COMPREHENSIVE CHIROPTICAL SPECTROSCOPY

Volume 2

Applications in Stereochemical Analysis of Synthetic Compounds, Natural Products, and Biomolecules

Edited by

Nina Berova
Prasad L. Polavarapu
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IN MEMORY OF CARLO ROSINI (1948–2010)

Carlo Rosini obtained his degree in Chemistry (1973) at the University of Pisa, where he completed his thesis on the stereochemistry of Ni(II) complexes. He entered the Italian CNR by joining the group of Professor Piero Salvadori and the research on determination of absolute configuration by Circular Dichroism. Later on, Carlo Rosini spent two years (1977–1979) at the King's College in London, under the supervision of Professor Stephen F. Mason. During this period he studied polarized-light-based spectroscopy and its application to structural determinations. He was appointed as associate professor (1992) at the University of Pisa and then as a full professor (1997) at the University of Basilicata, Potenza. The field of chirality was fundamental to the scientific activity of Carlo Rosini. His broad scientific interests included many aspects of organic stereochemistry, like asymmetric organic synthesis, chiral discrimination mechanisms, chiral stationary phases for enantioselective chromatography, and structural characterization of organic molecules by Circular Dichroism. The last research projects of Carlo Rosini were oriented toward chemical/computational approaches for the determination of absolute configuration by linking experimental and theoretical studies.

We miss his enthusiasm and his charisma, but we will remember his life and his contributions to the science and the chemical community.

Carlo Rosini was one of the first scientists who accepted to contribute a chapter to this volume. Although his premature and tragic death prevented his submission, his spirit never died and is now, not only in the chapter contributed by his co-workers and former students, but also in the minds of all of us who had the privilege to know him and collaborate with him.

CONTENTS

PREFACE

Chirality is a phenomenon that is manifested throughout the natural world, ranging from fundamental particles through the realm of molecules and biological organisms to spiral galaxies. Thus, chirality is of interest to physicists, chemists, biologists, and astronomers. Chiroptical spectroscopy utilizes the differential response of chiral objects to circularly polarized electromagnetic radiation. Applications of chiroptical spectroscopy are widespread in chemistry, biochemistry, biology, and physics. It is indispensable for stereochemical elucidation of organic and inorganic molecules. Nearly all biomolecules and natural products are chiral, as are the majority of drugs. This has led to crucial applications of chiroptical spectroscopy ranging from the study of protein folding to characterization of small molecules, pharmaceuticals, and nucleic acids.

The first chiroptical phenomenon to be observed was optical rotation (OR) and its wavelength dependence, namely, optical rotatory dispersion (ORD), in the early nineteenth century. Circular dichroism associated with electronic transitions (ECD), currently the most widely used chiroptical method, was discovered in the mid-nineteenth century, and its relationship to ORD and absorption was elucidated at the end of the nineteenth century. Circularly polarized luminescence (CPL) from chiral crystals was observed in the 1940s. The introduction of commercial instrumentation for measuring ORD in the 1950s and ECD in the 1960s led to a rapid expansion of applications of these forms of chiroptical spectroscopy to various branches of science, and especially to organic and inorganic chemistry and to biochemistry.

Until the 1970s, chiroptical spectroscopy was confined to the study of electronic transitions, but vibrational transitions became accessible with the development of vibrational circular dichroism (VCD) and Raman optical activity (ROA). Other major extensions of chiroptical spectroscopy include differential ionization of chiral molecules by circularly polarized light (photoelectron CD), measurement of optical activity in the X-ray region, magnetochiral dichroism, and nonlinear forms of chiroptical spectroscopy.

The theory of chiroptical spectroscopy also goes back many years, but has recently made spectacular advances. Classical theories of optical activity were formulated in the early twentieth century, and the quantum mechanical theory of optical rotation was described in 1929. Approximate formulations of the quantum mechanical models were developed in the 1930s and more extensively with the growth of experimental ORD and ECD studies, starting in the late 1950s. The quantum mechanical methods for calculations of chiroptical spectroscopic properties reached a mature stage in the 1980s and 1990s. *Ab initio* calculations of VCD, ECD, ORD, and ROA have proven highly successful and are now widely used for small and medium-sized molecules.

Many books have been published on ORD, ECD, and VCD/ROA. The present two volumes are the first comprehensive treatise covering the whole field of chiroptical spectroscopy. Volume 1 covers the instrumentation, methodologies, and theoretical

simulations for different chiroptical spectroscopic methods. In addition to an extensive treatment of ECD, VCD, and ROA, this volume includes chapters on ORD, CPL, photoelectron CD, X-ray-detected CD, magnetochiral dichroism, and nonlinear chiroptical spectroscopy. Chapters on the related techniques of linear dichroism, chiroptical imaging of crystals and electro-optic absorption, which sometimes supplement chiroptical interpretations, are also included. The coverage of theoretical methods is also extensive, including simulation of ECD, ORD, VCD, and ROA spectra of molecules ranging from small molecules to macromolecules. Volume 2 describes applications of ECD, VCD, and ROA in the stereochemical analysis of organic and inorganic compounds and to biomolecules such as natural products, proteins, and nucleic acids. The roles of chiroptical methods in the study of drug mechanisms and drug discovery are described.

