Coherent Enantiomer-Selective Population Enrichment using Tailored Microwave Fields**

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Abstract: We report the experimental demonstration of coherent enantiomer-selective enrichment of chiral molecules by employing a novel microwave five-pulse scheme. Our results show that enantiomers can be selectively transferred to a rotational level of choice by applying sequences of resonant microwave pulses in a phase- and polarization-controlled manner. This is achieved by simultaneously exciting all three kinds of electric-dipole allowed rotational transitions and monitoring the effect on a fourth rotational transition of choice. Using molecular beams, we apply our method to two chiral terpenes and obtain a 6% enantiomeric enrichment, which is a one order-of-magnitude larger than that recently reported in a buffer-gas cell experiment. This approach establishes a robust scheme for controlled manipulation of enantiomers using tailored microwave fields and opens up new avenues for chiral purification and enrichment that can be used in a broad scope of analytical or spectroscopic applications.

Chirality is ubiquitous in nature and involved in many aspects of life, making it an important phenomenon to understand.¹ A molecule that cannot be superimposed with its mirror image by pure translation and/or rotation is termed chiral, with the non-identical mirror images being called enantiomers. Enantiomeric pairs have identical physical properties (despite the predicted small contributions due to parity-violating weak interactions),^{2,3} while their chemical and biochemical properties can dramatically differ. Due to these differential behaviors, the development of sensitive spectroscopic methods that can differentiate and/or separate molecules of opposite handedness, particularly on complex sample mixtures, are of utmost importance.

In a collaborative effort, we have recently developed a technique for enantiomer differentiation using microwave (mw)

fields that can be tailored to the molecule of study.^{4–8} This technique relies on the fact that the dipole moments (distribution of charge) of enantiomers are mirror images of each other. As a result, the scalar triple product of the dipole-moment components $\vec{\mu}_a \cdot (\vec{\mu}_b \times \vec{\mu}_c)$ within the principal moment of inertia coordinate system of molecules has opposite sign between enantiomers (see also Figure 1 of Ref.⁹). This feature is exploited by a combined, resonant excitation of rotational energy levels that are connected by a-, b-, and c-type dipole-allowed transitions in a microwave three-wave mixing (M3WM) approach.^{4,7,10,11} We have demonstrated species-selective enantiomer differentiation on a number of different chiral molecules, mostly terpenoids, such as carvone,⁵ menthone,¹² 4-carvomenthenol,⁶ alcohols such as 1,2-propanediol,^{4,7} and solketal.¹⁰

In addition, schemes to achieve enantio-separation¹³ and even purification¹⁴ by purely optical means have been proposed. A cyclic population transfer (CPT) process¹³ has been suggested as a way to perform enantio-separation based on the sign difference of the Rabi frequencies between enantiomers^{15–17}. This idea can also be exploited to achieve enantiomeric enrichment by performing population transfer processes on three rovibrational quantum states connected by three mutually perpendicular (linearly polarized) microwave (mw) fields as recently demonstrated by Patterson and co-workers in a buffer gas cell.¹⁸

In this communication we demonstrate an experimental implementation of this latter experiment that allows for a one order-of-magnitude enhancement in the achieved enantiomeric enrichment of a rotational level of choice with a given enantiomer. Figure 1 illustrates this approach, in which three rotational transitions, each corresponding to one of the electric-dipole allowed rotational transitions, are simultaneously excited in a mutually orthogonal direction and in a phase-controlled manner. The induced population difference is then probed by applying a fourth pulse resonant with a rotational transition connected to either $|2_{02}\rangle$ or $|3_{13}\rangle$, as shown in Figure 1b. The observed magnitude of these probe transitions is dependent on the population difference between rotational levels and serves as a trace of the achieved enrichment.

