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# Molecular Dynamics of Isotopically Substituted Chiral Solutions

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The technique of molecular-dynamics computer simulation is used to investigate the modification of dynamical properties brought about by mixing different isotopes of two enantiomers in equal proportion. Moving-frame, cross-correlation functions are constructed from the trajectories of 54 enantiomers of fluorochloroacetonitrile dissolved either in 54 other *R*-type enantiomers or 54 of the *S* type. The exercise is repeated for the *S* enantiomers and the results discussed in terms of rotation–translation coupling.

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The statistical correlation between the linear velocity ($\boldsymbol{v}$) of a molecule's centre of mass and its own angular momentum ($\boldsymbol{J}$) is fundamentally important to our understanding of chemical reactions in solution[1] and the nature of vibrational relaxation. It is possible to look at this correlation in two frames of reference:[2] the laboratory frame and a moving frame of reference, the frame (1, 2, 3) of the three principal molecular moments of inertia.[3] The details of the statistical correlation can be investigated with the matrix $\langle \boldsymbol{v}(t)\boldsymbol{J}^{\mathrm{T}}(0)\rangle$ (laboratory frame) or $\langle \boldsymbol{v}(t)\boldsymbol{J}^{\mathrm{T}}(0)\rangle_m$ (moving frame). This matrix has nine elements, the symmetry properties of which are discussed in detail by Ryckaert *et al.*[3] using the moving frame. The higher the symmetry of the molecule, the fewer elements this matrix contains. For all molecular symmetries higher than chiral, the laboratory-frame matrix $\langle \boldsymbol{v}(t)\boldsymbol{J}^{\mathrm{T}}(0)\rangle$ vanishes for all $t$, as first discussed in a hydrodynamical context by Ailawadi *et al.* and in a molecular context by Ryckaert *et al.*[3] This is because the hamiltonian is invariant to parity reversal, and because the parity symmetries of $\boldsymbol{v}$ and $\boldsymbol{J}$ are opposite.[5] This is also true in a racemic mixture of two enantiomers but not necessarily[4] in the two enantiomers considered separately, because of the right- or left-handedness in these systems. Some elements of the moving-frame matrix $\langle \boldsymbol{v}(t)\boldsymbol{J}^{\mathrm{T}}(0)\rangle_m$, however, exist for $0 < t < \infty$ for all dipolar molecular symmetries. Therefore

$$\langle \boldsymbol{v}(t)\boldsymbol{J}^{\mathrm{T}}(0)\rangle = 0 \quad \text{for all } t \text{ (except for chiral molecules)}$$

$$\langle \boldsymbol{v}(t)\boldsymbol{J}^{\mathrm{T}}(0)\rangle_m \neq 0, \qquad 0 < t < \infty$$

where

$$\langle \boldsymbol{v}(t)\boldsymbol{J}^{\mathrm{T}}(0)\rangle = \frac{1}{N}\sum_{j=1}^{j=N}\left(\int_{t'=0}^{t'=t_{\max}} \boldsymbol{v}_j(t'+t)\boldsymbol{J}_i^{\mathrm{T}}(t')\,\mathrm{d}t'\right).$$

It has been discovered recently[6] that two of the off-diagonal elements of $\langle \boldsymbol{v}(t)\boldsymbol{J}^{\mathrm{T}}(0)\rangle_m$ have particularly interesting properties in enantiomers and their 1:1 (racemic) solution. Each element is the other's exact mirror image in time dependence. In the racemic mixture the dependence on time of the cross-correlation function (c.c.f.) elements in question vanishes. The symmetry of the matrix $\langle \boldsymbol{v}(t)\boldsymbol{J}^{\mathrm{T}}(0)\rangle_m$ is therefore different in each enantiomer and their racemic mixture. The computer-simulation method has therefore revealed a difference between the dynamical properties of two enantiomers which can be attributed directly to the basic property of $R$ or $S$ molecular symmetry (*i.e.* right- or left-handedness). For a given atom–atom potential this can be used as an explanation for the usually small, but nevertheless observable, differences between absorption bands (*e.g.* far-infrared bands) or refractive indices in the $R$ or $S$ enantiomers and their 1:1 mixture. The importance of precise observations such as these is that they provide a method of looking at the effects of rotation–translation coupling isolated from the background dynamics by comparing two systems (enantiomers and racemic mixture) whose only dynamical difference can be traced (with computer-simulation back-up) to the $\langle \boldsymbol{v}(t)\boldsymbol{J}^{\mathrm{T}}(0)\rangle_m$ symmetry characteristics.

