toward skill at conformity, showmanship, and the dignified hypocrisy that often brings mundane success and high position (*9, 10*). This would have been a far greater danger in the case of the old-style eugenics.

But, it may be objected, does all this really represent conscious control in an over-all sense? Is it not merely a type of floating along in a chaotic manner, each straw making its own little movement independently of the rest, without a general plan or goal or stream? The answer is that humanity is as yet too limited in knowledge and imagination, too undeveloped in values, to see more than about one step ahead at a time. That step, however, can be discerned clearly enough, and by enough people, to give rise to a general trend in a salutary direction. And at the higher level to which each step taken will bring us we will be able to see an increasing measure of advance ahead. So we humans will achieve, not through dictation but through better general understanding and ever more clearly seen values, increasing mutual consent both concerning the means to be used and the aims toward which to orient. Thus an ever wider over-all view will emerge, and a surer, greater over-all plan, or rather, series of plans. To create them and to put them into effect will then enlist our willing efforts. And the very enjoyment of their fruits will bring us further forward in our great common endeavor: that of consciously controlling human evolution in the deeper interests of man himself (*11*).

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Optical Rotatory Dispersion

Investigation of the phenomenon 140 years after its discovery sheds light on problems of organic chemistry.

Carl Djerassi

The organic chemist, notably the investigator in the natural products field, has always been very ready to use new physical tools for the solution of his problems. Nowadays, it is difficult to conceive of modern organic chemical research being conducted without the use of ultraviolet, infrared, or nuclear magnetic resonance spectroscopy, and it is profitable to consider for a moment how these tools became acceptable to the organic chemist. Invariably, the initial discovery was made by the physicist or physical chemist, who was usually concerned only with the phenomenon itself, rather than with its application to the more mundane everyday problems of the organic chemical research laboratory. Application in the laboratory of the organic chemist occurred only when instrumentation became sufficiently advanced or simplified so that a relatively large number of measurements could be conducted on organic compounds. These measurements then lent themselves to empirical correlation with some structural feature of the organic molecule, and this invariably led to two developments—one, a rapid acceptance by other organic chemists, with a consequent enormous increase in the number of measurements and hence refinements in empirical correlation, and the other, a revival (or continuation) of interest in the theoretical aspects of this particular tool and a more fundamental explanation of the generalities uncovered by the semiempirical studies of the laboratory chemist.

This has been the history of virtually all physical methods which have found a temporary or a permanent place in organic and biochemical research; only the time lag between the initial physical discovery and the first widespread use by the organic chemist has differed. For instance, in the field of infrared spectroscopy, this interval amounted to approximately 40 years, while less than a dozen years intervened between the discovery of the nuclear magnetic resonance phenomenon and its extremely wide use in organic chemistry.

Early Studies

The development of optical rotatory dispersion followed precisely the same path, except that nearly 140 years elapsed between the original discovery by Biot (*1*) of the change of optical rotation of quartz with wavelength and the actual application of this general phenomenon to organic chemical problems (*2*). In the interval, a substantial amount of research in this area was conducted largely by physical chemists, and reviews (*3*) by three of the pioneers—Lowry, Levene, and Kuhn—show on the whole a rather understandable preoccupation with theoretical aspects of optical rotation and rotatory dispersion. During this entire period, up to around 1954, considerably less than 100 optical rotatory-dispersion curves had been recorded in the ultraviolet region of the spectrum, principally because of the instrumental difficulties involved in such studies. Indeed, between the 1930's—when experimental work by these three

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research groups (*3*) had terminated—and 1955, only a handful of publications appeared on ultraviolet optical rotatory-dispersion measurements, and there are practically no instances on record where this method was used for the solution of an organic or biochemical problem. This state of affairs should be contrasted with two striking indications of revived activity and interest in optical rotatory dispersion, especially as it applies to organic chemistry and biochemistry. The advances in instrumentation are illustrated by the observation that in our laboratory at Wayne University and later at Stanford University, approximately 3000 ultraviolet rotatory-dispersion curves were measured in less than 8 years, while a quantitative index of general acceptance of optical rotatory dispersion as a physical tool is afforded by the fact that during the past 18 months approximately 200 publications have appeared in which ultraviolet optical rotatory-dispersion measurements have been employed for the solution of some organic chemical or biochemical problem.