Thus, this work is unique in presenting an extensive coverage of the instrumentation and techniques of chiroptical spectroscopy, theoretical methods and simulation of chiroptical spectra, and applications of chiroptical spectroscopy in inorganic and organic chemistry, biochemistry, and drug discovery. In each of these areas, leading experts have provided the background needed for beginners, such as undergraduates and graduate students, and a state-of-the-art treatment for active researchers in academia and industry.

We are grateful to the contributors to these two volumes who kindly accepted our invitations to contribute and who have met the challenges of presenting accessible, up-to-date treatments of their assigned topics in a timely fashion.

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PART I

A HISTORICAL OVERVIEW

1

THE FIRST DECADES AFTER THE DISCOVERY OF CD AND ORD BY AIMÉ COTTON IN 1895

Peter Laur

1.1. SCOPE: SUBJECTS AND TIME FRAME TO BE REVIEWED

The story of the Cotton effect begins with its discovery in 1895. Although the news was hailed by leading physicists and chemists, studies to extend, exploit, and apply Cotton's findings developed at a slower pace than one might have anticipated. One of the reasons for this delay was simply the necessity of the researchers to construct their own optical apparatus. Gradual technical improvements eventually allowed one, in the 1920s, to take chiroptical measurements in the ultraviolet as well as the visible, thus making accessible in principle a great many Cotton effects in colorless (mostly organic) compounds. Despite the paramount importance of such developments, neither the technical details nor the physics involved will be discussed in the following. Rather, a chemist's view will prevail, paying attention chiefly to experimental results and the application of chiroptics to chemical problems.

Since much of the work during the first 20 or so years after Cotton's discovery was done by physicists and physicochemists, it is not surprising that many investigations were interconnected with or even motivated by the concomitant progress of the theory of optical activity. But also the discussion of this part of (theoretical) physics will be curtailed in the following. The exclusion in this chapter appears justified, because various comprehensive reviews are readily available, as they are for the field of optical instrumentation.

By about 1935, Cotton effect measurements were possible with most organic and inorganic chromophores. It is rather surprising that not much use was made of the chiroptical techniques, especially by organic chemists. On the other hand, physical chemists had demonstrated the feasibility of Cotton effect studies in various classes of chemical compounds, but seemed satisfied with this result. Likewise, the advancement of optical

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instruments for chiroptical measurements slowed down. All this led to a certain climax of chiroptical studies in the early 1930s, to be followed by a near standstill. It is not unreasonable to symbolically connect this phenomenon with the death in 1936 of T. M. Lowry, one of the most active scholars in the field.

Arguably, the death of T. M. Lowry ended the first, pioneering period of chiroptical studies. The present chapter will concentrate on reviewing these first "historical" decades.

Some work on the experimental study of the Cotton effect continued after 1936 until World War II on a minor scale, on, for example, organic compounds (S. Mitchell) or platinum complexes (I. Lifschitz). But at exactly the same time, new developments took place in the theory of optical activity and its application to chemical problems: Werner Kuhn's calculation of the absolute configuration of lactic acid in 1935 rang in a new era. The waning interest of the experimentalists contrasts with the increased activity of theoretical chemists like J. G. Kirkwood, E. U. Condon, H. Eyring, or W. Kauzmann, who in the late 1930s advanced different models of optical activity. Still, chemistry had to wait for the period of 1950–1960 for a revitalization of chiroptics. Some reasons for the animation are: (1) the development of X-ray scattering methods for the determination of the absolute configuration, thus anchoring the stereochemistry unambiguously, following J. M. Bijvoet's seminal publication of 1951; (2) the advent of new, commercially available measuring devices of ORD and CD; and (3) growing interest in natural products chemistry and, generally, optically active systems. But to discuss these topics would need another chapter.

