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Why biphenyl configuration still matters

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ABSTRACT: More than 40 years ago, Kurt Mislow synthesized restrained biphenyl derivatives, classically resolved them and correlated their absolute configuration with the sign of the Cotton effect. We have encountered biphenyl dyes in mixed crystals and crystalline tissues that were presumably resolved by interaction with chiral crystal facets or by adsorption to biopolymers. Understanding association mechanisms required that we likewise determine the absolute configuration, but inside organized media which traditionally do not reveal optical rotation or circular dichroism because of the dominance of linear anisotropies. We therefore recently invented the first circular extinction imaging microscope that can detect circular dichroism in low-symmetry media, and also a new effect in crystal optics that we call anomalous circular extinction. Here, we show what information can be obtained from dyed, organized substances containing biphenyl derivatives by exploiting this new tool. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: biphenyl; configuration; circular extinction imaging microscopy; dyes; crystals

INTRODUCTION

Our study of dyeing crystals[1] was stimulated more than 10 years ago by the photograph shown in Plate 1 of K_2SO_4 crystals grown with the dye Brilliant Congo R (**1**).[2] While we have made extensive studies of the linear dichroism (LD) and linear birefringence (LB) of such anomalous mixed crystals in an effort to understand gross violations of the principle of isomorphism, two outstanding problems remain which are illustrated in Plate 2. For a given view along a birefringent direction, we cannot distinguish the two crystals (a) and (b) through measurements of LD because the dye transition dipole moments make equal projections on the eigendirections of the medium, a mirror symmetric 2D crystal in this case. However, the mode of association with the crystal facets [(11) and $(\bar{1}1)$] is different in the two models; the long axis of the dye is parallel to the faces in (a) but is perpendicular in (b). Hence we cannot know the recognition mechanism, a consequence of the ambiguity in the *absolute orientation*. If our dye is an equilibrium racemic mixture as in (c) and (d), then even if we were to know the absolute orientation of transition moment with respect to the eigendirections, we cannot know the *absolute configuration* of the enantiomer associated with a particular facet. Both ambiguities of absolute orientation and absolute configuration can in principle be resolved with a new tool, a circular extinction imaging microscope (CEIM) that is described here.

In the late 1950s and early 1960s, Kurt Mislow established the correlation between resolved biaryl configuration and the sign of the Cotton effect.[3] However, there are many equilibrium racemic mixtures of intrinsically chiral chromophores such as biaryls or triarylmethyls, commonly resolved by ordered media but at the same time embedded within them and thus disconnected from traditional solution-phase stereochemical analyses. Besides **1** in K_2SO_4, consider Congo Red (**2**), a common histological stain, that is used to reveal proteinaceous amyloid plaques associated with a variety of neurodegenerative disorders including Alzheimer's disease (Plate 1). What is the configuration of the biaryl associated with the twisted peptide fibrils that comprise the highly anisotropic plaque? Despite an enormous literature on the mechanism of association of **2** with amyloid,[4] no researchers have addressed what for Mislow would have been the essential questions of enantioselectivity and configuration because of the absence of tools for making chiroptical measurements in organized media.

We set out to study the stereochemistry of biaryl chromophores such as **1** and **2** in the two types of dyed media represented in Plate 1: (1) dyed crystals, the objects of our long-standing investigation,[1] and (2) dyed crystalline tissues as are common in histological preparations.[5] In the first instance we are well practiced, and in the second we are just now gaining experience. However, the questions we ask are essentially the same whether we are studying **1** in K_2SO_4 or **2** in amyloid plaques. As such, both inquiries will inform one another when pursued in tandem.

AN ASIDE: THE CONGO IN BERLIN

No curious reader will fail to wonder why the two compounds introduced thus far, **1** and **2**, were named

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after the Congo. The reason, revealed by Steensma,[6] can be traced to events in Berlin, Kurt Mislow's home town, and therefore not entirely irrelevant in this context.

