij,\alpha\beta} = \frac{1}{4\pi\epsilon_0} \frac{-15r_{ij,\alpha}r_{ij,\beta}r_{ij,\gamma} + 3(\delta_{\alpha\beta}r_{ij,\gamma} + \delta_{\gamma\alpha}r_{ij,\beta} + \delta_{\beta\gamma}r_{ij,\alpha})r_{ij}^2}{r_{ij}^7},$$

$r_{ij,\alpha} = r_{j,\alpha} - r_{i,\alpha}$, $c = 1/\sqrt{\epsilon_0\mu_0}$ is speed of light, ϵ_0 is vacuum permittivity, and μ_0 is vacuum permeability.

Now, let us consider the total electric dipole moment of Eq. (2a), which, using Eqs (3a) and (4a–4c), becomes

$$\begin{aligned} \mu_\alpha &= \sum_i [\alpha_{i,\alpha\beta} (\delta_{\beta\chi} + \sum_{j \neq i} T_{ij,\beta\delta} \alpha_{j,\delta\chi} - \frac{1}{3} \sum_{j \neq i} t_{ij,\beta\delta\gamma} A_{j\chi,\delta\gamma}) + \\ &+ \frac{1}{3} A_{i\alpha,\beta\gamma} \sum_{j \neq i} t_{ij,\beta\gamma\delta} \alpha_{j,\delta\chi} + \frac{1}{c^2} G'_{j\alpha\beta} \sum_{j \neq i} T_{ij,\beta\gamma} G'_{i\chi,\gamma}] E_{0,\chi}, \end{aligned} \quad (5)$$

where we used $\dot{E}_{0,\alpha} = -\omega^2 E_{0,\alpha}$, and retained only terms proportional to E_0 . Therefore, for the polarizability, from Eqs (1a) and (5), we get

$$\alpha_{\alpha\beta} = \sum_i \alpha_{i,\alpha\beta} + \sum_{j \neq i} \left[\alpha_{i,\alpha\chi} T_{ij,\chi\delta} \alpha_{j\delta\beta} + \frac{1}{3} (A_{i\alpha,\chi\chi} t_{ij,\chi\gamma\delta} \alpha_{j,\delta\beta} - \alpha_{i,\alpha\chi} t_{ij,\chi\delta\gamma} A_{j\beta,\delta\gamma}) + \frac{1}{c^2} G'_{i\alpha\chi} T_{ij,\chi\chi} G'_{j\beta,\gamma} \right]. \quad (6)$$

It is interesting to note that the last term in Eq. (6) becomes zero for static polarizability ($\omega = 0$). Even for the dynamic case, however, as shown below, it is usually quite small, and can be neglected.

Similarly, we can elaborate the total magnetic moment (component proportional to \dot{E} will be written only)

$$m_\beta \cong - \sum_i \left\{ \frac{1}{\omega} G'_{ia,\beta} \left(\delta_{a\alpha} + \sum_{j \neq i} T_{ij,a\delta} \alpha_{j,\delta\alpha} - \frac{1}{3} \sum_{j \neq i} t_{ij,a\delta\gamma} A_{j\alpha,\delta\gamma} \right) + \frac{1}{2} \sum_i \varepsilon_{\beta\gamma\delta} r_{i,\gamma} \left(\alpha_{i,\delta\alpha} \left(\delta_{a\alpha} + \sum_{j \neq i} T_{ij,\alpha\chi} \alpha_{j,\chi\alpha} - \frac{1}{3} \sum_{j \neq i} t_{ij,a\beta\gamma} A_{j\alpha,\beta\gamma} \right) + \frac{1}{3} A_{i\delta,b\gamma} \sum_{j \neq i} t_{ij,b\gamma\alpha} \alpha_{j,\alpha} \right) \right\} \dot{E}_{0,\alpha} \quad (7)$$