1.2. EARLY CHIROPTICAL STUDIES

The discovery of optical activity is credited to the two distinguished French mathematicians, physicists, astronomers, and geodesists (and more) Dominique-François Jean Arago (1786–1853, of Catalan origin) and Jean-Baptiste Biot (1774–1862) [1]. Arago and Biot had been closely associated at least since 1806 in the pursuit of other scientific subjects, and they sometimes published together. Both investigated the optical activity of quartz, and apparently they also shared their equipment to some extent. If, on the one hand, Arago was the first to go into print, Biot, on the other hand, soon became more active in this field and extended the studies. He undoubtedly observed optical activity for the first time in organic compounds such as natural oils and terpenes, or solutions of camphor [2] and cane sugar [3]. Biot continued his research on optical activity throughout his life, later concentrating particularly on tartaric acid. He noticed the wavelength dependence of the optical rotation even at the very beginning of his studies, albeit in a rather qualitative way. Whereas eventually the rotatory dispersion of quartz could be elucidated satisfactorily (which led to Biot's law, stating that the rotation is inversely proportional to the square of the wavelength), similar solution studies were seriously impeded by experimental deficiencies, particularly the lack of suitable monochromatic light sources.

Genuine chiroptical studies were, therefore, rather infrequent until the end of the nineteenth century. One of the most important papers here is a report by the Norwegian physicist Adam Arndtsen, who discussed his studies of aqueous solutions of (+)-tartaric acid [4]. Using sunlight, he was able to visually determine the angle of rotation at some of the principal Fraunhofer lines, that is, C (656), D (589), E (527), b (517), F (486), and e (438 nm). He could confirm and extend Biot's earlier finding that the rotation exhibits a maximum in the spectral region studied, with its wavelength shifting from the

blue to the red on increasing concentration. This unexpected and intriguing result led the Swiss chemist Hans Landolt (an important pioneer of the investigation and application of optical activity, as well as one of the "fathers" of Physical Chemistry) in 1877 to introduce the expression "*anomale Rotationsdispersion*" (anomalous rotation dispersion) [5], which since has become established for the description of such rotatory dispersion curves that run through a maximum or minimum, or show a reversal of sign.

It had thus become apparent that spectropolarimetry promised to develop into an interesting field in the future. In his last and comprehensive paper on optical activity, Biot [6] suggested, therefore (translation from the French by the present author):

> I should like to draw the attention of experimentalists to a class of phenomena which, hitherto, has been little studied but which, nevertheless, for both theoretical and practical purposes, ranks in importance with that of the optical rotatory power itself of which it is a constituent element. I refer to the specific mode of dispersion that each optically active substance or compound imparts to plane polarized light of different wavelengths [literally: refrangibility].

Despite this exhortation, reports on rotatory dispersion remained scarce until the end of the century. This is also evident from the very first book on optical activity, where all data known at that time are summarized, which was published in Germany in 1879 by Landolt [7]. Here, he also describes in detail the optical equipment used by himself and his predecessors. Therefore, it is not necessary to dwell at this point on the measuring devices and optical methods. Although most of the rotations listed (many of which had been determined or redetermined by Landolt himself) refer to the sodium D line only, his book also has short sections on normal and anomalous rotatory dispersion. It is important to realize that so far all reported optically active liquids or solutions were based on organic compounds without absorption bands in the visible. In fact, Landolt emphasized that there is not a single inorganic substance known which shows optical activity in solution (or in the gas phase), from which he tentatively—but incorrectly—concluded that optical activity might be restricted to carbon compounds, except for the solid phase. Surprisingly, he gave no reference to any optically active transition metal complex, although at least Fehling's solution (a mixture of several Cu(II) tartrate complexes) had been around since 1848 [8]. One might speculate whether such coordination compounds (of a still unknown nature) were ignored as a result of theoretical considerations.

It should also be mentioned that measurements in general were limited to practically colorless samples and to merely certain frequencies of the visual solar spectrum. The only other reasonably monochromatic light sources available were based on lithium, sodium, and thallium salts heated in a Bunsen burner (invented in 1866), giving access to the wavelengths 671 nm (Li), 589 nm (Na), and 535 nm (Tl), respectively.

It is worthwhile to briefly turn to the "anomalous" refractive dispersion using unpolarized light—that is, the characteristic sigmoidal variation of the index of refraction in the absorption region, running through a maximum and minimum, instead of steadily increasing as the wavelength decreases, as in normal dispersion. This behavior had been discovered in iodine vapor in 1862 by the French physicist F.-P. Leroux [9], and around 1870 it attracted the attention of several investigators, who published independently on anomalous dispersion in the visible, using solutions of organic dyes like fuchsine [10]. There was some dispute as to priority among the Danish physicist Christian Christiansen, the Swiss chemist and physicist Jacques-Louis Soret, and the German physicist August Kundt. While it is clear that Christiansen was the first to publish, the most extensive studies were carried out by Kundt. The relevance of these findings to the present subject

lies in the fact that here was proven the possibility of successfully studying the index of refraction even near absorption bands in the visible. Consequently, a similar anomalous dispersion could be expected to exist for the optical rotation, keeping in mind the relation between the velocity of light, the index of refraction, and the optical rotation. This anomalous dispersion feature of the rotation should have been accessible by existing techniques, if only suitable colored optically active samples had been available. It took more than two decades, however, before this problem was addressed.