In this paper we extend the computational work in order to make a direct comparison between the statistics of 54 $R$ (or $S$) molecules dissolved ($a$) in 54 other $R$ (or $S$) molecules of the same type and ($b$) 54 other $S$ (or $R$) molecules of the opposite type. For a given atom–atom potential this provides numerical information on the way the statistical dynamics of 54 molecules are modified by the introduction of chiral molecules of opposite symmetry. Results are reported for the enantiomers and racemic mixture of the hydrogen and tritium isotopes of fluorochloroacetonitrile in terms of the matrix $\langle \boldsymbol{v}(t)\boldsymbol{J}^{\mathrm{T}}(0)_m$.

## ALGORITHM AND METHOD

The algorithm integrates Newton's equations for the translational motion and Euler's equations for the rotational motion of 108 chiral molecules, either all of one type or 54 $S$ type and 54 $R$ type (table 1). The molecules are assumed to interact *via* a Lennard-Jones atom–atom potential with $\varepsilon/k$ and $\sigma$ parameters in the usual way, and with partial charge terms situated on each atom used to represent the electrostatic part of the total pair potential. These terms are described fully in the literature,[2] together with thermodynamic details and conditions (table 2). It is assumed that the Lennard-Jones and partial-charge terms between atom A and atom B (or between like atoms) do not change when considering $R$–$R$, $S$–$S$ or $R$–$S$ molecule–molecule interactions (table 3). This means that the effect of atom–atom chiral discrimination between the $R$–$R$ and $R$–$S$ potential-energy surface is neglected when summing the total molecule–molecule pair interaction from the atom–atom terms. Chiral discrimination in this context would mean that an $R$–$R$ atom–atom potential term for a given pair of atoms would not be the same as the equivalent $R$–$S$ term. The total chiral discrimination usually amounts to a few hundred cal $\mathrm{mol}^{-1}$ in the condensed state,[7] *ca.* 1% or less of the total intermolecular pair potential. Inclusion of this effect would accentuate the differences between the laboratory- and moving-frame properties of enantiomers and racemic mixture reported in the paper and previous work.[2,6]

Correlation functions have been computed in this work using averages over 54 enantiomers of type $R$, for example, dissolved in 54 others of the same type (pure enantiomers) or different type (racemic mixture). This enables one to draw exact parallels between the dynamics of one type of enantiomer in both environments. A comparison of this type between the elements of the matrix $\langle \boldsymbol{v}(t)\boldsymbol{J}^{\mathrm{T}}(0)_m$ is particularly interesting, and also between autocorrelation functions (a.c.f.) in the laboratory frame, such as rotational velocity a.c.f., that bear an inverse Fourier-transform relation to observable spectra (*e.g.* the far-infrared[8-10] power-absorption coefficient).

**Table 1.** Principal Cartesian coordinates[a]

| atom | $e_1$/Å | $e_2$/Å | $e_3$/Å |
|---|---|---|---|
| | tritium isotope ($R$ enantiomer) | | |
| N | −2.26 | 0.01 | 0.88 |
| $C_1$ | −1.28 | −0.14 | 0.29 |
| $C_2$ | −0.04 | −0.33 | −0.46 |
| T | 0.01 | −1.36 | −0.84 |
| Cl | 1.35 | −0.03 | 0.60 |
| F | −0.02 | 0.56 | −1.53 |
| | hydrogen isotope ($R$ enantiomer) | | |
| N | −2.28 | 0.35 | 0.75 |
| $C_1$ | −1.29 | −0.03 | 0.27 |
| $C_2$ | −0.05 | −0.51 | −0.34 |
| H | −0.38 | −1.59 | −0.34 |
| Cl | 1.33 | 0.07 | 0.61 |
| F | 0.06 | 0.02 | −1.64 |

[a] (1, 2, 3) frame of the principal moments of inertia.