so that

$$G'_{\alpha\beta} = \sum_i \left(G'_{i\alpha,\beta} - \frac{\omega}{2} \varepsilon_{\beta\gamma\delta} r_{i,\gamma} \alpha_{i,\delta\alpha} \right) - \frac{\omega}{2} \sum_{i \neq j} \left[\varepsilon_{\beta\gamma\delta} r_{i,\gamma} \alpha_{i,\delta\alpha} T_{ij,ab} \alpha_{j,b\alpha} + - \frac{1}{3} \varepsilon_{\beta\epsilon\delta} r_{i,\epsilon} (\alpha_{j,\alpha a} t_{ij,\lambda\gamma a} A_{i\delta,\lambda\gamma} - \alpha_{i,\delta a} t_{ij,\lambda\gamma a} A_{j\alpha,\lambda\gamma}) - \frac{\omega}{2} G'_{i\gamma,\beta} T_{ij,\gamma\delta} \alpha_{j,\delta\alpha} \right]. \quad (8)$$

Finally, we obtain the A tensor for the whole system. Starting from (2c), using (3a), (3b), (4a)–(4c), and leaving only terms proportional to the electric intensity, we get the quadrupole,

$$\begin{aligned}
\Theta_{\alpha\beta} = & \sum_i \left\{ \left(A_{ia,\alpha\beta} + \frac{3}{2}(r_{i,\alpha}\alpha_{i,\beta a} + r_{i,\beta}\alpha_{i,\alpha a}) - \delta_{\alpha\beta}r_{i,c}\alpha_{i,ca} \right) \times \right. \\
& \times \left(\delta_{\alpha\gamma} + \sum_{j \neq i} T_{ij,\alpha\gamma} \alpha_{j,\gamma\lambda} - \frac{1}{3} \sum_{j \neq i} t_{ija,be} A_{j\gamma,be} \right) + \\
& + \left[\frac{1}{2}(r_{i,\alpha} A_{i\beta,ae} + r_{i,\beta} A_{i\alpha,ae}) - \frac{1}{3} \delta_{\alpha\beta} r_{i,f} A_{if,ae} \right] \sum_{j \neq i} t_{ij,aec} \alpha_{j,c\gamma} + \\
& \left. + \frac{1}{c^2} \left[\frac{3}{2}(r_{i,\alpha} G'_{i\beta b} + r_{i,\beta} G'_{i\alpha b}) - \delta_{\alpha\beta} r_{i,\gamma} G'_{i\gamma b} \right] \sum_{j \neq i} T_{ij,bv} G'_{j\gamma,v} \right\} E_{0,\gamma} \quad (9)
\end{aligned}$$

and from (3b) and (9), we obtain

$$\begin{aligned}
A_{\gamma,\alpha\beta} = & \sum_i \left(A_{i\gamma,\alpha\beta} + \frac{3}{2}(r_{i,\alpha}\alpha_{i,\beta\gamma} + r_{i,\beta}\alpha_{i,\alpha\gamma}) - \delta_{\alpha\beta}r_{i,c}\alpha_{i,c\gamma} \right) + \\
& + \sum_{j \neq i} \left\{ \left(\frac{3}{2}(r_{i,\alpha}\alpha_{i,\beta a} + r_{i,\beta}\alpha_{i,\alpha a}) - \delta_{\alpha\beta}r_{i,c}\alpha_{i,ca} \right) T_{ij,ae} \alpha_{j,e\gamma} + A_{ia,\alpha\beta} T_{ij,ae} \alpha_{j,e\gamma} \right\} + \dots \quad (10)
\end{aligned}$$

COMPUTATIONS

To estimate the importance of the various terms in the above expressions, the dynamic polarizability tensors α , G' and A of two water molecules (Fig. 2) separated by $r = 4, 4.5, 5, 5.5, 6, 7, 8.5$ and 10 \AA were calculated by Gaussian²⁰ at the HF/6-31G** and HF/aug-cc-pVTZ levels, using the excitation wavelength of 532 nm, which corresponds to a typical ROA experiment⁵. Only the latter larger basis set results are shown; they were qualitatively similar to those obtained with the smaller basis. Alternatively, the tensors were calculated for one water molecule only, and the total polarizabilities calculated from the formula derived above. Our transfer CCT³³ and smaller programs were used for the tensor transfer and analyses.