From 15 November 1884 through 26 February 1885, representatives of the European powers gathered in Berlin at the behest of Chancellor Bismarck in order to 'carve-up' the Congo basin. This was a major geopolitical event, later to be known as the Berlin West African Conference.[7] It was widely followed in major newspapers and the name 'Congo', evocative of an exotic locale, was on the tips of tongues of cosmopolitan Europeans.

The azo dyes were developed at this time. Congo Red (**2**), the first so-called direct textile dye not requiring a mordant, was synthesized by Böttinger in 1883 at the Friederich Bayer Company. Böttinger left his employer, patented the compound under his own name and then sold the patent to AGFA in 1885. AGFA made a fortune selling **1** as 'Congo Red'. The naming of this dye and others after the Congo was undoubtedly a marketing ploy, intended to conjure a sense of exciting, new vistas. Given the unfortunate history of the Belgians in King Leopold's Congo Free State, today, 'Congo Red' conjures a sense of venality.[8]

CIRCULAR EXTINCTION IMAGING MICROSCOPY

For generations, measurements of chiroptical properties, circular dichroism (CD) or optical rotation (OR), of organized media[9] have foundered on much larger linear anisotropies absent in isotropic solutions. In 1982, Maestre and Katz adapted a Carey spectropolarimeter to a microscope[10] for single point measurements of the CD spectra of chromatin. [CD is a special case of circular extinction (CE), the differential transmission of left and right circularly polarized light (CPL), albeit the most important and commonly measured]. They had to overcome instrumental artifacts[11] arising from electronic polarization modulators in commercial instruments that typically generate sinusoidally varying polarization states,[12] thereby introducing a small admixture of linearly polarized light into the circularly polarized output. Residual ellipticity, when coupled with the LB and LD of ordered media, generates false CD signals.[13,14] Strain in photoelastic modulators (PEMs) compounds these artifacts.[15] Attempts have been made to skirt these problems by adding additional modulators,[16] rotating the sample[17] and performing complex analytical transformations of independent chiroptical measurements.[18] The latest contribution to the chemical literature on the CD spectra of anisotropic media was published by Kuroda *et al.*, in collaboration with JASCO.[19] They tailored a CD spectropolarimeter for solid-state samples by selecting a photomultiplier tube with the smallest polarization bias and a PEM with the least residual static birefringence.

The most recent advances in light detection, charge-coupled devices (CCDs), have not been coupled to CD spectropolarimeters because, operating at 1 kHz, CCDs are incompatible with PEMs that operate at $\sim$100 kHz. While others are trying to force compatibility[20] by speeding up the CCD[21] or slowing the electronic modulation,[22] these designs remain constrained by limited spectral ranges, noise and parasitic ellipticities.[23]

We constructed the first visible light circular extinction imaging microscope (CEIM).[24] In our CEIM we employed CCD detection to make images by eschewing electronic polarization modulation in favor of apparently retrogressive mechanical modulation of near perfect CPL—akin to the original procedure of Cotton.[25] Moxon and Renshaw in 1990[26] and Kremers and Meekes in 1995[27] each built single-point CD spectropolarimeters for anisotropic media via schemes using mechanical light modulation. We further abandoned broadband $\lambda/4$ modulation in favor of a variable retarder that is tilted so that it functions as a perfect $\lambda/4$ plate at each wavelength.

To demonstrate the viability of CD imaging microscopy, we chose crystals of 1,8-dihydroxyanthraquinone (**3**). Despite the clearly tetragonal morphology and x-ray crystal structure [$P4_{1(3)}$][28] of **3**, the crystals showed pronounced LB along [001], the direction that should be the optical axis.[29,30] Stress resulting from twinning could account for the anomalous birefringence, but we could not detect any such twinning in Laue patterns. Only pernicious enantiomorphous twinning could so go unnoticed. We therefore examined the crystals under the CEIM. CD micrographs (Plate 3), recorded at 515 nm, show mirror image domains as red (CD is positive) and blue (CD is negative) heterochiral pinwheels.[24] These images are independent of azimuthal sample rotation. This test is the surest way to rule out linear biases in the optical train.