The experiment consists of a modified chirped-pulse Fourier transform microwave (CP-FTMW) spectrometer used for M3WM, as reported elsewhere.^{5,6,12} Only minimal modifications to our existing M3WM experimental setup were nec-

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essary. In order to broadcast the multiple pulse sequences in all three orthogonal polarizations, we equipped our instrument with a new dual-polarization horn antenna. In the first set of experiments we used menthone, a chiral terpenoid, as well as carvone. Figure 1a shows the rotational energy levels of menthone (conformer A)¹² involved in the experiments reported here and the pulse sequence employed. As in the typical M3MW approach, two mw pulses (blue and black in Figure 1a) were applied to coherently generate the enantiomer-dependent signature (green in Figure 1a) between the energy levels $|1_{01}\rangle$ and $|2_{12}\rangle$. To achieve population transfer, we added a third mw pulse connecting these same energy levels, to transfer the coherence difference between the enantiomers into a population difference. Simulations of the system’s time evolution based on density matrix formalism and Bloch equations can be found in the SI. This induced population difference is opposite between enantiomers, and its extent varies as the transfer pulse phase is changed.

In our experiment, the resulting signal can be influenced by several simultaneously competing events. This three pulse sequence mentioned above creates an environment in which one-, two-, and/or three-photon processes can occur. Simply driving a single rotational transition, such as the transfer pulse between $|1_{01}\rangle \rightarrow |2_{12}\rangle$ in Figure 1a, induces a one-photon process as in traditional Fourier transform microwave spectroscopy (FTMW). Negating the emitted photon, the traditional M3MW experiment comprises of a two-photon process. When combined, these two processes interfere either constructively or destructively depending on the relative phases (laboratory controlled) between the one- and two-photon paths. The three-photon situation arises when the same molecule is simultaneously driven by the two “arms” of this interferometer and leads to enantiomer-selective enrichment. It is important to note that this enrichment competes with the two- and one-photon processes, and it is only achieved when the same molecule is simultaneously driven by the three fields. In contrast, when the interaction is sequential or the molecular response arises from different molecules, a more simple interferometric response that mostly depends on the relative phases of the two emitted fields takes place. This can be monitored by simply applying three orthogonal fields and monitoring the phase-dependent signal at the one-photon frequency. Both phenomena were explored and observed in this work as illustrated in Figure 1.

Prior to performing the three-pulse experiment, the relevant nutation curves were measured so that the optimal pulse sequence was applied (as given in the SI). The maximum chiral signal for the M3MW experiment^{5,7,10,11} was observed at Rabi flip angles of $\frac{\pi}{2}$ (120 ns, mw drive) and π (350 ns, RF twist). These values were fixed to maximize the signal response in our experiment. The final pulse scheme is summarized in Figure 1a. Both the pulse duration and the relative phase of the

third pulse at 3713.18 MHz were systematically changed in order to map the evolution of the interferometric response. The pulse duration was incremented in steps of 40 ns from 0 to 400 ns. This latter value corresponds to the determined optimal $\frac{\pi}{2}$ pulse condition observed in the single-photon direct excitation at 3713.18 MHz. The phase was varied in steps of 18 degrees (0.31 rad) from $-\pi$ to π rad. See Figure S1 for more experimental details.

Figure 2 shows the observed variation of the amplitude of the $|2_{12}\rangle \rightarrow |1_{01}\rangle$ transition of menthone at 3713.18 MHz following the pulse scheme displayed in Figure 1a. We performed separate measurements using nearly enantiopure commercial samples of (+)- and (-)-menthone (conformer A) as well as a commercially available mixture of isomers (which we recently analyzed to be non-racemic but having (-)-menthone in excess¹²). The signal intensity is normalized with respect to the basic M3WM signal, and the results show clear phase dependence in the observed signal upon changes in the phase of the transfer pulse. As expected, the results are opposite for the enantiomers (Fig. 2a and b).

