

# Capturing the Chirality of Photoexcited States with Ultrafast Circular Dichroism

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**Abstract:** Chiral molecules exist in two forms, called enantiomers, which are mirror images of each other but non-superimposable. Even though enantiomers share most chemical and physical properties, they may differ greatly in their (bio-)chemical activities, which turns chirality into a key design feature for (bio-)chemical function. In this spirit, the incorporation of chiral structures into photochemical systems has emerged as a powerful strategy to control their functions. For example, uni-directional molecular motors, chiral photocatalysts, and chiral metal nanostructures permit new levels of stereocontrol over mechanical motion, energy transfer, and electric charge-carriers on the nanoscale. However, the direct characterization of the underlying chiral photoexcited states remains a formidable experimental challenge - especially in the native solution phase of many photochemical processes. Crucially, this requires analytical techniques that combine a high chiral sensitivity in solution with ultrafast time resolution to capture the excited state dynamics. This brief perspective article presents recent progress in the development of ultrafast chiral spectroscopy techniques that address this challenge.

**Keywords:** Chirality · Photochemistry · Structural dynamics · Ultrafast spectroscopy



**Malte Oppermann** studied physics in Bremen (Germany). In 2013 he obtained a PhD in physics from Imperial College London (UK), where he studied the ultrafast ionization and fragmentation dynamics of small gas-phase molecules in intense laser fields under the supervision of Prof. Jon Marangos. Afterwards he joined the group of Prof. Majed Chergui at EPFL Lausanne (Switzerland), where he was a postdoctoral

researcher and laboratory manager from 2015–2022. During this time, he shifted his research focus to the photochemistry of (bio-)chemical systems in solution and the development of ultrafast spectroscopy techniques in the deep ultraviolet spectral regime. Since 2022 he is an assistant professor at the Department of Chemistry at the University of Basel, where he develops ultrafast chiral spectroscopy techniques to capture (bio-)molecular dynamics in solution.

## 1. Introduction

All life is chiral. Naturally occurring amino acids exist in a single enantiomeric form, a phenomenon that is called homochirality. As a direct consequence, natural proteins and enzymes have chiral structures, which play an important role in their molecular interactions. For example, their binding of natural and synthetic drugs has chiral selectivity with drastic consequences for their therapeutic activities. Here molecular chirality reveals a fascinating double role: it is both a marker of molecular structure and a functional design feature. The identification and control of molecular chirality is thus an essential requirement for the design and synthesis of (bio-)molecular systems with tailored (bio-)chemical functionalities and is particularly relevant in the pharmaceutical, food and fragrance industries.

In this respect, it is perhaps not surprising that an impressive range of strategies have been developed to characterize and control the chirality of molecular systems and their transformations in their electronic ground state. However, extending these

approaches to electronically excited states, and thus to the realm of photochemistry, has remained particularly challenging. Indeed, the stereochemistry of typical excited electronic states is notoriously difficult to control due to their short lifetime, high chemical reactivity, weak intermolecular interactions and increased conformational flexibility.<sup>[1]</sup> However, despite these challenges, the past decade has seen remarkable progress in the synthesis of chiral molecular systems for photochemical applications,<sup>[2,3]</sup> for example: light-driven uni-directional molecular motors for nanoscale synthetic machines,<sup>[4]</sup> (metallo-)organic systems for generating circularly polarized luminescence,<sup>[5,6]</sup> chiral photocatalysts for enantioselective synthesis,<sup>[7]</sup> and chiral metal nanoparticles for chiral sensing and enantioselective photochemistry.<sup>[8,9]</sup> Through the chirality of the involved photoexcited states, these systems achieve unprecedented levels of stereocontrol of mechanical work, energy transfer, electric charge carriers, and optical properties on the nanoscale. However, resolving the chirality of photoexcited states directly has remained a formidable experimental challenge, despite its potential to advance the rational design and optimization of chiral photoactive molecules and materials.