When we examined crystals of K_2SO_4 stained with biarylazosulfonates, like Buckley's sample shown in Plate 1, we observed in thin sections a chromatic phenomenon that we initially attributed to optical rotatory dispersion resulting from the resolution of chiral dyes between mirror image {111} facets.[31] We observed signals of opposite signs in the CEIM for these mirror image domains; however, *unlike in* **3**, when we flipped the mixed crystals over, the sign of the apparent CD signal changed. We attributed this behavior to a new phenomenon in crystal optics, to which we gave the name anomalous circular extinction (ACE), that we previously observed by more laborious means, and ascribed to Rayleigh scattering.[31] A fuller analysis including the dispersion of the new effect showed that the phenomenon is associated with absorption.[32] ACE can come about when strong oscillators are remotely separated from one another, yet oriented in a biased manner with respect to the eigenmodes of the medium in which they are embedded (Plate 2). The CPL, which becomes elliptical on passing through the sample is preferentially absorbed

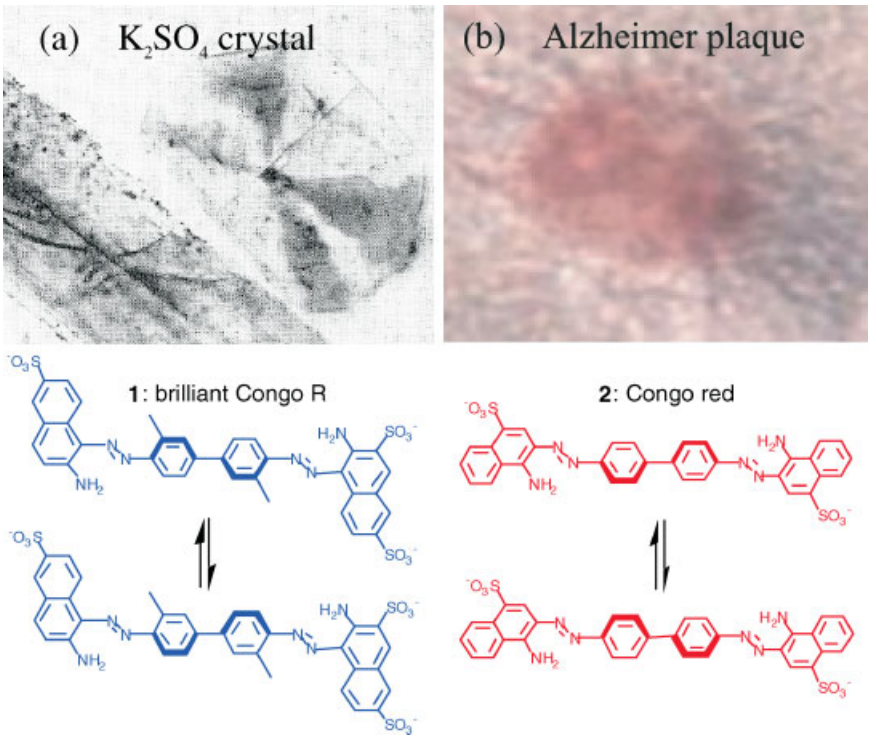

Plate 1. Organized media having interacted with equilibrium racemic mixtures of biaryl dyes. (a) Photograph, from Ref. 2, of K_2SO_4 crystal with Brilliant Congo R (**1**) in the {111} growth sectors whose corresponding facets are chiral and pairwise enantiomorphous, being related to one another by the three orthogonal mirror planes of the achiral crystal. (b) Proteinaceous amyloid plaque (10 μm thick) stained with Congo Red (**2**), from the brain of a deceased Alzheimer's disease subject