**Table 2.** Sample thermodynamic data, $T = 133$ K; input molar volume, 91.4 $cm^3$; time steps per c.c.f. segment, 1000

| liquid | potential energy /kJ $mol^{-1}$ | translational kinetic energy/kJ $mol^{-1}$ | rotational kinetic energy/kJ $mol^{-1}$ |
|---|---|---|---|
| $H_R - H_R$ | −48.46 | 1.76 | 1.83 |
| $H_R - H_S$ | −47.78 | 1.75 | 1.75 |
| $T_R - T_S$ | −47.65 | 1.76 | 1.79 |

**Table 3.** Lennard-Jones atom–atom and partial charge parameters

| atom | $\sigma$/Å | $(\varepsilon/k)$/K | $q$ |
|---|---|---|---|
| N | 3.0 | 47.8 | −0.16 |
| $C_1$ | 3.4 | 35.8 | −0.02 |
| $C_2$ | 3.4 | 35.8 | 0.03 |
| H or T | 2.8 | 10.0 | 0.51 |
| Cl | 3.6 | 127.9 | −0.16 |
| F | 2.7 | 54.9 | −0.20 |

It is also interesting to extract the sample number dependence of autocorrelation functions and cross-correlation functions in the pure $R$ or $S$ enantiomers by building up a.c.f. using 54 and 108 molecules in the averaging. Under ideal conditions there should be no difference. Any observable difference must be put down to noise in the computer simulation, periodic boundary conditions *etc.* When dealing, however, with the racemic mixture, there is no reason why the a.c.f. or c.c.f. of 54 molecules

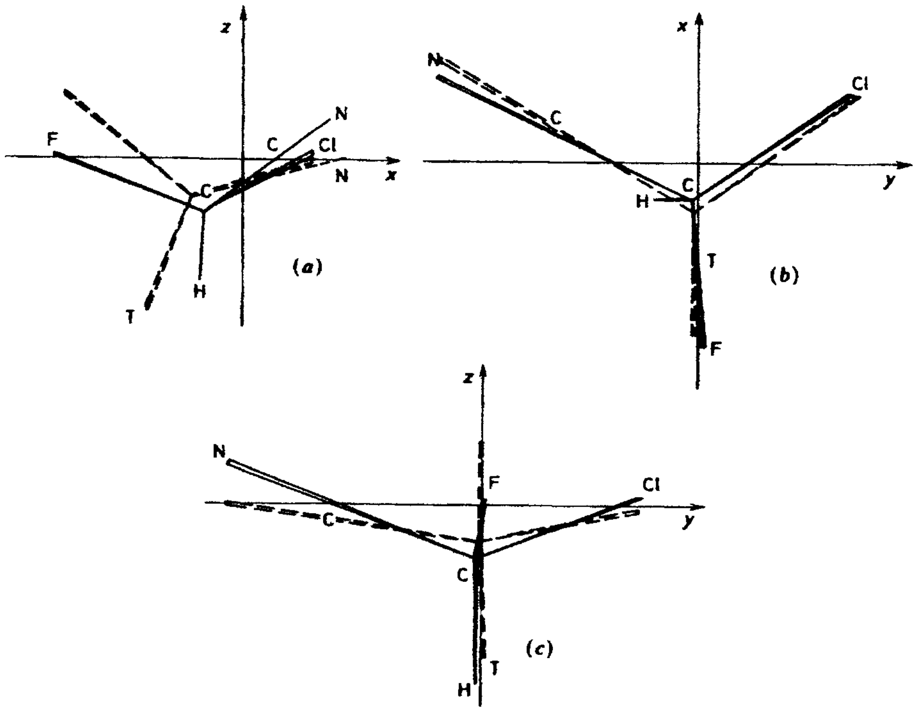

**Fig. 1.** Projections in three planes of the principal moment of inertia frame of protonated and tritiated chlorofluoroacetonitrile. The axes in these diagrams intersect at the centre of mass. The atoms are positioned at the principal cartesian coordinates (see table 1).

of *R* or *S* type should be the same as the total a.c.f. or c.c.f. counterparts in the mixture. Computer simulation seems to be the only means available of extracting information of this type specifically about the *R* or *S* component in a racemic mixture. This emphasizes once again the incisiveness of the technique.

## RESULTS AND DISCUSSION

The results presented here for chlorofluoroacetonitrile represent a small fraction only of the data available in principle with isotopic substitution. These results are given for the proton and tritium isotopes only using the natural abundance of the other isotopes in the usual way (*e.g.* $m_{\mathrm{Cl}} = 35.5$ a.m.u. *etc.*).