General Principles

To appreciate the reasons for this renaissance, a brief discussion of optical rotatory dispersion, in terms of its dispersive and absorptive character, is required. We may consider a beam of plane-polarized light to be made up of a right and a left circularly polarized component. Although no rotation will be observed if these two components pass through a medium with equal velocity, the plane of polarization of the emergent light will be rotated if the refractive indices of the medium for right and left polarized light are unequal. This dispersive feature is the principal factor in monochromatic polarimetry, as, for instance, in the conventional measurement of optical rotation of an optically active substance at one wavelength, such as the sodium D line (5890 A). In addition to unequal velocity of transmission, there may also be unequal absorption of left and right circularly polarized light. The emergent light will then be elliptically polarized, and this absorptive aspect is called circular dichroism. The combined phenomena of circular dichroism (unequal absorption) and optical rotation (unequal velocity of transmission) are named the "Cotton effect," after its discoverer. As will be shown, it is the experimental measurement of this Cotton effect and its correlation with certain structural and stereochemical features that is chiefly responsible for the application of optical rotatory dispersion in organic chemistry.

In principle, the experimental determination of an optical rotatory-dispersion curve is a simple matter that involves the measurement of optical rotation of a given substance at different wavelengths, rather than just at the conventional sodium D line. All that is required is a light source, a monochromator for yielding light of a given wavelength, a polarizer, a cell containing the optically active material in solution, an analyzer, and a device for measuring the angle of rotation. The polarizer and analyzer are usually quartz Rochon prisms, and the angle of rotation is measured visually when one is working with visible light (such as the sodium D line). However, most organic compounds are colorless and absorb only in the ultraviolet region of the spectrum. Consequently, if one wishes to measure experimentally the Cotton effect of colorless substances, then one must carry out optical rotation determinations in the ultraviolet spectral range. This cannot be done visually, and it is here that experimental difficulties arise. In the earlier work (*3*), determinations in the ultraviolet region were made with laborious photographic procedures, and it was only the development of a commercially available spectropolarimeter (see *2*, chap. 3) that made possible the relatively rapid and simple measurement of a rotatory-dispersion curve in the ultraviolet. With the spectropolarimeter the measurement could be made in one or two hours, whereas the photographic method required several days.

Plain and Anomalous Curves

There are two types of dispersion curves (*2*, chap. 2; *4*). Figure 1 illustrates some plain curves—that is, dispersion curves that exhibit no "maxima" or "minima" but a simple increase in rotation as one proceeds into the ultraviolet. Curves *A* and *B* of Fig. 1 are called positive plain curves even though curve *B* starts out on the negative rotation side in the visible and crosses the zero rotation axis in the ultraviolet; curve *C* is called a negative plain curve.

An anomalous optical rotatory-dispersion curve is one that exhibits rotational maxima and minima; an idealized example is reproduced in Fig. 2. Anomalous curve *A* represents a single positive Cotton effect, while curve *B* is typical of a negative Cotton effect, since the first extremum in going from the visible to the untraviolet is a rotational minimum. The rotational maxima and minima are called peaks and troughs (*2*, chap. 2; *4*), so as not to confuse them with ultraviolet absorption maxima and minima. Thus, the positive Cotton effect of curve *A* in Fig. 2 would be exhibited by an optically active substance with a chromophore absorbing at wavelength λ_0, which represents approximately the mid-point in terms of wavelength units between the positions of the peak and the trough of the rotatory-dispersion curve. It is this intimate relationship between the absorption spectrum and the optical rotatory dispersion of a given substance that usually indicates whether the substance will exhibit an anomalous rotatory-dispersion curve in a given wavelength region.

Thus, plain curves of the type shown in Fig. 1 will be exhibited generally by optically active substances (for example, hydrocarbons, alcohols, and carboxylic acids) that do not absorb in an accessible region of the spectrum, while an anomalous curve (for example, *A* and *B* in Fig. 2) will be shown by a substance containing a chromophore (such as a carbonyl or nitro group) that does absorb in such a region. Actually, every plain curve will eventually become anomalous as it approaches its optically active absorption band, but in many compounds these bands may occur so far down in the ultraviolet, or may absorb with such intensity, that rotation measurements are not feasible in that spectral region. To illustrate this point, the anomalous rotatory-dispersion curves shown in Fig. 2 are actually plain curves over the range 7000 to 4500 A and become "anomalous" only as they approach the region of the absorption maximum ($\lambda_0 = 3000$ A).