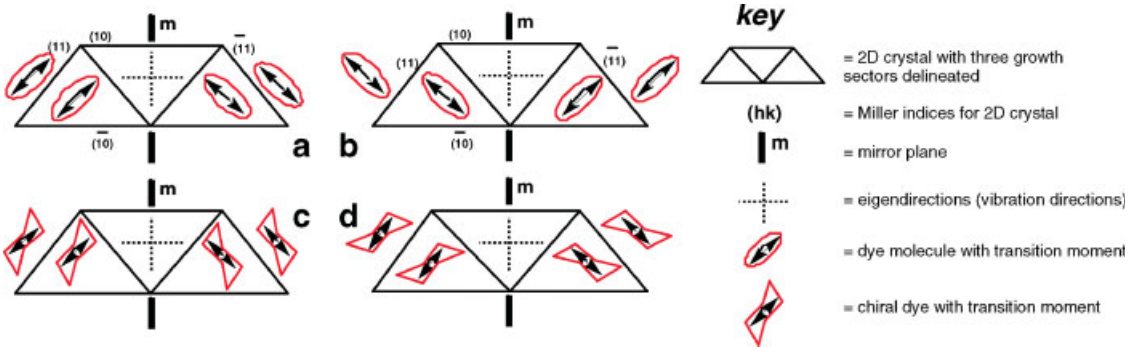

Plate 2. Schematic representations of 2D crystals with three growth sectors, two of which (11) and ($\bar{1}$1) orient and overgrow dyes. In pair (a) and (b) we can not know the *absolute orientation* of the dyes with respect to the eigenmodes. In pair (c) and (d) with a dye that is an equilibrium racemic mixture, we cannot know the *absolute configuration* of the enantiomers associated with the (11) and ($\bar{1}$1) mirror image facets without a mechanism for detecting chirality in orienting media

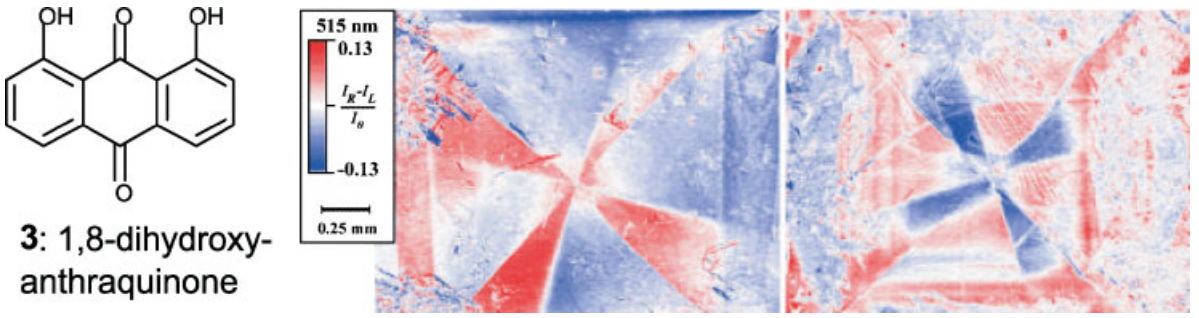

Plate 3. Two CD micrographs of enantiomorphous twins in 1,8-dihydroxyanthraquinone (**3**)