The characteristics of the moving-frame translation to rotation cross-correlation matrix $\langle \boldsymbol{v}(t)\boldsymbol{J}^{\mathrm{T}}(0)\rangle_{\mathrm{m}}$ for the proton isotope of chlorofluoroacetronitrile (denoted as H) have been worked out and published previously.[2] In this paper we concentrate exclusively on the (1, 3) and (3, 1) moving frame elements, defined by

$$(1,3) = \frac{\langle v_1(t)J_3(0)\rangle}{\langle v_1^2\rangle^{1/2}\langle J_3^2\rangle^{1/2}} \quad \text{and} \quad (3,1) = \frac{\langle v_3(t)J_1(0)\rangle}{\langle v_3^2\rangle^{1/2}\langle J_1^2\rangle^{1/2}}$$

respectively. The moving frame (1, 2, 3) is defined by that of the principal moments of inertia, and changes relative to the laboratory frame, where the hydrogen atom is replaced by the tritium atom (fig. 1 and table 1). The (1, 3) and (3, 1) elements defined above are the ones which change sign when the *R* enantiomer is replaced by the *S* enantiomer, and vanish within the uncertainty caused by the computer noise for the racemic mixture if the running-time averaging $\langle\ \rangle_m$ is carried out over all 108 molecules. We therefore call them the 'switching' elements.

More subtly, however, we can restrict the averaging to 54 molecules as discussed already. The first results of this type are illustrated in the panels of fig. 2, where the hatching denotes the computer noise, *i.e.* the difference between two different computer runs on the same c.c.f. element to one of faster and more powerful computers, and future developments in software will reduce this noise level considerably. [The nature of the computer noise can be gauged by reference to curve 1 of fig. 2(*a*), which is that for the (1, 3) element of the $H_R$–$H_S$ racemic mixture. This is known from symmetry arguments and previous work to be zero for all *t*.] Curves (2) and (3) of fig. 2(*a*) are direct comparison between the average $\langle\ \rangle_m$ carried out over 54 $H_R$ molecules in the racemic mixture and in 108 $H_R$ molecules, respectively. The only difference between these averages is that coming from the 'solvent': in one case 54 $H_S$ molecules and in the second 54 $H_R$ molecules. This solvent effect works its way through to the cross-correlation function as shown in curves (2) and (3). There seems to be a small effect which lies outside the computer noise boundaries (the hatched areas). It is clear that the 54-molecule average does not vanish in the racemic mixture, unlike its 108-molecule counterpart. The reason for this is given by curve (4), which is the 54-molecule average for the $H_S$ molecules in the racemic mixture. Within the noise, this seems to be the mirror image of curve (3). The racemic solution is generally regarded as a thermodynamically more or less ideal solution,[7] *i.e.* the excess entropy of mixing is more or less zero. If this is also the case dynamically then curves (2) and (3) must be identical and curve (4) the exact mirror image of (3). If, however, there is any kind of 'dynamical chiral discrimination', this will not be the case. [Recall that we have not built any static chiral discrimination into the atom–atom potential (table 3)]. Any real difference between curves (2) and (3) must therefore be purely dynamical in origin.]

Fig. 2(*b*) illustrates the difference between the 108- and 54-molecule averages (cf. $H_R$ molecules) for the (3, 1) switching element in the $H_R/H_S$ racemic mixture.

The tritium isotope (denoted as T) makes its first appearance in fig. 2(*c*). Curve (1) of this figure is the normal 108-molecule average for the (1, 3) element of the $T_R/T_S$ racemic mixture. Curve (2) is the 54-molecule average of the $T_S$ molecules, and curve (3) that for the $T_R$ molecules. The same type of behaviour is exhibited as in fig. 2(*a*). Similarly for the (3, 1) $T_R$–$T_S$ elements of fig. 2(*d*) [although in this case there seems to be a slight asymmetry as regards the 54-molecule $T_S$ and $T_R$ averages, curves (2) and (3), respectively].

We are now ready to mix in equal proportions the hydrogen and tritium isotopes, and the first result of this type is illustrated in fig. 2(*e*) for the (1, 3) element of the $T_S$–$H_S$ mixture. In this case both the 108- and 54-molecule averages rise above the noise level on the positive side. It is interesting that the two cross-correlation functions are identical within the noise level. The situation is echoed in figs. 2(*f*) for the (1, 3) element of the $T_R$–$H_R$ mixture.