For enantiopure menthone, an almost complete destructive interference was observed when the phase of the transfer pulse was shifted by $\frac{\pi}{2}$ radians with respect to the drive and twist pulses. This is illustrated by the blue minima shown in Fig. 2a and 2b. For (-)-menthone, a signal modulation of 83% compared to the basic M3WM signal level was recorded. The relative position of this modulation gives accurate information about the phase and magnitude of the sum-frequency generated signal. First, the minimum appears at a phase where the two- and one-photon processes interfere destructively, giving us the experimental phase associated with the enantiomer in excess. Second, from the relative location in the vertical axis (pulse duration), one can extract a measure of the ee. This is due to the fact that the magnitude of the two-photon path (which corresponds to the chiral signal in M3WM) is directly proportional to the ee^{5,7} and is “probed” by the one-photon process via interference. The magnitude of the resulting interference depends upon the relative magnitude of the signals arising from both one- and two-photon processes. The larger the ee, the larger the one-photon path signal will have to be to yield maximum interference and thus minimum signal.

In Fig. 2c, we show the results of this experiment for a menthone mixture comprised of approximately 80% (-)- and 20% (+)-menthone.¹² While for the enantiopure sample the optimal pulse duration for maximum destructive interference is located at 150 ns for the transfer pulse, it is shifted to lower values in the mixture, which indicates a smaller ee. Minimum and maximum interferences appear at the same transfer pulse phases as those for enantiopure (-)-menthone, confirming thus that the (-) enantiomer is in excess in the mixture. Apart from an accurate determination of the enantiomer in excess in a mixture, this pulse sequence can also be used to detect weak chiral

signatures in a similar manner to that of homodyne interferometry.

In a second set of experiments we used carvone. We applied the corresponding pulse sequence to an enantiopure sample of (-)-carvone (conformer EQ2), using a loop of transitions previously reported⁵: ($|2_{02}\rangle \rightarrow |3_{12}\rangle$ at 5557.91 MHz (100 ns), $|3_{12}\rangle \rightarrow |3_{13}\rangle$ at 459.75 MHz (800 ns) and $|2_{02}\rangle \rightarrow |3_{13}\rangle$ at 5098.12 MHz. As for menthone, both pulse duration and phase of $|2_{02}\rangle \rightarrow |3_{13}\rangle$ were systematically scanned from 0 to 400 ns and $-\pi$ to π rad respectively. The energy level scheme used is shown in Figure 1b (central triangle), while the interferometric response is displayed in Figure 2d. The relevant nutation curves can be found in the supplementary materials. It is worth noting here that (-)-carvone shows opposite behavior compared to that of (-)-menthone. As stated above, the sign of the phase depends on the quantity $\vec{\mu}_a \cdot (\vec{\mu}_b \times \vec{\mu}_c)$. This product is positive for (-)-menthone (conformer A), and it is negative for (-)-carvone (conformer EQ2).^{5,12} Because of this, it is expected that these two samples will show opposite behavior (neglecting dispersion effects of the components in the mw circuit) under the same relative phase conditions.

This experimental approach can also be used to selectively populate or depopulate a rotational level with an enantiomer of choice. To prove this, the induced population variation between rotational levels can be transformed into measurable coherences. Therefore, in order to probe this effect, after the three-pulse sequence, an additional pulse connected to either $|2_{02}\rangle$ or $|3_{13}\rangle$ was applied. We chose two different a-type rotational transitions: $|3_{13}\rangle \rightarrow |2_{12}\rangle$ at 3591.12 MHz and $|2_{02}\rangle \rightarrow |1_{01}\rangle$ at 2469.12 MHz (see Figure 1b). Note that the relative phases and polarizations of these pulses are unimportant as the magnitude of the observed signal directly depends on the population difference between rotational levels. Also, for a given rotational level, the enantiomeric enrichment will be mainly limited by the thermal population of the undesired enantiomer. In order to maximize the population differences and therefore enhance the effect of our enantiomer-selective enrichment, we preceded our experiment with a strong chirp pulse fulfilling the rapid adiabatic passage (RAP)¹⁹ regime. In this regime, the population of the involved rotational levels can be swapped with higher, less populated rotational states. This was done in our experiment by applying a short (250 ns) chirp pulse spanning 10 MHz (4780-4790 MHz) around $|4_{14}\rangle \rightarrow |3_{13}\rangle$ at 4785.14 MHz. Although, in principle, this adiabatic pulse is not strictly necessary, we did not observe a clear effect in our probe transitions when it was not applied. The relevant rotational levels as well as the experimental pulse sequence are shown in Figure 1b. Note again that the applied polarizations are only important for the rotational transitions involved in the M3WM loop, while the RAP pulse as well as those used to probe the induced population enrichment can be applied in any polarization (see Figure 1a top-left).