Reliability of the transfer of the tensors derivatives was investigated with the valinomycin and insulin peptides (Fig. 3). For the propeller conformer (**I** in the Figure)⁸ the polarizability tensor derivatives were calculated at the HF/6-31G level, using also the excitation wavelength of 532 nm. Alterna-

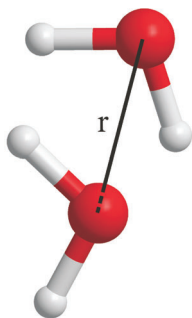


FIG. 2
Water dimer (parallel water planes, rotated by 45°) used for the tests, $d_{\text{OH}} = 0.943 \text{ \AA}$, $\angle\text{HOH} = 106^\circ$

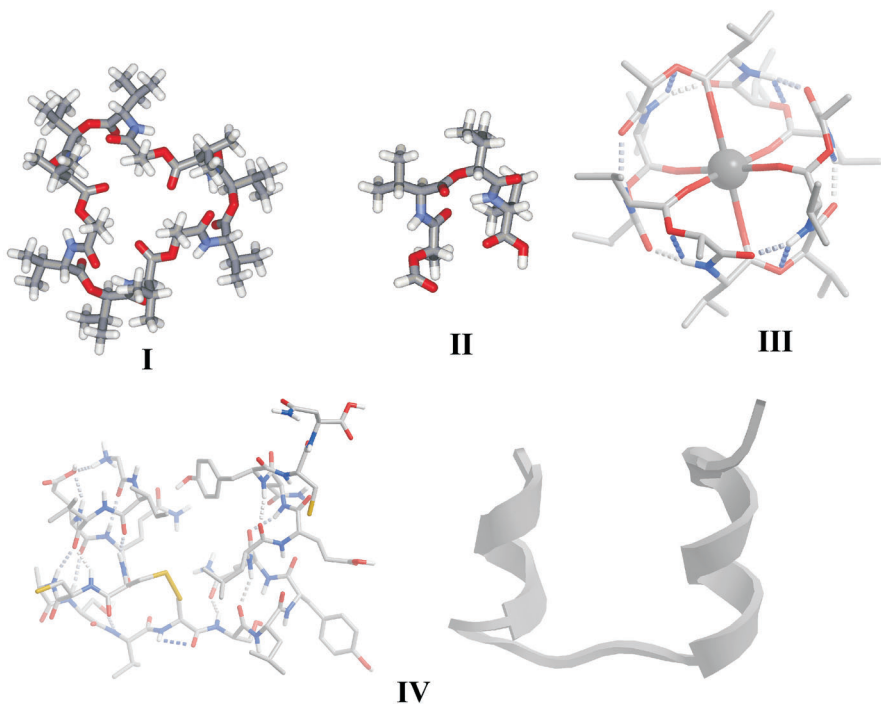


FIG. 3
The valinomycin molecule (I), its fragment (II), potassium complex (III), and insulin peptide chain (IV, with its ribbon representation, PDB code 2A3G) used for the tests

tively, with CCT³³, some derivatives were transferred from a smaller fragment (II) comprising four acid residues. The geometry of the fragment mimicked exactly those of the valinomycin. Various sized fragments and the HF/3-21G level were used for to the valinomycin potassium complex (III) and bovine insulin (chain A only, structure IV in Fig. 3). Details of the fragmentation and aminoacid sequence are given in Table I. The error of the ROA and Raman intensities (I) was evaluated as $\delta = \int |I_{\text{exact}} - I_{\text{transferred}}| d\omega / \int |I_{\text{exact}}| d\omega$ within 200–1800 cm^{-1} . The force fields obtained for the full molecules were used to generate the spectra.

TABLE I
Definition of the CCT fragmentation schemes

1) Valinomycine

ID ^a	L-Lac	L-Val	D-Hiv	D-Val	L-Lac	L-Val	D-Hiv	D-Val	L-Lac	L-Val	D-Hiv	D-Val
O2L4	[Orange]				[Light Orange]				[Light Green]			
O2L8	[Orange]								[Pink]			
O4L8	[Orange]								[Light Orange]			

2) Insulin A Chain

ID ^a	G	I	V	E	Q	C	C	A	S	V	C	S	L	Y	Q	L	E	N	Y	C	N					
O2L5	[Orange]					[Light Orange]					[Light Green]					[Grey]										
O4L8	[Orange]								[Light Orange]								[Light Green]				[Light Blue]					
O5L10	[Orange]										[Light Orange]										[Light Blue]					
O6L12	[Orange]										[Light Orange]										[Light Blue]					
O7L14	[Orange]														[Light Orange]						[Pink]					

^a $O_mL_n^a$ means that the fragment and the overlapped region contains n and m amino acids, respectively.