1.3. THE DISCOVERY OF THE COTTON EFFECT

In 1895, two short papers ("notes") appeared in the fortnightly journal of the French Academy of Sciences, entitled "*Unequal absorption of right and left circularly polarized light by certain optically active substances*" [11] and "*Anomalous rotatory dispersion of absorbing substances*" [12]. The author was the 26-year-old physicist Aimé Auguste Cotton (Bourg-en-Bresse 1869–Sèvres 1951), a PhD student at the prestigious École Normale Supérieure in Paris. The first of these papers describes and names the property of "*dichroïsme circulaire*" (what we now call "CD") associated with an absorption band of an optically active compound in solution, and the second one introduces the corresponding effect in the dispersion mode (now called "ORD"). The full paper of 85 pages, also incorporating studies on magnetic optical activity, was published in 1896 under the heading "*Investigations of the absorption and the dispersion of light by optically active media*" [13]. It summarizes A. Cotton's *Thèse de Doctorat*, which he prepared from November 1893 to July 1896 at the Physics Laboratory of the École Normale with Professors Marcel Brillouin and Jules Violle as advisors. Based on his important discoveries, Cotton was accorded the degree of *Docteur ès Sciences* in 1896.

In his thesis, Cotton for the first time reports data of (a) optical rotations close to both sides of an absorption band in the visible, using solutions of Cu(II) and Cr(III) coordination compounds with tartrate or malate ligands, and (b) the associated circular dichroism. It is quite obvious that Cotton was successful to a large degree owing to both the quality of his optical components and the skillful and precise construction of the measuring devices, especially for the determination of very small values of the ellipticity, but also to his power of observation, and—last but not least—to a fortunate choice of optically active samples. In this chapter, however, his technical equipment and the underlying physical principles shall not be discussed in detail, because Cotton himself gives a full description in his major paper, and there are also comprehensive reviews elsewhere as, for example, in the books by Mitchell and Lowry (see below).

While Cotton's expression "*dispersion rotatoire anomale*" (anomalous rotatory dispersion) is self-explanatory, a comment concerning his novel term "*dichroïsme circulaire*" (circular dichroism) may be appropriate. Cotton did not always measure directly or indirectly the difference in absorption of left- and right-circularly polarized light by his sample [*i.e.*, $(\varepsilon_L - \varepsilon_R)$], but rather the ellipticity of the emerging elliptically polarized light. In this case, his measuring device included, apart from a Nicol prism to provide plane-polarized light, a "double circular polarizer" consisting of two quarter-waveplates placed side by side in the plane-polarized light beam in such a way that their principal axes are at 90° to one another and at 45° to the plane of the incident light. This arrangement allowed the observation of left- and right-circularly polarized light beams next to each other. On the introduction of a sample showing circular dichroism, the beams would be differently absorbed, which could be detected visually or photometrically. The field of vision was thus divided into two halves by these $\lambda/4$ plates. When

he used white instead of monochromatic light for the examination of his optically active sample solutions, these two halves showed different colors. This reminded him of the dichroism observed with certain doubly refracting crystals, where the ordinary and the extraordinary ray are absorbed unequally, as found by Biot in tourmaline and later by the Austrian mineralogist Haidinger in many other cases [14]. Cotton therefore chose the term "*circular dichroism*." In fact, Haidinger had already discovered this phenomenon in amethyst quartz in 1847 [15].

Nowadays, the expression "*circular dichroism*" probably just awakens vague memories of the original visual observations; this context has been largely forgotten nowadays, with the advent of automated electronic spectropolarimeters. Actually, Cotton himself had already performed some photometric measurements, but had found them inferior to his visual results.

1.4. THE FIRST CD AND ORD CURVES

Cotton's measurements obviously were not only restricted to the visible, but also quite limited as to the wavelengths available. Even under favorable conditions, at most eight spectral lines were at his disposal, namely, 657 (red, near C), 589 (yellow, sodium D line), 581 (orange, near D), 562 (greenish yellow), 522 (green, between E and b), 475 (blue, near F), 459 (blue-violet), and 437 nm (violet, near e) [the letters C, D, E, b, F, and e refer to the Fraunhofer lines so designated]. A comparison with Arndtsen's paper of 1858 [4] shows that hardly any improvement of the spectral availability had taken place until the end of the nineteenth century. However, on the positive side it can be seen that these lines are spread rather evenly across the whole visual region. Nevertheless, the generation of continuous absorption and rotation curves, as often published, on the basis of observations at some of these individual wavelengths, leaves much to the whim of the draftsman, especially concerning the position and magnitude of any maxima and minima. Such "data" should not be overinterpreted. This situation would prevail in the decades to come.