Closing this gap requires techniques that can capture the stereochemistry of photoexcited molecular systems with femtosecond (1 femtosecond =  $10^{-15}$  seconds) time resolution – the natural scale of the vibrations, formation and breaking of chemical bonds, and many photochemical phenomena.<sup>[10]</sup> Most ultrafast spectroscopy techniques achieve the required time resolution through a so-called pump-probe scheme, where a first laser pulse (the pump) photoexcites the molecular system and a second pulse (the probe) records the response of the system at increasing time delays. In this respect, the time resolution is only limited by the duration of the pulses interacting with the sample. However, adopting this scheme for chiral spectroscopic techniques is particularly challenging due to the weak chiral signatures of typical chiral molecules in solution, which are usually three orders of magnitude smaller than comparable achiral signals. Consequently, detailed ultrafast chiral spectroscopic studies with sub-picosecond resolution (1 pico-second =  $10^{-12}$  seconds) have thus far only been achieved for a handful of chiral photochemical systems with exceptionally large signal strengths, most notably ruthenium<sup>[11]</sup> and iron<sup>[12]</sup> based polypyridines, bi-naphthol derivatives,<sup>[13,14]</sup> myoglobin<sup>[15,16]</sup> and chiral poly-

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meric systems.<sup>[17–19]</sup> The field of ultrafast chiral photochemistry is thus still largely unexplored.

With a growing interest in chiral excited state phenomena across chemistry, physics and material science, this is a timely challenge. While this has recently motivated the development of several exciting new approaches to ultrafast chiral spectroscopy,<sup>[20–23]</sup> the present article focuses on a technique called electronic circular dichroism. I will then present my recent contributions to extend this approach to the analytically relevant deep ultraviolet (UV) regime and indicate its potential impact on the field of chiral photochemistry *via* two recent studies.

## 2. Electronic Circular Dichroism

The most established approach for characterizing the chirality of molecular systems in solution is circular dichroism (CD) spectroscopy, which measures the absorption difference of left- and right-circularly polarized light.<sup>[24]</sup> While CD can be measured across the electromagnetic spectrum, we focus here on electronic CD (ECD), which is caused by electronic transitions in chiral molecules. Generally, ECD arises from the interference of electric-dipole and magnetic-dipole transition moments (and possibly weak electric quadrupole transition moments), which can thus be associated with a helical charge displacement during the transition.

However, the strongest ECD signals in chiral molecules are usually caused by groups of electric-dipole transitions, which are coupled electrostatically (an effect known as excitonic coupling) and thus excited collectively (Fig. 1).<sup>[25]</sup> The associated coupling of several linear charge displacements may then contain a helical contribution without the need for any magnetic-dipole transitions. As electric-dipole transitions are usually associated with light absorbing chemical groups within a molecular system (so-called chromophores), ECD is sensitive to their local and global geometrical arrangement within a chiral molecular system. This illustrates how ECD encodes structural information of molecular systems – even in solution phase. In this respect, ECD spectroscopy is especially well-established in the far and middle UV regimes <300 nm, where it is routinely used to characterize the equilibrium structures of proteins, DNA and chiral organic complexes, *via* the chiral distributions of important UV-chromophores, such as peptide bonds, amino acids, nucleotides and small organic ligands, respectively. Importantly, ECD spectra can offer high degrees of spectral specificity even for closely overlapping transitions, as the helical arrangement of the associated transition dipoles is directly encoded into ECD couplets with characteristic sign changes (Fig. 1). However, ECD is a relatively weak effect, which can be characterized by a molecule's absorptive dissymmetry factor  $g_{\text{abs}} = \Delta\epsilon/\epsilon$ , the ratio of its molar ECD ( $\Delta\epsilon$ ) and molar extinction coefficient ( $\epsilon$ ). Organic molecules in solution rarely exceed values of  $g_{\text{abs}} = 10^{-3}$ , especially at probe wavelengths  $\lambda > 300$  nm,<sup>[26]</sup> meaning that their ECD is typically 1000-times weaker than their total absorption.