RESULTS AND DISCUSSION

Water dimer polarizability. The average tensor elements, and the average deviations of the α , G' and A tensors if calculated from the approximate formulae (6), (8), and (10), respectively, are summarized in Fig. 4. In the common origin, the α -polarizability of the dimer is approximately the same for all distances (panel a in Fig. 4), as all the terms in the Eq. (6) are either independent on the chromophore separation, or decrease as $\sim r^{-3}$ (see the definition of the distance tensors T and t above). On the other hand, because of the origin-dependence of the magnetic dipole and electric quadrupole moments, tensors G' and A are approximately linearly proportional to the distance, in agreement with Eqs (8) and (10).

In the transfer, polarizabilities on one molecule were rotated according to the dimer geometry, and the origin-dependent terms in Eqs (8) and (10) for

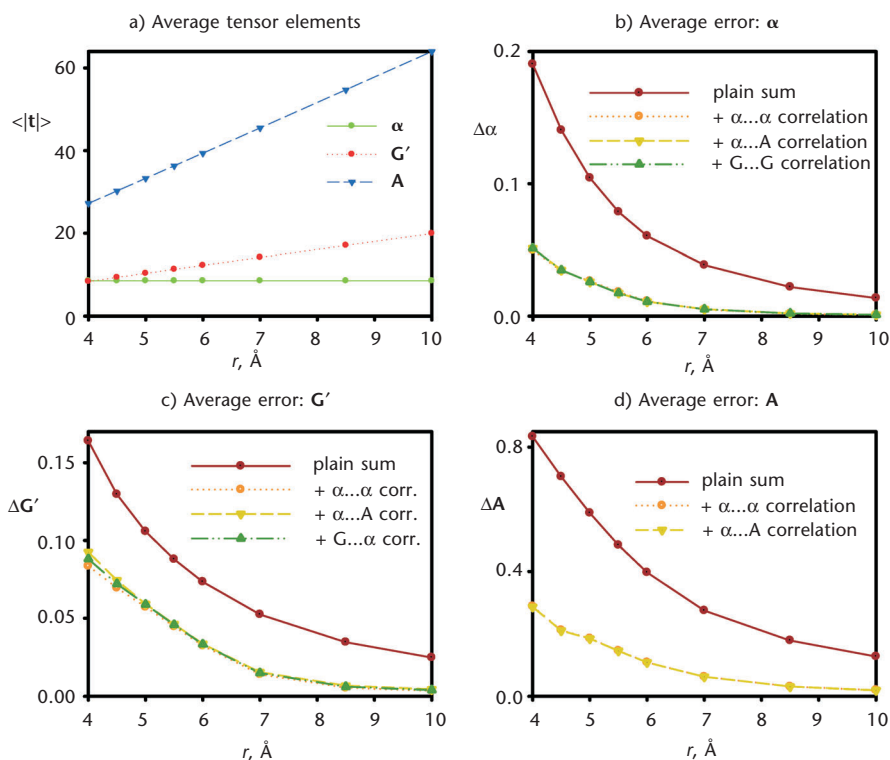


FIG. 4

Water dimers of 4–10 Å separation distance (Fig. 2): average tensor elements (a), and errors of the α (b), G' (c) and A (d) polarizabilities calculated by various approximations

G' and A were included in the plain sums. From the average errors (panels b–d in Fig. 4), we can see that already the plain sums of two water polarizabilities reasonably well approximate the properties of the whole dimer. For example, for the 4 Å separation the average error is less than 3% for all polarizability types.