The results from this five-pulse sequence are shown in Figure 3. First, we recorded the molecular response of (-)-carvone using the rotational transition $|3_{13}\rangle \rightarrow |2_{12}\rangle$ at 3591.12 MHz as a gauge of enantiomeric enrichment. As it can be seen in Figure 3a (blue), the intensity varies sinusoidally with the phase (ϕ_1) of the applied $|3_{13}\rangle \rightarrow |2_{02}\rangle$ pulse at 5098.12 MHz, which clearly shows that the molecules are being selectively transferred. As shown in the SI, the behavior of the opposite enantiomer can be reproduced by simply shifting the phase of any of the drive pulses by π rad. This is shown in the red trace where we performed the same experiment applying in this case a pulse at 459.75 MHz with a phase of π rad with respect to the others. As expected, the observed behavior is opposite between enantiomers, showing that the two enantiomers can be selectively manipulated. In a second set of experiments, we reproduced these two pulse sequences using now the rotational transition $|2_{02}\rangle \rightarrow |1_{01}\rangle$ at 2469.12 MHz as our population trace. The results can be seen in Figure 3b. The sinusoidal trend is clearly apparent and exhibits a phase shift of π rad respect to that of $|3_{13}\rangle \rightarrow |2_{12}\rangle$ at 3591.12 MHz. These opposite trends confirm that our experiments exchange population of (-) or (+)-carvone between the states $|2_{02}\rangle$ or $|3_{13}\rangle$. While one enantiomer is promoted to the upper $|3_{13}\rangle$ state, the other is simultaneously transferred to the lower $|2_{02}\rangle$ state and viceversa. The extent of the achieved enrichment is shown in Figure 4c and d. In both cases we observed an enrichment of about 6%. Recently, using buffer-gas cooled 1,2-propanediol, an enantiomeric enrichment of about 0.6% was reported.¹⁸ In our experiment we obtained an enhancement of one order-of-magnitude. This can be mainly attributed to the lower rotational temperature reached in the molecular beam and the enhanced contrast from the additional RAP pulse. Although a 6% enrichment can be considered modest, we believe that this can be significantly enhanced by increasing the mw power of the applied electric fields as well as more advanced RAP pulse schemes.

In summary, we have demonstrated an experimental approach to achieve enantiomer-selective enrichment in chiral molecules using only microwave radiation. The experiment is based on the previously demonstrated M3WM technique with the addition of two mw pulses in a phase- and polarization-controlled manner. The extent of our enrichment is then traced by the magnitude of a fourth rotational transition whose intensity is enantiomer-dependently modulated upon the relative phases of the applied mw fields. We achieved an enantiomer enrichment of about 6% which represents an one order-of-magnitude improvement compared to that recently reported in a buffer-gas cell¹⁸. The pulse scheme presented here leads to either population and/or depopulation of a particular rotational state with a chosen enantiomer while its counterpart is selectively transferred to a different rotational level. Combined with more sophisticated laser-pulse schemes

and/or electrostatic deflectors,^{16,20} excited and non-excited enantiomers could be selectively manipulated leading to significant enantiomeric enrichment or even separation. Additionally, our method exploits the traditional and well-known features of rotational spectroscopy and therefore, it is highly sensitive, resonant and mixture compatible. These particular attributes make it possible to assess its full analytical potential beyond basic research applications.