## 3. Ultrafast Circular Dichroism

### 3.1 State-of-the-art

From a technological point of view, ECD spectroscopy has several advantages: it is based on table-top instrumentation with simple, well-established data-treatment protocols, low sample preparation and volume requirements and fast data acquisition (DAQ) speeds. Crucially, ECD offers chiral sensitivity in the optical spectral regime. This holds the promise of taking ECD to the ultrafast time domain *via* a pump-probe scheme, where circularly polarized probe pulses measure the ECD at increasing time delays after the pump pulse. As the ECD measurement is confined to the duration of the probe pulses, one may thus follow changes in the chirality of the excited molecules with femtosecond time resolution. This potential of time-resolved CD (TRCD) was first

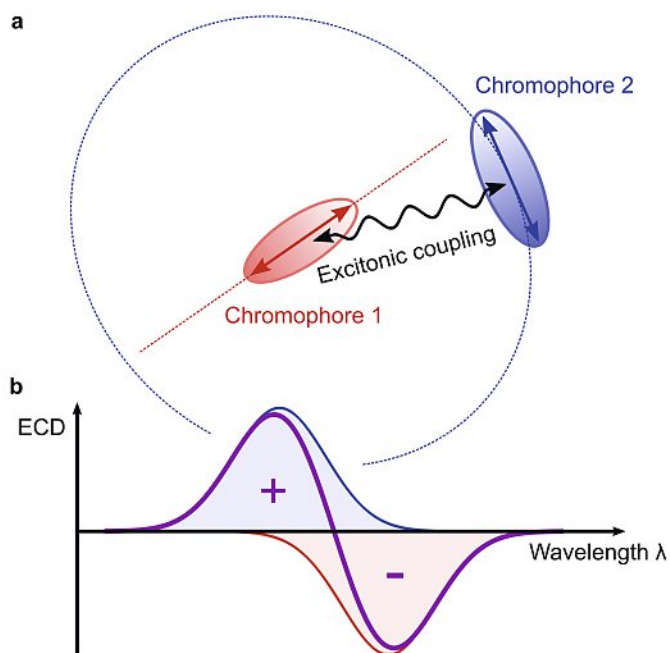


Fig. 1. a) Schematic representation of two excitonically coupled chromophores that undergo a collective excitation of their electric-dipole transition moments (solid arrows). When the chromophores are arranged in a chiral geometry, the associated charge displacements contain helical contributions, which is illustrated from the point of view of chromophore 1, for which the charge motion on chromophore 2 provides a circular component. This affords a rotational strength to the electronic transition on chromophore 1 (and *vice versa* for chromophore 2) b) The chromophore arrangement is directly encoded in the resulting ECD spectrum (purple line), which displays a characteristic sign change, indicating a positive exciton couplet.

demonstrated by Kliger and co-workers in 1985 with nanosecond resolution,<sup>[27]</sup> followed by a picosecond instrument by Xie and Simon in 1989.<sup>[28]</sup> The first femtosecond experiments were achieved by Hache and co-workers in 2005.<sup>[15]</sup> However, after these pioneering contributions, further progress has been notably limited (see the recent review by Chagenet and Hache).<sup>[29]</sup> Indeed, there have only been few isolated TRCD studies with sub-picosecond time resolution, which can generally be attributed to three technical challenges.

First, since the ECD of typical chiral molecules is in the order of  $10^{-3}$  of their absorbance, TRCD requires a sensitivity of  $10^{-5}$  to resolve small photoinduced changes. While current state-of-the-art ultrafast transient absorption (TA) set ups have demonstrated noise levels on the order of  $10^{-6}$ , this nevertheless still requires the in-house development and careful optimization of specialized instrumentation to minimize DAQ times to a practical level.<sup>[30]</sup>

Second, efficient ultrafast TRCD measurements require the polarization control of broadband femtosecond laser pulses. In the most widely adopted strategy, the probe pulse polarization is switched between left- and right-circular with an active polarization switch, for example a Pockels cell<sup>[15,31,32]</sup> or a photoelastic modulator.<sup>[33]</sup> It is then possible to directly record the differential absorption between the two polarization states with technology commonly used in TA instruments. Generally, these switches differ with regards to their maximum spectral bandwidth, acceptance angle, maximum switching rate, sophistication of control electronics, and cost. In addition, alternative strategies have been implemented with their own advantages. High measurement sensitivities and DAQ speeds have been achieved in a so-called ellipsometric scheme, where the change in ellipticity of the probe pulse is recorded after passing a chiral sample.<sup>[34–37]</sup> Two recent TRCD implementations avoided complex control electronics by

generating probe pulse pairs with opposite circular polarization states from passive optical elements: first by generating a mirror-image polarization state through a series of calibrated mirror reflections,<sup>[38]</sup> and second *via* a polarization grating.<sup>[19]</sup> Finally, an interferometric approach to steady-state ECD measurements has been demonstrated with femtosecond pulses in the visible regime.<sup>[39,40]</sup> While this could potentially enable sensitive, broadband TRCD measurements, a pump-probe implementation has not yet been reported.