An obvious conclusion from either the plain or the anomalous dispersion curves shown in Figs. 1 and 2 is that optical rotations will invariably be much greater in the ultraviolet than in the visible, and that the historical choice of the sodium D line at 5890 A for monochromatic rotation measurements is a rather poor one. Much smaller amounts of optically active substrate are required for rotation measurements in the ultraviolet than in the visible, and most of the ultraviolet optical rotatory-dispersion measurements in our laboratory have been conducted with 0.1 to 1.0 milligram of material, a quantity that is usually totally inadequate for rotation measurements at the sodium D line.

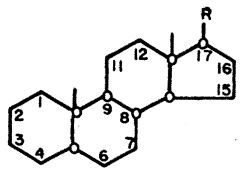
Between 1812 and 1954, only approximately 50 Cotton-effect curves had been measured experimentally (*3*). Among the various chromophores that had been investigated there were a few ketones, such as camphor, whose rotatory-dispersion curve was similar to curve *A* in Fig. 2. While this experimental material had not led to any widespread applications, it nevertheless demonstrated the feasibility of measuring Cotton effects, provided substances with suitable chromophores are selected. Therefore, when the first commercially available model of the Rudolph spectropolarimeter was delivered to our laboratory, we set out to test certain assumptions.

Applications to Stereochemistry

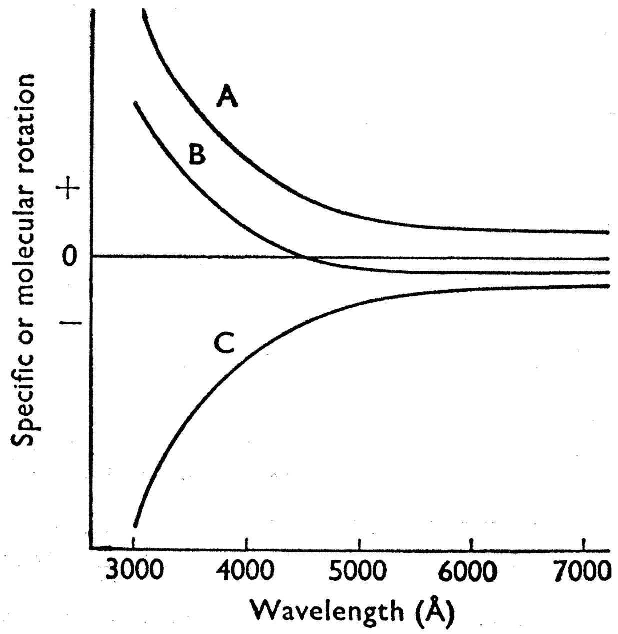
While plain rotatory-dispersion curves (Fig. 1) are preferable for stereochemical correlation (*2*, chap. 16; *5*) over single rotation measurements at the sodium D line, especially when the curves cross the zero line (curves *A* and *B* in Fig. 1), they are obviously limited in scope. On the other hand, if variations in the asymmetric environment of a given spectroscopically accessible chromophore should result in Cotton-effect curves of different shape or sign, and if these differences could be related to certain structural or stereochemical features of the molecule, then a valuable physical tool would be available to the organic chemist.

For initial experimental examination we selected the carbonyl chromophore, since it absorbs in an accessible spectral region (2800 to 3300 A), with a rather low extinction that would permit rotation measurements through this region of maximal absorption, an indispensable feature if Cotton effects are to be determined experimentally. Furthermore, earlier work (*3*) on camphor and a few related terpene ketones had shown that such ketones exhibit Cotton-effect curves —in other words, that the intrinsically symmetrical carbonyl chromophore $>\mathrm{C{=}O}$ became "optically active" when placed in an asymmetric environment—although it could not be determined from these few studies whether the Cotton effect would reflect structural changes in its asymmetric surroundings. A further reason for selecting the carbonyl chromophore was the ready availability of many optically active ketones and aldehydes, or at least of alcohols from which they could be obtained by oxidation.

With the choice of the chromophore —that is, the "absorptive" component of the rotatory dispersion—settled, it was then necessary to decide upon a reasonable asymmetric framework that would offer sufficient scope for selective alteration to find whether such changes would result in variations in shape or sign of the Cotton effect. For this purpose we chose a group of compounds that was uniquely suitable, the steroids, which are characterized by the following skeleton:



The advantages of this group of compounds are manifold. All of them are optically active, of known absolute configuration, and usually of fixed and known conformation. Furthermore, probably several thousand representatives of this class have been prepared during the past 30 years, largely because of the great biological importance of the steroids. Finally, and perhaps most importantly for our purposes, most of the steroids possess a chain of seven contiguous asymmetric carbon atoms (circled in the structure shown above), so that irrespective of where a carbonyl group is placed in this molecule, it can, at best be only one carbon atom away from this asymmetric chain. When a carbonyl group is placed in the