As expected, for increased water molecules' separations, the error diminishes. However, a closer look reveals that the error of α fades most quickly with the distance, for $r = 7$ Å, for example, it is reduced to 20% from the original magnitude for $r = 4$ Å. For G' and A , the respective errors decrease to 38 and 35% only. For larger distances, the difference is even more apparent. Thus we see that the G' and A optical activity tensors are less local than the electric polarizability α .

The error can be significantly reduced, when the total polarizabilities are corrected to the mutual polarization of monomers. For α (panel b in Fig. 4), the " $\alpha\dots\alpha$ " term (second in Eq. (6)) is clearly the most important, which reflects the dominance of the dynamic electric dipole–electric dipole interaction. The " $A\dots\alpha$ " term (third in Eq. (6)) is quite negligible, which corresponds to the fast ($\sim r^{-4}$) decrease of the t tensor with the distance, and so is the last " $G\dots G$ " term, which reflects the weakness of the magnetic forces among molecules in comparison with the electric ones.

Similar reduction of the error by the dipole–dipole interaction (" $\alpha\dots\alpha$ " term) is obtained for the G' and A tensors. For G' , also the " $G\dots\alpha$ " correction (fifth term in Eq. (8)) contributes significantly, however, still much less than the dipolar interaction. Overall, we can conclude that the model of individual chromophores only approximately valid for separated molecules, and that the tensors obtained from the monomers can be further improved by involving the dipole–dipole interaction, but without any ab initio calculation for the whole dimer.

The error for the fragment (II→I) transfer. When the polarization tensors, in this case their atomic derivatives, are obtained from a part of the molecule, the differences between the "dipolar" α and "optical active" G' and A tensors are much more pronounced than for the water dimer. From Fig. 5, where we compare the exact tensor components for the whole molecule (calculated at the HF/6-31G level) with those obtained from the fragment (corresponding to the plain sum for the water dimer), we can see a much nicer correlation for the dipolar polarizability ($cc = 0.986$) than for G' and A ($cc = 0.900$ and 0.875 , respectively). This reflects the contribution of the terminal effects in the fragment to the polarizability derivatives, and the higher sensitivity of the optical activity tensors (cf. Fig. 4) to the mutual group polarization.

Indeed, tensor derivatives related to atoms distant from the fragment termini agree better with those in the whole valinomycin molecule (Fig. 6). With the distance the error diminishes very quickly for α derivatives, in agreement with the two-molecule model (Fig. 4). However, the G' and A tensors are less local, and significant error is expected to be introduced in the simulated ROA spectra by the transfer. Different atomic kinds behave similarly.

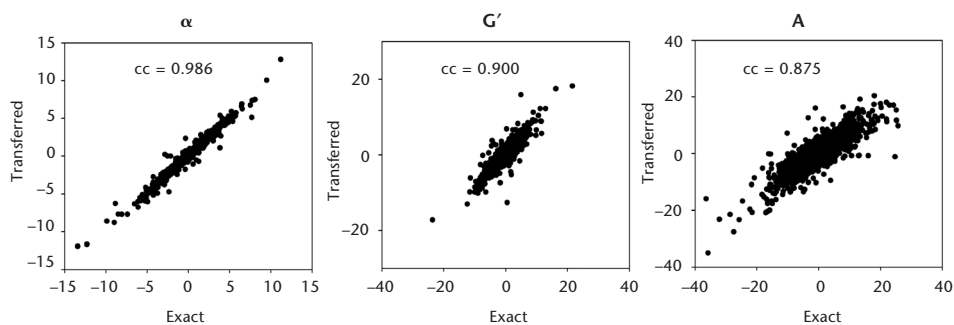


FIG. 5

Correlation of the transferred and exact α , G' and A tensor components in valinomycin, for the model valinomycin fragment (Fig. 3, transfer from II to I). Correlation coefficients (cc) are given in the graphs