Fig. 2(g) and (*h*) illustrate the useful case (experimentally) of mixtures of the $T_S$ enantiomer in the $H_R$ species. In this case there is a slight imbalance between the *R* and *S* enantiomers, the average over 108 molecules exists and is no longer identical with the average over the 54 $T_S$ molecules in the mixture. By comparing accurately the behaviour in the laboratory frame of the three mixtures, $H_S$–$H_R$, $T_S$–$H_R$ and $T_R$–$H_S$, there will be differences, on the basis of fig. 2(*g*) and (*h*), which can be used with the aid of computer simulation to give precise information on the

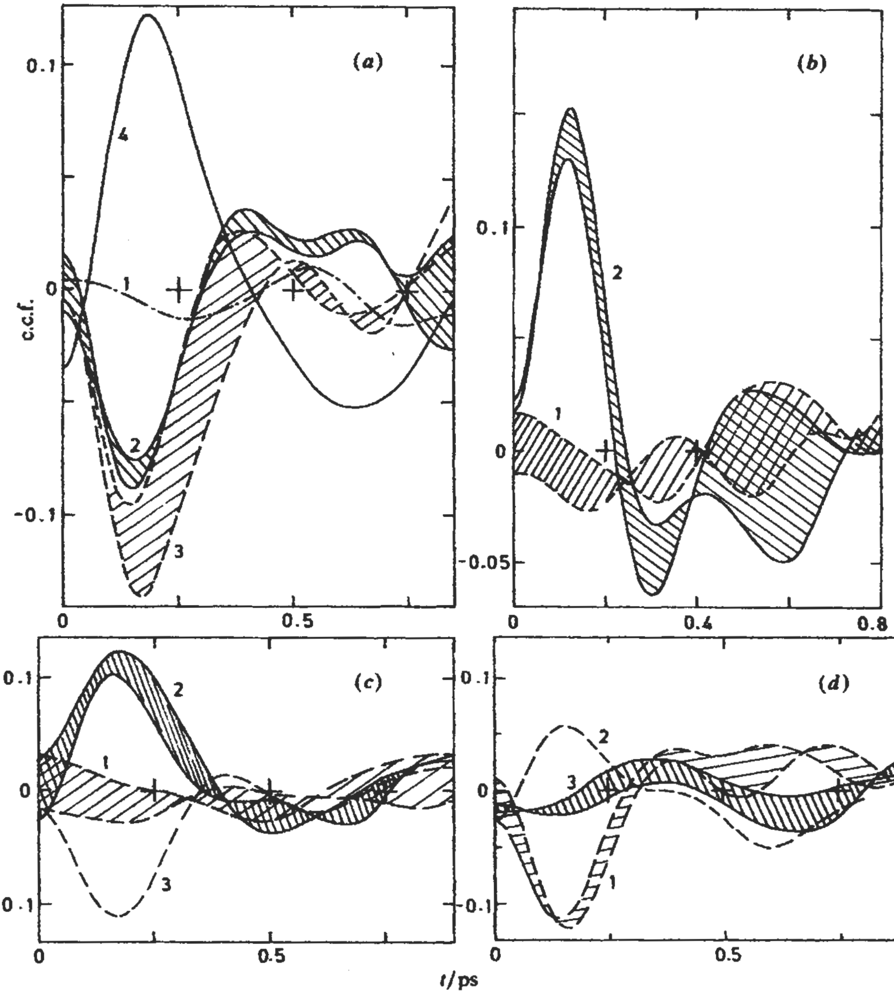

**Fig. 2.** (*a*) The (1, 3) switching element, moving-frame cross-correlation function for a mixture of $H_R$ in $H_S$ (chlorofluoroacetonitrile): (1) 108 molecules of $H_R$ in $H_S$, 54 *R* molecules in the racemic mixture, 54 *R* molecules in 108 *R* molecules and 54 *S* molecules in the racemic mixture. The cross-correlation functions are normalised as discussed in the text. The hatching denotes noise level (the difference between two successive runs). (*b*) (3, 1) switching element c.c.f., $H_R$–$H_S$: (1) 108 molecules of $H_R$ in $H_S$ and (2) 54 molecules of $H_R$ in the racemic mixture. (*c*) (1, 3) switching element c.c.f., $T_R$–$T_S$ (*i.e.* the racemic mixture of tritiated chlorofluoroacetonitrile): (1) 108 molecules of $T_R$ in $T_S$, (2) 54 *S* molecules in the racemic mixture and (3) 54 *R* molecules in the racemic mixture. (*d*) (3, 1) switching element c.c.f., $T_R$–$T_S$: (1) 54 *S* molecules, (2) 54 *R* molecules and (3) 108 molecules of $T_R$ in $T_S$. (*e*) (1, 3) element, $T_S$–$H_S$ mixture: (1) 108 molecules and (2) 54 $T_S$ molecules. Note that the (1, 3) element now exists when averaging over 108 molecules. (*f*) As for (*e*), $T_R$–$H_R$. (*g*) (3, 1) element, $T_S$–$H_R$ mixture: (1) 108 molecules and (2) 54 $T_S$ molecules. By symmetry, the 108 element exists just above the noise of the simulation. (*h*) (3, 1) element, $T_R$–$H_S$ mixture: (1) 108 molecules and (2) 54 $T_R$ molecules.