Keywords Rotational Spectroscopy · Population Transfer · Enantiomers · Chirality

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Figure 1 (a) Energy level schematic of menthone (conformer A) exploited for the microwave three-pulse technique. Timing scheme of the three mw pulses applied (bottom). The pulse durations were optimized to achieve maximum coherence through a drive pulse between the $|2_{11}\rangle$ and $|1_{01}\rangle$ energy levels and maximum coherence transfer via a twist pulse to the $|2_{12}\rangle$ and $|1_{01}\rangle$ energy levels. The transfer pulse, resonant with the $|2_{12}\rangle$ and $|1_{01}\rangle$ energy levels, transfers the induced coherence for the two enantiomers into a population difference depending upon the relative phase. The interference between the one-photon ($|1_{01}\rangle \rightarrow |2_{12}\rangle$) and the two-photon excitation ($|1_{01}\rangle \rightarrow |2_{11}\rangle \rightarrow |2_{12}\rangle$) is either destructive or constructive depending on the enantiomer, and it was monitored through the signal magnitude at 3713.18 MHz. (b) Relevant rotational levels of carvone used to determine the achieved enantiomer-selective population enrichment. The $|2_{02}\rangle$ and $|3_{13}\rangle$ rotational states are populated or depopulated with the desired enantiomer depending upon the relative phase of the applied pulse $|3_{13}\rangle \rightarrow |2_{02}\rangle$ at 5098.12 MHz (green). The orientation of the polarized microwave fields used in the experiment is highlighted in the top-left. Probe transitions are shown in red. Their corresponding excitation pulses were applied in the same polarization as the population transfer pulse in dark green.

Figure 2 Experimental signal amplitude variation for the $|2_{12}\rangle \rightarrow |1_{01}\rangle$ transition at 3713.18 MHz for menthone (conformer A) employing the three-pulse scheme in Figure 1a. For each measurement, the dependence of the signal amplitude of this transition is given as a function of the phase and duration of the transfer pulse at 3713.18 MHz. The intensity is normalized with respect to the M3WM signal when the transfer pulse is not applied. Measurements were performed on (-)- and (+)-menthone using the same pulse sequence (panels (a) and (b) respectively). Panel (c) shows results for a commercially available mixture of menthone isomers. Panel (d) shows the results for (-)-carvone when monitoring the amplitude of $|2_{02}\rangle \rightarrow |3_{13}\rangle$ at 5098.12 MHz with respect to the phase and pulse duration of the transfer pulse applied at the same frequency.

Figure 3 (a) Experimental evidence of enantiomer-selective enrichment in the $|3_{13}\rangle$ rotational level. The effect is monitored on the phase-dependent amplitude of the $|3_{13}\rangle \rightarrow |2_{12}\rangle$ transition at 3591.12 MHz. The blue trace is the observed signal for (-)-carvone while the red trace shows the (+)-carvone response when the phase of the RF pulse at 459.75 MHz was shifted by π rad. ϕ_1 , the phase of the drive transition 5098.12 MHz, was sequentially changed in 18 degrees (0.31 rad) steps and the molecular response averaged 25000 times per phase. (b) Experimental enantiomer enrichment in the $|2_{02}\rangle$ rotational transition. The dataset was built in a similar manner as described in (a). The population enrichment was probed in this case through the magnitude of the $|2_{02}\rangle \rightarrow |1_{01}\rangle$ rotational transition at 2469.12 MHz. (c) and (d) show the normalized enantiomer-selective population enrichment in $|3_{13}\rangle$ and $|2_{02}\rangle$. An enrichment of 6% is achieved.

Figure 4 Shuffling enantiomers with microwave fields.

Enantiomer-selective population enrichment can be achieved by simultaneously exciting a chiral sample with three orthogonal microwave pulses. Careful control of the applied fields allows for enantiomers to be selectively transferred to a rotational level of choice. Combined with further developments, this result has the potential enable new avenues for chiral analysis.

1 Graphical Abstract