It is not unexpected that, at the onset of his investigations, Cotton chose Fehling's solution ("*liqueur de Fehling*") for his studies. It is, after all, in the direct line of Biot's research to look at derivatives of active tartaric acid. Secondly, the only area of importance where the application of optical activity had become established was saccharimetry; and thirdly, Fehling's solution was a proven and powerful reagent in carbohydrate chemistry [16]. It seems that Cotton systematically progressed from the complex and notoriously unstable Fehling's solution to simpler alkali copper(II) tartrates, the preparation of which he describes in detail. By the way, it is amusing to note that in one case he reports the precipitation of copper tartrate from a copper sulfate solution by adding the aqueous solution of a crystal of Seignette salt (potassium sodium tartrate); this crystal had been prepared by Pasteur himself. Unfortunately, these copper complexes proved to be very unstable; they changed or simply decomposed with time or at elevated temperature and were also light-sensitive. Furthermore, the chemical composition of these aqueous solutions was unknown (and, to some extent, still is), and attempts at isolating any well-defined compound failed. A solution of crystalline copper malate, perhaps more stable, did not show any observable circular dichroism. Despite these drawbacks, Cotton did obtain many ORD and some CD data, but obviously the reproducibility of the experiments remains questionable, and the curves shown in print [13] should be interpreted with caution.

The most convincing chiroptical effects, however, were observed with aqueous solutions of potassium chromium(III) tartrate, prepared *in situ*. They shall be discussed here in some detail. Figure 1.1 is Cotton's Figure 18 on page 408 of reference 13, and it shows a complete "*Cotton effect*" in the ORD and the CD near 570 nm. Because of its seminal importance, this figure has been later reprinted by others a number of times. The actually measured data are given as follows: 657 nm, rotation $\rho + 1^\circ 26'$, ellipse [sic] $\phi + 32'$; similarly: 589, $+2^\circ 30'$, $(-3^\circ 40')$; 581, $+1^\circ 46'$, $-4^\circ 54'$; 562, $-1^\circ 21'$, $-4^\circ 16'$; 522, $-2^\circ 50'$, $-1^\circ 25'$; and 475, $1^\circ 52'$ [no sign given in the paper; from the curve it is evident that ρ must be negative], $+28'$. Data were thus collected at six wavelengths only, because the onset of a second strong absorption band made observations at shorter wavelengths impossible. The parentheses around the ellipticity value at the sodium D line are Cotton's and indicate that this number results from photometric measurements.

Despite its beautiful appearance, there are unfortunately some flaws in this figure and the data as printed. A comparison of the figure with the data listed above makes evident two discrepancies at 562 nm: In the figure, the angle ϕ is given as $-4^\circ 46'$ (not $-4^\circ 16'$), and the corresponding angle ρ is given as $-0^\circ 21'$ (not $-1^\circ 21'$). On reexamination, the true values were verified to be $\phi - 4^\circ 46'$ and $\rho - 1^\circ 21'$. The figure should be redrawn, therefore, using this value of ρ. Such a modification would necessarily modify the shape of the ORD curve, while not basically changing it. Cotton gives these corrections in

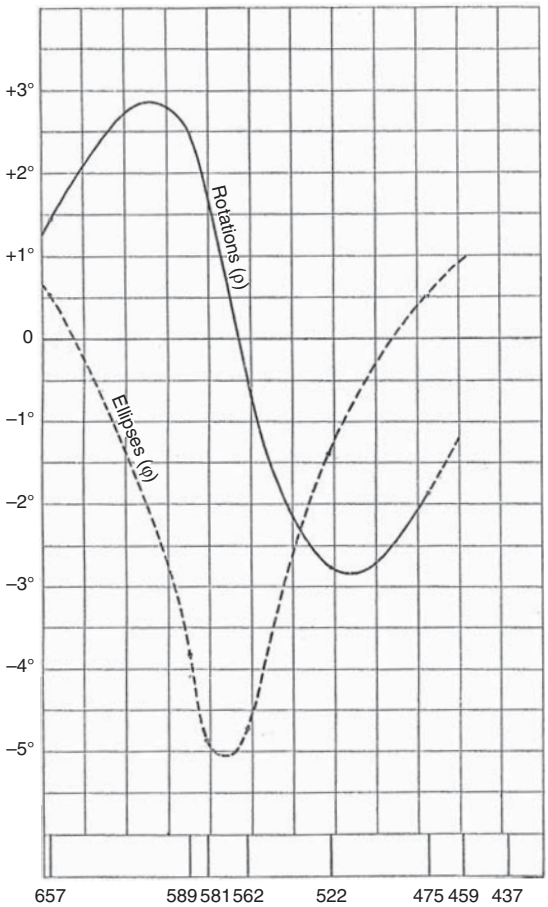

Figure 1.1. CD and ORD of potassium chromium(III) tartrate (solvent H_2O). (From A. Cotton, *Ann. Chim. Physique* **1896**, [7] *8*, 347; Figure 18, p. 408.)

a letter to Professor Ladislas Natanson in Cracow, Poland, quoted on pages 33/34 of reference 17. He explains the first error as a misprint, and he states that the second one is a mistake by the "*dessinateur*" (draftsman).