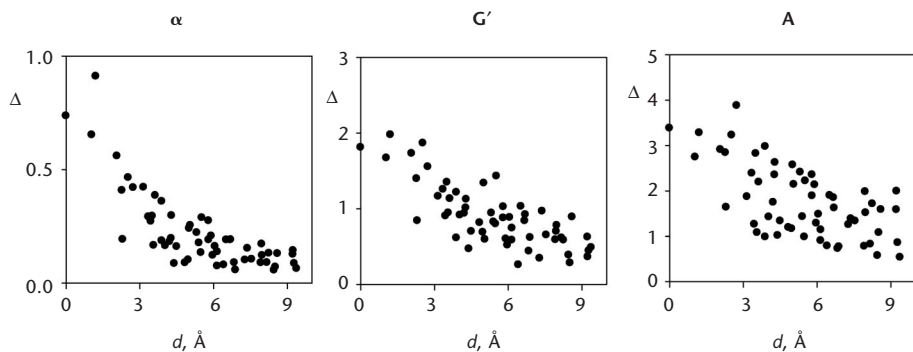


FIG. 6

Dependence of the error of atomic tensor derivatives on the distance from the fragment terminus, for the valinomycin II→I transfer. $d = \min(d_1, d_2)$, where d_1 and d_2 is s distance from the terminal hydrogen (H-O) and oxygen (O=C), respectively

The Raman and ROA spectral simulation. Finally, we can document the limited precision of the Raman and ROA spectra simulated for the valinomycin complex from six fragments in Fig. 7. For insulin the results (not shown) were similar. Whereas the Raman spectra (Fig. 7a) obtained from the fragments are almost indistinguishable from the exact result, the approximate ROA spectra contain a large error. Interestingly, for ROA, the simpler polarization model^{29,34}, where the derivatives of G' and A are not used, agrees more with the ab initio spectrum. Although the O4L8 fragmentation provides somewhat better results than O2L8 (see Table I for the definition), the results clearly show that the error introduced by the transfer local approximation is not acceptable for ROA. In particular, the error of the local part of the G' and A (see also Fig. 5) is larger than their contribution to the ROA spectrum.

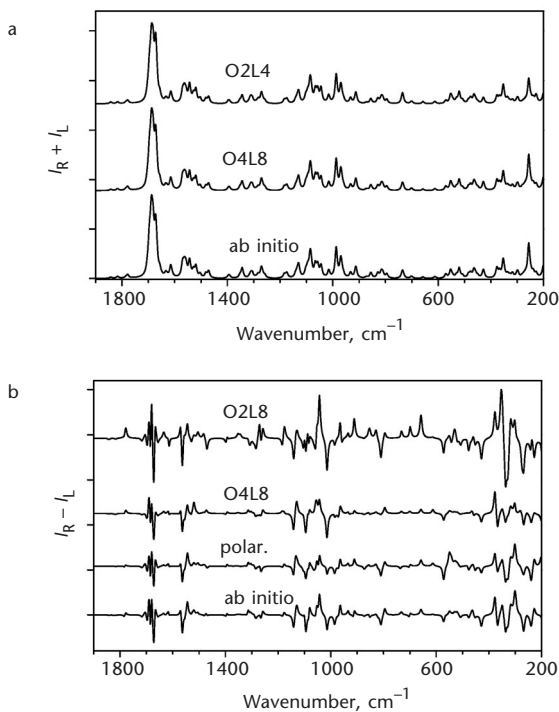


FIG. 7

Raman (a) and ROA (b) spectra of the valinomycin complex calculated ab initio and with the fragmentation schemes defined in Table I. The ROA spectrum obtained from the polarization model using only the α -polarizability derivatives is also plotted

On the other hand, the Raman spectrum (Fig. 7a) simulated from the fragments is almost indistinguishable from the exact one, which can potentially lead to significant savings of the computer time. Also, note that the ROA spectra (Fig. 7b) simulated by the transfer contain a smaller error in the higher-frequency region than for lower wavenumbers. This can be explained by the delocalization of the lower-frequency vibrations, more sensitive to the long-distance polarization effects.