Third, broadband detection is extremely challenging due to the polarization sensitivity of dispersive and reflective optics. This severely distorts TRCD spectra and limits their absolute measurement sensitivity.<sup>[41]</sup> Indeed, most polarization spectroscopy techniques, including ECD, are usually not limited by the instrument's noise level, but by the size of its polarization artifacts, which in most cases cannot be subtracted *via* a simple baseline measurement. This has restricted commercial steady-state ECD instruments and several TRCD setups<sup>[31,34,36]</sup> to monochromatic detection schemes, which strongly extend the DAQ time and limit spectral information. Nevertheless, broadband detection has been achieved in the visible regime  $>400$  nm,<sup>[19,32,35,37]</sup> the deep-UV covering 250–370 nm,<sup>[33]</sup> and recently over a very large bandwidth of 260–700 nm, albeit with a relatively high noise level of  $3 \times 10^{-4}$ .<sup>[17]</sup>

Despite these technological challenges, several research milestones have been achieved. The Kliger group first demonstrated the potential of broadband TRCD for capturing the structural dynamics of biological systems on a nano- to microsecond scale.<sup>[42]</sup> In this respect, Chagnenet, Hache and co-workers recently extended this scope by tracking the folding kinetics of peptides and DNA G-quadruplexes with TRCD on the micro- to millisecond scale.<sup>[43]</sup> The Hache group also achieved the first detailed kinetic studies with TRCD on the sub-picosecond time scale and reported excited state conformational changes in bi-naphthol derivatives,<sup>[13,14]</sup> an analysis of the excited state chirality of photoexcited ruthenium(II) tris(phenanthroline),<sup>[11]</sup> and sub-nanosecond conformational changes in myoglobin.<sup>[15,16]</sup>

As suggested by the excitonic coupling model for ECD, TRCD is highly suited to the investigation of aggregated photochemical systems. After early proof-of-principle experiments on merocyanine helical aggregates by Trifonov *et al.*,<sup>[32]</sup> Oum, Lenzer and co-workers extended this scope through detailed TRCD studies of the supramolecular chirality and electronic relaxation of chiral copolymer films.<sup>[17,18]</sup> Most recently, Ress *et al.* reported a detailed study of a chiral squaraine polymer in solution, focusing on the excitonic coupling dynamics between the squaraine units and demonstrating the exquisite sensitivity of TRCD to local chromophore interactions.<sup>[19]</sup>

### 3.2 Extension to the Deep Ultraviolet

As mentioned previously, the analytical capabilities of ECD are particularly attractive in the deep-UV region  $<300$  nm. However, this spectral range is still markedly underdeveloped in ultrafast spectroscopy,<sup>[44]</sup> as commonly employed femtosecond continuum sources are either limited by low photon fluxes (and thus higher shot noise) or rather narrow bandwidths (see for example the discussion in reference<sup>[45]</sup> and references therein). To address this challenge, and extend TRCD to the deep-UV, we employed a femtosecond continuum source that combines a high flux with a large bandwidth covering 250–370 nm, and an exceptional shot-to-shot intensity stability.<sup>[46]</sup> On this basis, we developed a broadband TRCD spectrometer<sup>[33]</sup> that suppresses polarization artefacts below the  $10^{-5}$  level and thus achieves an unprecedented absolute sensitivity of  $\pm 1 \times 10^{-5}$ . As displayed in Fig. 2, the set up uses a photoelastic modulator to achieve fast broadband shot-to-shot polarization state switching and probe detection at 20 kHz, thereby reaching the required noise levels in several minutes per TRCD spectrum. Importantly, it is now possible to acquire spectrally- and temporally-resolved TRCD maps with sufficient signal-to-noise to apply common spectro-kinetic data analysis tools<sup>[47]</sup> and extract the ECD spectra of the photoexcited molecules and their evolution in time. In combination, these technological developments have extended the scope of ultrafast chiral spectroscopy to new classes