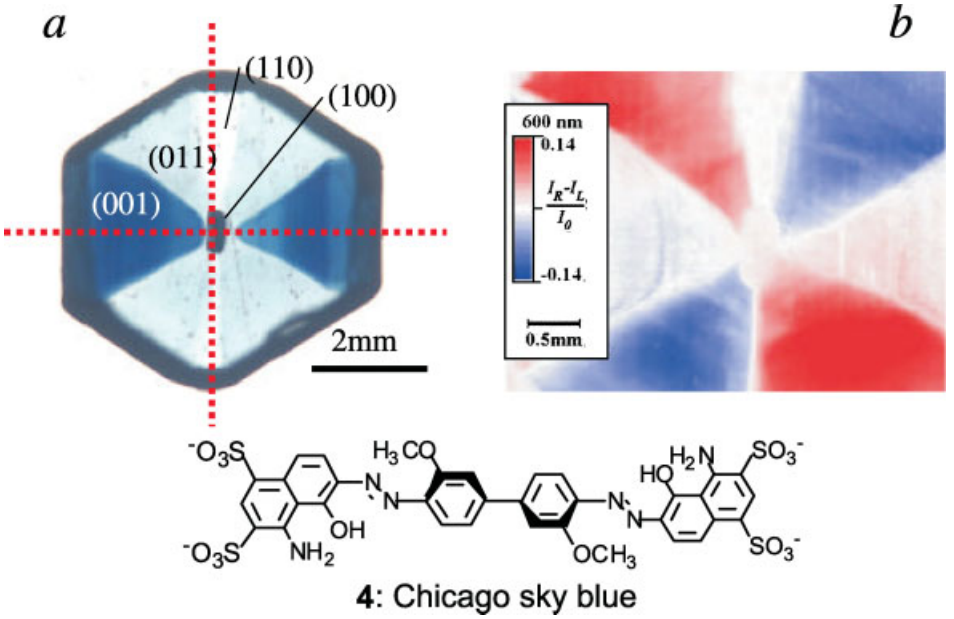

Plate 4. (a) Photograph of $LiKSO_4$ dyed with **4**. View along [100]. Dashed red lines indicate mirrors. (b) CEIM micrograph. Orthogonal mirrors separate the vertically and horizontally related {110} domains

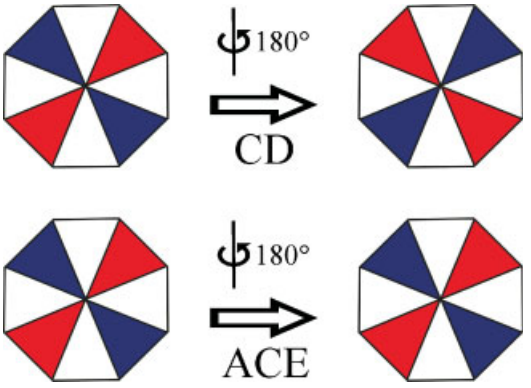

Plate 5. Transformation properties of CD and ACE. Flipping the sample about a vertical axis changes the sign of ACE (thus the picture appears unaltered) whereas the sign of intrinsic CD is independent of the sign of the wavevector

when the azimuthal orientation of the ellipse best matches the inclination of the dipoles. ACE, we discovered, is an effect that can in principle solve the ambiguity of absolute orientation.

We recently discovered that ACE is strong in $LiKSO_4$ crystals that have oriented and overgrown the dye Chicago Sky Blue (**4**). Dyed, hexagonal crystals ($P6_3$)[33] are represented in Plate 4. The {001} growth sectors were heavily colored whereas the {011} growth sectors were less optically dense by a factor of 4. When viewed through the (100) face, the crystals showed a strong differential transmission near the absorption maximum of the dye in the lightly dyed sectors. Curiously, the micrograph showed oppositely signed CE in adjacent {011} sectors. The opposing signs between quadrants is a consequence of the well-known enantiomorphous twinning of $LiKSO_4$ previously revealed by x-ray topography that are dramatically shown in the CE micrographs.[34] From the signs of the effect, we can surmise that the dipoles are oriented with respect to the {001} growth sectors as in Plate 2(b) as opposed to Plate 2(a).

Our CEIM microscope measures simultaneously CD and ACE. These speak to absolute configuration and absolute orientation, respectively. However, in order to use these convolved effects to make stereochemical judgements, we must be able to distinguish and separate them from one another. This can be done by comparing their behavior when the sample is transformed (Plate 5) if one effect is dominant. If CD and ACE are of comparable magnitude they can be separated through their distinct dependences on phase. We have shown[24] that CD is proportional to $\sin\delta/\delta$ whereas ACE is proportional to $\sin^2(\delta/2)/(\delta/2)$ (Fig. 1).[32] Therefore, by comparing images from samples successively thinned by cleavage or polishing, we can plot our expectations for the combined effects with appropriate weighting factors.