However, the really important disagreement between the ORD and CD, as we can see immediately from the curves—with hindsight—lies in the incompatibility of their signs. If we accept the rotation values as correct, as seems reasonable, the sign of the CD is in error. And so it is! Cotton himself redressed this flaw two years later [18] in a paper, the first sentence of which runs as follows (translated from the French): '*It is easy to be mistaken as to the sense of a circular vibration*.' Admitting his mistake in the assignment of the direction of the rays circularly polarized by a Fresnel rhomb, he imputed it to his misinterpretation of some of Billet's tenets in the latter's "*Traité*" [19]. Apparently, Billet had used the expression "*principal section*" of a mica crystal in an unorthodox way and had also treated this crystal as positive, contrary to the common practice. Therefore, all of Cotton's CD curves, and the sign of all ellipticities published before 1898, ought to be inverted.

But not everyone read or responded to this correction; others did so, but without indicating it. The confusion that might have been generated was fortunately curtailed by the fact that very few scientists, apart from Frenchmen, studied the circular dichroism in the following decades. But as late as in 1923, (Ms.) N. Wedeneewa in Moscow (for example) still used the earlier "wrong" sign of the CD, when she reported the ORD and CD of camphor quinone [20]. Similarly, T. M. Lowry just reprinted Cotton's Figure 18 in his famous classic of 1935 [21] without any comment, whereas S. Mitchell in his treatise on the Cotton effect [22] of 1933 simply shows an inverted CD curve in ostensibly the same figure (see Figure 1.2), also without any further comment.

Another point of criticism could be raised because of the all-too-vague identity of the samples investigated. Although Cotton carefully describes the preparation of his samples, as mentioned earlier, their inherent instability cannot preclude changes with time, perhaps also as the result of shifting equilibria between the several complexes present. Indeed, small changes even in the synthesis of the tartrate complexes can lead to the total inversion of the anomalous rotatory dispersion, as has been observed by Wedeneewa [20]. All this calls for caution with respect to the early ORD and CD publications. However, concerning the key compound discussed at length, potassium chromium(III) tartrate, all doubts were finally set to rest by W. Kuhn [23], who much later very carefully repeated Cotton's work and found it fully correct (Figure 1.3).

1.5. THE REACTION OF THE LEARNED WORLD TO COTTON'S DISCOVERIES

Cotton's papers raised the immediate attention of Wilhelm Ostwald (Nobel Prize 1909), who, one year after the publication of the original notes in the *Comptes Rendues* [11, 12], wrote two abstracts thereof himself for his journal *Zeitschrift für Physikalische Chemie* [24]. This was followed by his six-page review of Cotton's full paper [13] in the same year [25], with several CD and ORD curves reprinted, including Cotton's original Figure 18, discussed above.

It should be pointed out that the lack of correspondence of the sign of the ORD and the CD could not have been noticed by Ostwald at that time, since the necessary theoretical background had not yet been provided. With these reviews, Ostwald acquainted the chemical world with Cotton's results, and his name carried much weight. It is certainly unusual that preliminary notes by a foreign physics student and extracts of his

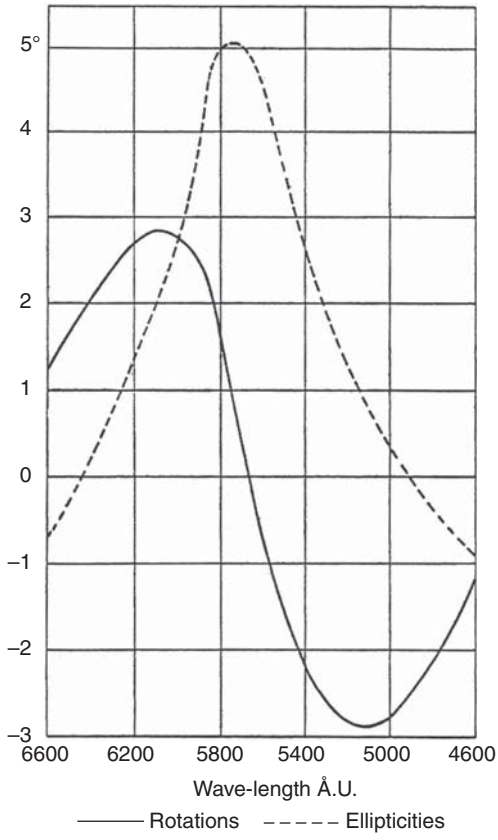

Figure 1.2. CD and ORD of potassium chromium(III) tartrate (solvent H_2O). (From S. Mitchell, *The Cotton Effect*, Bell, London, 1933; Figure 12, p. 23; reproduced with permission.)