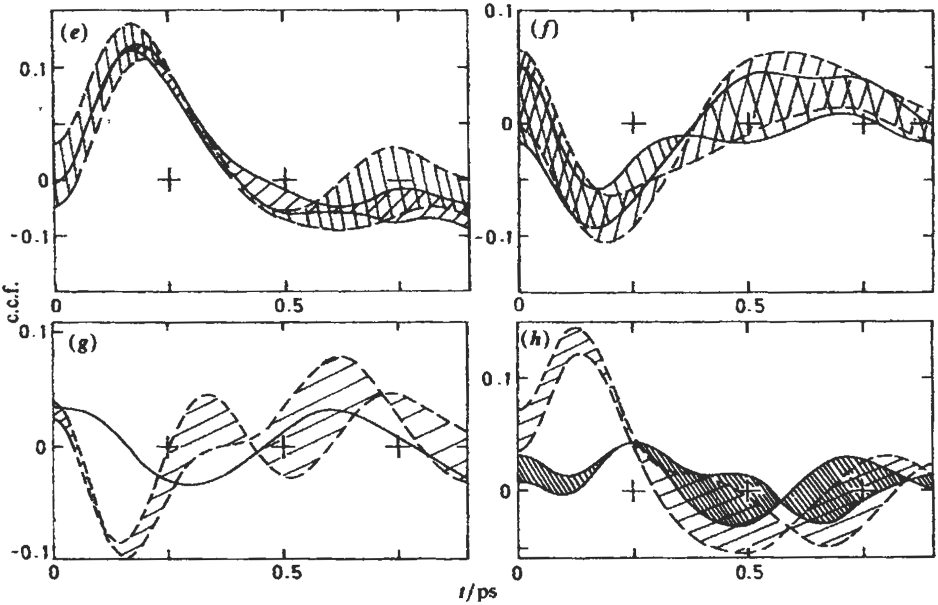

**Fig. 2** (*cont.*)

cross-correlation between rotation and translation. All other elements being almost equal, this will be the only dynamical difference between, for example, the $H_S$–$H_R$ and $T_S$–$H_R$ mixtures, and therefore laboratory-frame spectroscopic differences between $H_S$–$H_R$ and $T_S$–$H_R$ can be attributed directly to the influence of the (3,1) [or (1, 3)] moving-frame elements on observable spectra. This is therefore another method of studying the dynamical correlation between rotation and translation. This type of comparison can be extended to, for example, (i) $T_S$–$T_R$ compared with $T_S$–$H_R$, (ii) $T_S/T_R$ compared with $H_S$–$T_R$ and (iii) $H_S$–$H_R$ compared with $H_S$–$T_R$.

In each of the cases (four in all), the (3, 1) and (1, 3) elements will vanish in the 'balanced' racemic mixtures (*i.e.* those with the same isotope in opposite enantiomers) but will have a finite dependence on time in the mixtures with different isotopes. Moreover, different types of isotopic substitution could be used to provide a great deal more information as discussed already in this paper. These spectral comparisons will have to be made, however, with precision, following the methods of isotopic dilution already in use in infrared spectroscopy.

## CONCLUSIONS

Cross-correlations between rotation and translation exist in the moving frame of reference for models of the enantiomers and racemic mixture of chlorofluoroacetonitrile and its tritium derivative.

By comparing accurately the behaviour in the laboratory frame of the appropriate isotope mixtures, precise information can be extracted on the effect of the cross-correlations in the laboratory frame of reference.

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