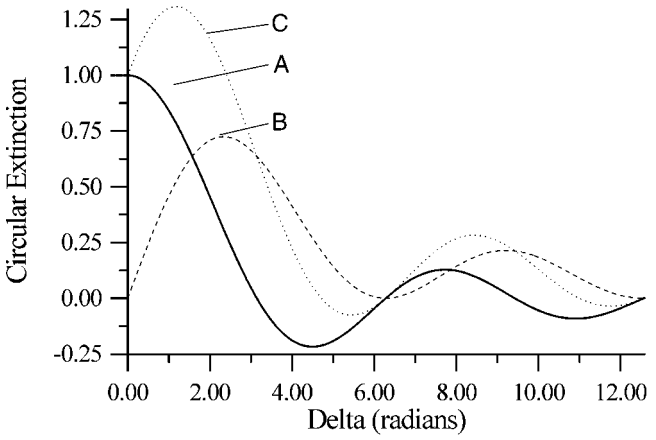

Figure 1. Dependence of CD (A) and ACE (B) and their sum (C) equally weighted, the total circular extinction (CE), on the phase difference, δ. The sum contains the proportions of the two effects that can be plotted experimentally by measuring circular extinction as a function of δ by successive sample thinning

DYEING CRYSTALS VERSUS DYEING CRYSTALLINE TISSUES: AMYLOIDOSIS

We circumscribed the science of dyeing crystals,[1] and aspired to bring our understanding of dyes in organized media to the study of chemical histology.[36] Ambronn was the only scientist who previously considered both crystal and tissue dyeing. Best remembered for his observation of LD from dye-stained cell membranes,[37] he also observed the LD from **2**, aligned within sucrose.[38] While he gave no adequate crystallographic description of his dyed crystals, we observed that the $\{1\bar{1}0\}$[39] faces recognize the dye, thus labeling the polar axis.

Compound **2** is most widely used for studying amyloidosis,[40] the deposition of insoluble peptide fibrils[41] as plaques[42] that are associated with a variety of devastating disorders, including Alzheimer's disease (AD).[43] Amyloid absorbs **2** and displays characteristic LD and LB that are used in the *post mortem* diagnosis of AD. Our current understanding of amyloid structure comes from synthetic peptides,[44] inadequate models of *in situ* plaques. Researchers have argued that new methods for studying amyloid must be developed if we ever hope to understand the relationship of amyloid to neurodegeneracy.[45] In principle, CD and ACE imaging are such methods. CD has frequently been used to monitor the conformational changes of amyloid peptides.[46–49] CD can be used to exploit the process of staining with **2**. While solutions of **2** are not optically rotatory, induced CD in the visible was seen in its complexes with chiral polypeptides and interpreted in terms of particular host–guest interactions.[50–52]

Two helical arrangements of **2** need to be sorted out in amyloid plaques, the biphenyl configuration and the supramolecular chirality.[53] Roterman and co-workers[54] predicted by molecular dynamics that amphililic dyes such as **1** and **2** form helical aggregates with the biaryl moieties stacked and rotated with respect to one another (Fig. 2). Such an aggregate should give a characteristic bi-signate exciton coupled CD spectrum.[55] Evidence has accumulated that **2** preserves its supramolecularity in complexation with amyloid proteins.[56] Only by knowing

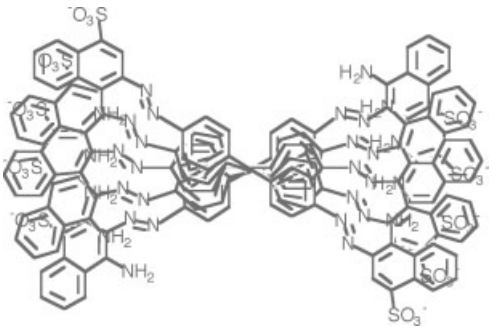

Figure 2. Cartoon of helical aggregate of **2** based on molecular dynamics simulations of Roterman and co-workers [54]

the state, orientation and configuration of the dye can we understand association mechanisms. Understanding mechanism is important because **2** not only reveals amyloid but inhibits its formation.[57]

CD and ACE signals from amyloid are small in the present configuration of the CEIM. However, our LB and LD imaging has already revealed aspects of plaque structure that were not previously known, especially the disordered cores.[58] Moreover, we have unambiguously established the orientation of the dipoles of **2** with respect to the fibrils, a matter of considerable controversy.[59] We aspire to rebuild and refine the CEIM, currently fabricated from spare parts, using optical components of the highest optical quality in order to detect small optical perturbations. At that stage we will be prepared to begin a general investigation of the stereochemistry of biological stains in action.

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