thesis should induce an already famous physical chemist to such a presentation. Incidentally, already the "sponsoring" of Cotton's notes by the renowned physicist Gabriel Lippmann from Luxembourg (Nobel Prize 1908)—such notes had to be presented by an academician—attests to the importance attributed to them. One might well say that chiroptics had a splendid start.

The speed with which the news was reported and hailed is altogether breathtaking. For example, the physical chemist Landolt referred to Cotton's studies already in the second edition of his book, published in 1898 [7]. Mention should also be made of the German physicist Paul Drude, who included a treatment of Cotton's "(anomalous) rotary dispersion" in his famous *Lehrbuch der Optik* of 1900 [26].

So, by the beginning of the twentieth century, the international world of physics and physical chemistry was well aware of Cotton's results.

It took only a few additional years before a thorough theoretical treatment was provided by L. Natanson, Professor of Theoretical Physics at the Jagiellonian University Kraków (Cracow, Poland). The title of his important paper, "*On the elliptic polarization of light transmitted through an absorbing naturally-active medium*" [27], with a supplementary note [17], needs no further comment. Here, Natanson treated the interdependence of absorption, optical rotation, and circular dichroism. Probably in order to spread his results further, also an amalgamated and shortened French translation of both papers by the Count of Ballehache was published very shortly thereafter [28]. The relations presented here between the sign of the rotation and the circular dichroism have become known as the "*Règle de Natanson*" or "*Natanson's Rule*" [29]. This finally allowed the

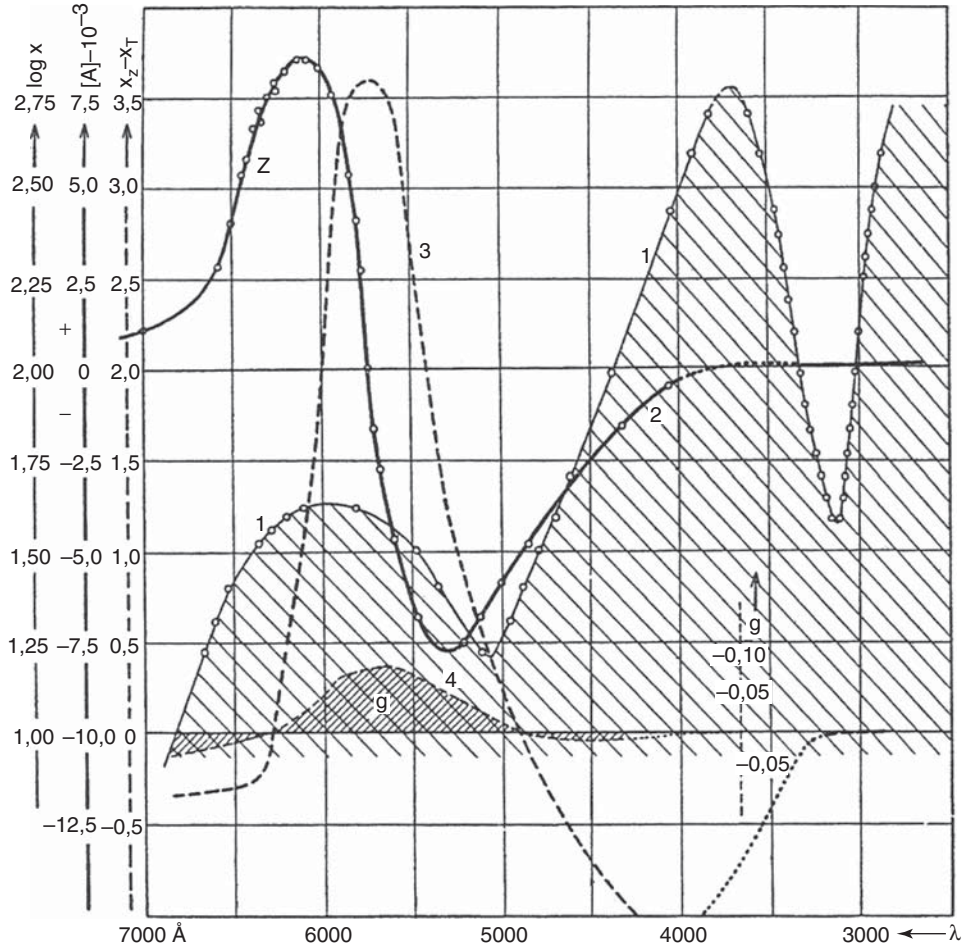

Figure 1.3. UV, CD, and ORD of potassium chromium(III) tartrate (solvent H_2O). (From W. Kuhn, A. Szabo, *Z. Phys. Chem*. **1931**, *B15*, 59; Figure 1, p. 62; Oldenbourg Wissenschaftsverlag München, reproduced with permission.)

prediction of the sign of the circular dichroism associated with a specific absorption band, based on just the anomalous rotation curve, which should not be too difficult to obtain.