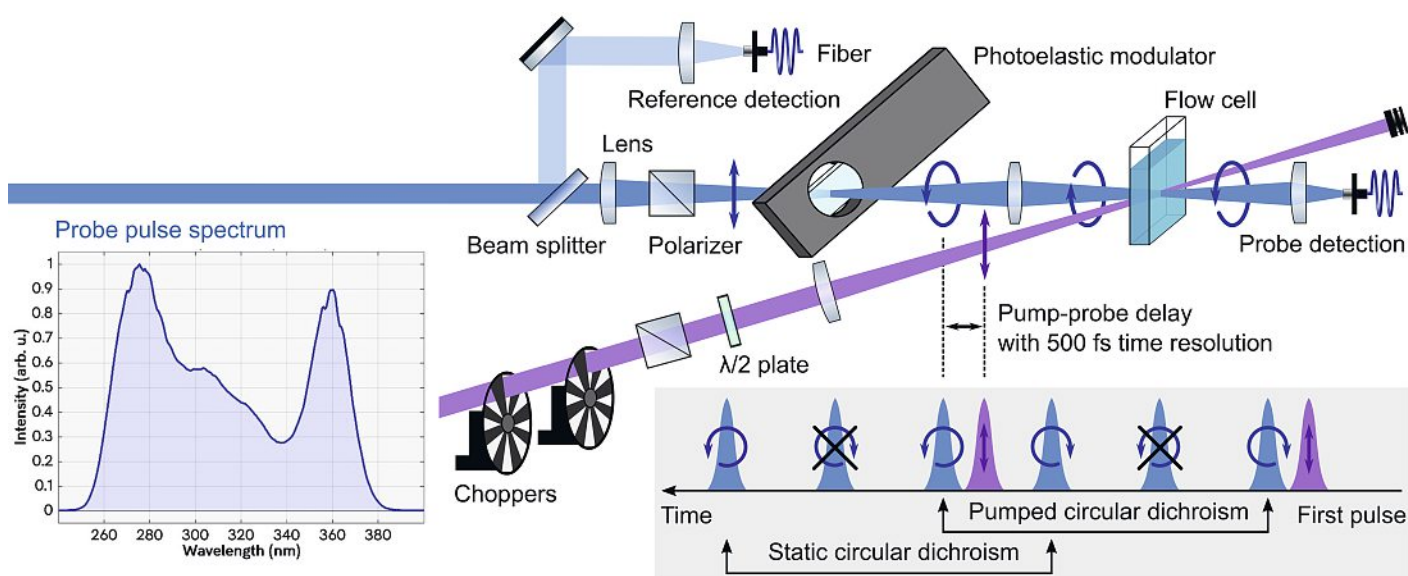


Fig. 2. Schematic illustration of the deep-UV TRCD set up reported in ref. [33] (figure adapted). Briefly, linearly polarized broadband deep-UV pulses (blue beam, spectrum in the inset) are split into a reference and a probe beam. A photoelastic modulator generates circularly polarized probe pulses, whose handedness switches from left- to right-circular on a shot-to-shot basis. After passing the sample flow cell, the probe pulse spectra are detected shot-to-shot *via* a fiber-coupled imaging spectrograph. The pump pulses (purple beam) are optically chopped to a third of the probe pulse repetition rate, resulting in a series of six consecutive probe pulses that either interact with a ground state sample or a partially photoexcited ensemble (see inset). Here, a static ECD spectrum is calculated as the difference of probe pulses with opposite handedness interacting with a ground state sample. A pumped ECD spectrum is calculated from probe pulses interacting with a pumped sample. A TRCD spectrum is obtained by subtracting the static from the pumped ECD spectrum to resolve small changes in ECD due to photoexcitation. By scanning the time delay between pump and probe pulses, the evolution of the ECD of the photoexcited sample can be recorded with a time resolution of 500 fs.

of photochemical systems, which we have demonstrated through two recent studies: 1) the application of a site-specific ECD-label for capturing conformational dynamics in peptides,<sup>[48]</sup> and 2) the discovery and control of a new reaction coordinate in the spin-crossover dynamics of chiral Fe(II) complexes.<sup>[12]</sup> Both studies are presented briefly below.