The performance of the transfer method for ROA could be partially improved by varying fine transfer parameters, in particular averaged tensors in the overlap regions provided better results than when one fragment was used only. When the each overlapped region contained four amino acids, the error significantly decreased compared to two amino acids only. This again points at the importance of the longer-distance polarization effects for ROA. With the longer fragments and longer overlapped regions, the error decreased for valinomycin (Fig. 8, top), although even with the largest

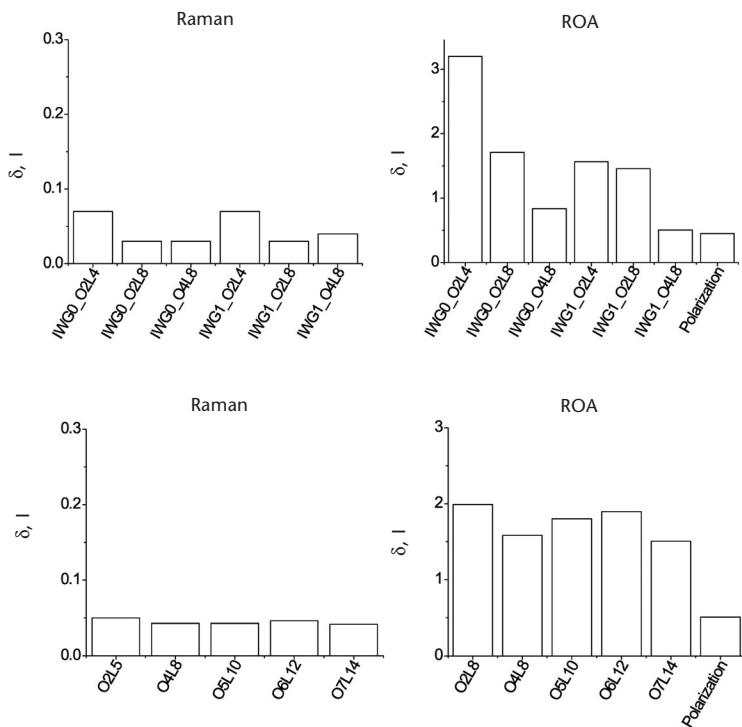


FIG. 8

Error of the valinomycin (top) and insulin (bottom) Raman and ROA spectra obtained from the fragments defined in Table I, and from the polarization model

fragments (O4L8) and error of about 50% remained. For the chain A of the insulin (Fig. 8, bottom) the error was in general smaller than for the valinomycin, however it could not be further decreased even for a very large fragment (O7L14). This can be explained by the tightly packed tertiary structure of insulin where many amino acid side chains are oriented inward and interact with other parts of the peptide, even with those separated by many amino acid residues (cf. Fig. 3).

Based on these results, we can say that the Raman tensor derivatives for the peptides can be thought of as highly localized, with a practical interaction span of 2–4 amino acid residues. On the other hand, the ROA tensors are more sensitive to long-distance polarization interactions. Our conclusions are consistent with detailed computational analyses of cyclic peptides' ROA^{7,8}. In some other experimentally studied systems, such as the alanine containing peptides³⁵, the ROA signal can be dominated by local components, because of an extended or flexible peptide structure. Indeed, in polyproline helix²⁹ or similar linear peptides^{28,30} the side chains separated by many amino acids are not close to each other, and CCT provided reasonable ROA spectra. On the other hand, we saw that in the insulin and valinomycin the contribution of the mutual polarization not included in CCT could not be neglected. In summary, the CCT method has serious accuracy limits for ROA, which should be considered when a high level of the agreement between theory and experiment is required.

CONCLUSIONS

On the water dimer we validated the model of separable polarizable chromophores, and numerically estimated the magnitude of the various correction terms stemming from the mutual dynamic polarization of the two molecules. We found significant differences between the electric polarizability (α) and the optical activity tensors (G' , A), the latter being less local and more influenced by the inter-chromophore coupling. The coupling was more pronounced in the valinomycin and insulin fragment models, where the local separated chromophore approximations introduced large error into the polarizability tensor derivatives, and consequently to the resultant ROA spectrum. For ROA simulations of large molecules, we thus recommend the transfer method be used with caution, for rod-like molecules much larger fragments are needed than for VCD (where only force field and dipole derivatives are transferred). For our more folded examples of insulin and valinomycin, the polarization model gave better results than the fragmentation. The modeling of the unpolarized Raman spectra based on

smaller molecular fragments is more reliable than for ROA, and can lead to significant savings of the computer time.

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