Natanson's papers included the following sentences on the first page: "*Effects of this kind have been observed and investigated by Monsieur A. Cotton*" [27] and "*Des phénomènes de ce genre ont été observé et analysés par M. Cotton*" [28]. Here we find the seed that has developed into the important technical terms "*Cotton's Phenomenon*" and "*Cotton Effect*," which have been used ever since, with the first one preferred in the early decades of the twentieth century.

At this point it may be timely to more formally give a definition of the Cotton effect as we understand it today. It may be interesting to compare the definition given in 1933 by Stotherd Mitchell on page 24 of his book on the Cotton effect (incidentally the first monograph of this kind) [22] with the definition by Werner Kuhn from 1960 [30].

Mitchell wrote: "A maximum ellipticity and zero rotation are found in this region [of the absorption band]. The rotation reaches a maximum value on one side of the band and

a minimum on the other. This variation of rotation and ellipticity in the neighbourhood of an absorption band has been called the *Cotton effect*." [Mitchell's italics]

Kuhn stated: "[Cotton] found that optical rotatory power as a function of the wavelength often shows, in the region where the substances show ordinary absorption, a characteristic *anomaly* which is associated with a *circular dichroism* in the absorption region and which after the name of its discoverer is called a *Cotton effect*." [Kuhn's italics]

It is satisfactory that both definitions, published some 30 years apart, fully agree with one another; furthermore, we still can subscribe to both of them, even 50 years later. Many similar definitions can be found over the last 80 years, all of them stressing the point that the ensemble of rotatory dispersion and circular dichroism in the absorption region *collectively* constitute the Cotton effect. Nevertheless, quite commonly the term Cotton effect has loosely been used to characterize merely the "anomalous" rotation features, since in the decades following Cotton's discoveries the available data were mostly limited to the optical rotation. In fact, in many cases it has been considered sufficient to have reached the first maximum of the rotatory dispersion curve, still outside the absorption band, to apply the term Cotton effect. In recent decades, when ORD effectively disappeared in favor of CD, the term usually means the CD curve only.

1.6. MORE TARTRATES: THE PHYSICIST'S PLAYGROUND

Cotton's discovery of circular dichroism raised so much interest in Brace's Physics Laboratory at the University of Nebraska that it was decided to construct an improved and more sensitive apparatus for measuring both elliptical polarization and rotation, in order to repeat and extend the French findings. The American physicist DeWitt Bristol Brace was himself active in the field of optical activity and had in 1904 described an elliptical polarizer and compensator that was incorporated not only in the optical system used in Nebraska, but also later in Europe. Brace died in 1905 and had, therefore, no part in the further development. The first results on, for example, complex chromium, copper, cobalt, and nickel tartrates and copper malate were presented by M. F. McDowell in 1905 [31]. The ellipticity had been measured in "all parts of the spectrum," which means at some 10 different wavelengths of the visual solar spectrum.

Unfortunately, the calculation of the ellipticity was found to be incorrect, and some compounds were irreproducible. This was carefully rectified at the same laboratory in 1912 by L. B. Olmstead, who studied tartrates, malates, and lactates of chromium, copper, cobalt, and manganese [32]. Also here, the so-called "monochromatic" light, with a spectral band width of perhaps 20 nm, was obtained from sunlight. Although the optical part of the investigation seems to be impeccable (except that Cotton's first—incorrect—sign protocol of the circular dichroism was still used), the identity of the compounds studied is uncertain. Olmstead himself points out: "No chemical analyses of the compounds were made; *the names assigned being merely for convenience*, and not indicating that the chemical formulæ are known." [Olmstead's italics]. He observed that Cotton's results for potassium chromium tartrate could be repeated quantitatively when the sample was prepared from potassium dichromate and potassium tartrate, but an oppositely signed Cotton effect developed when the potassium dichromate was replaced by chromium acetate. Undoubtedly, the samples consisted of a mixture of complexes, as was also indicated by color changes of the solutions, depending on variations of the concentration and with time. As a result, even these carefully collected data are of a qualitative nature only.