It has previously been demonstrated that a thioamide substitution in the peptide bond red-shifts its  $\pi\pi^*$  transition from the far- to the deep-UV near 270 nm. Pairs of substitutions in close proximity may then couple excitonically and act as spectrally isolated, site-specific ECD labels, that encode the local conformation of the peptide backbone.<sup>[49,50]</sup> In collaboration with the group of Dr. Jan Helbing we performed proof-of-concept TRCD experiments of the photo-isomerization of a thio-labeled di-peptide. In analogy to isotope labeling in IR spectroscopy, this study shows that combining the employed ECD labels with TRCD enables the measurement of site-specific peptide backbone dynamics on an ultrafast time scale. Recently, Spekowius *et al.* explored this strategy for monitoring the unfolding dynamics of a tryptophan zipper.<sup>[51]</sup>

Iron(II)-based spin-crossover (SCO) complexes hold tremendous promise as multifunctional switches in molecular devices due to a low-spin (LS) to high-spin (HS) state transition that can be triggered by light, pressure and temperature.<sup>[52]</sup> However, while ultrafast spectroscopy studies have achieved a detailed understanding of the photo-induced forward-SCO to the HS state, the back-SCO mechanism has remained unresolved – despite its crucial role in governing the technologically relevant lifetime of the HS state. In a collaboration with Prof. Jérôme Lacour and Dr. Francesco Zinna, we addressed this question *via* the prototypical chiral SCO complex Fe(II) (4,4'-dimethyl-2,2'-bipyridine)<sub>3</sub> (Fig. 3). Combining TRCD with TA and transient anisotropy measurements, we find that the HS-state decay is accompanied by ultrafast changes in its ECD, reflecting the coupling to an asymmetric torsional twisting mode known as the Ray-Dutt twist, which breaks the chiral symmetry of the complex. Quite remarkably, we then find that stereo-controlling its configuration *via* enantiopure counterions<sup>[53]</sup> suppresses the identified reaction coordinate, thereby slowing down the spin-decay. These results now provide a complete picture of the Fe(II) SCO mechanism with two active reaction coordinates (Fig. 3): the well-known symmetric stretch

mode of the metal-ligand bonds and the newly discovered Ray-Dutt twist.

#### 4. Conclusion

On the molecular level, chirality serves a double role: it is both a structural and a functional design feature. In this respect, time-resolved circular dichroism (TRCD) spectroscopy takes molecular chirality to the time domain, where it opens two new research avenues. First, TRCD is one of only a few ultrafast techniques with structural sensitivity in solution and thus provides a complementary, laboratory-based approach to capture conformational changes of solvated (bio-)chemical systems. Second, TRCD can capture the chiral features of photoexcited states and follow their evolution in time. Based on the progress reported in this article, this unique capability opens new approaches to the analysis of chiral photoactive molecules and materials and promises to expand the current scope of the rapidly evolving field of chiral photochemistry.

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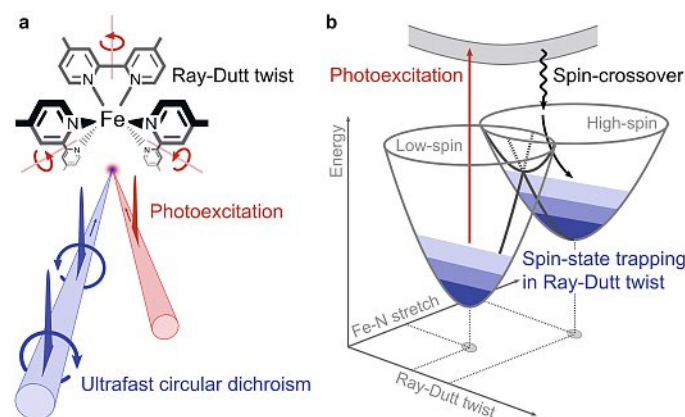


Fig. 3. a) Ultrafast circular dichroism reveals that the spin relaxation of a prototypical Fe(II) spin-crossover (SCO) complex is driven by the symmetry-breaking Ray-Dutt twist. b) The SCO mechanism of Fe(II) complexes thus involves two reaction coordinates: the well-known symmetric stretch mode of the metal-ligand bonds and the newly discovered Ray-Dutt twist. In the reported experiments, ion-pairing with enantiopure counterions was found to suppress the vibrational population of the Ray-Dutt twist, which slowed down the relaxation of the HS-state, akin to trapping it in the vibrational potential of the Ray-Dutt twist. Figure adapted from ref. [12].

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