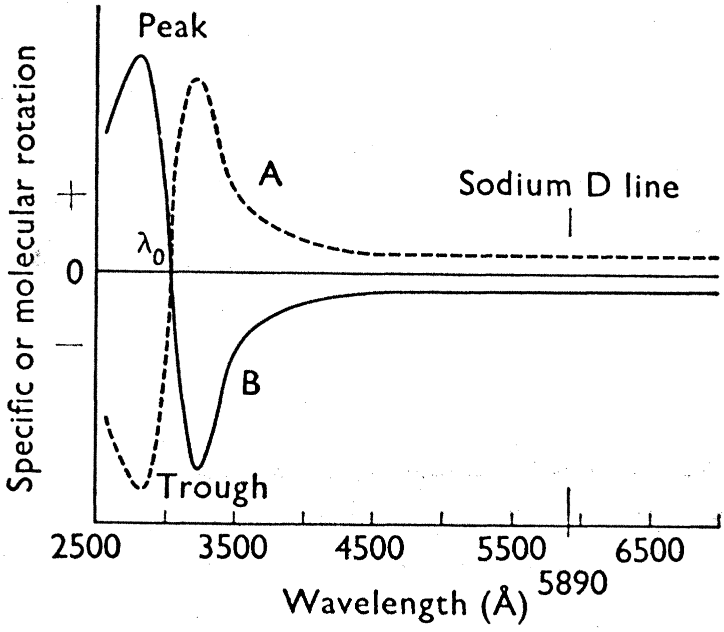


Fig. 1 (left). Typical plain rotatory-dispersion curves: *A* and *B*, positive; *C*, negative. Fig. 2 (right). Typical anomalous rotatory-dispersion curves: *A*, positive Cotton effect; *B*, negative Cotton effect.

eleven possible locations of the four-ring skeleton, not only will the chromophore find itself in different asymmetric situations but the incorporation of a trigonal carbon atom into any one of the rings will cause a displacement of the valency angles with a concomitant ring-geometry distortion that may make itself felt through varying ranges of this asymmetric backbone.

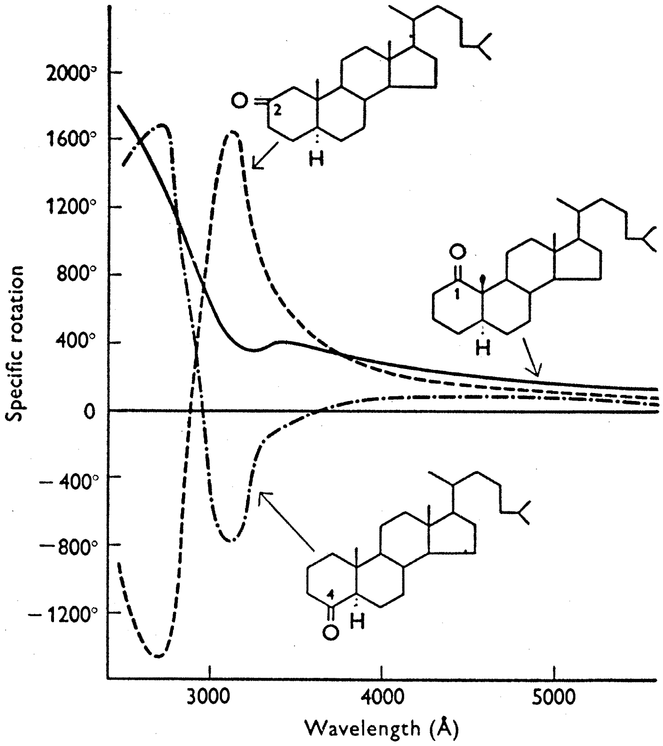
Since many such steroids and a modern spectropolarimeter were available in our laboratory, we were able to measure, in a rather short time, many hundreds of ultraviolet rotatory-dispersion curves of closely related ketones. This initial work (*6*) demonstrated that variations in the shape and sign of such Cotton effects can indeed be related to many important molecular parameters. This prompted us to carry out a much more extensive investigation of the application of optical rotatory-dispersion measurements to organic chemistry than had been contemplated initially. Much of this work appeared between 1955 and 1960, in some 40 articles from our laboratory, and I have recently summarized it in book form (*2*). Therefore, I will give only a few highlights below, to indicate the general scope of the method and the directions of future research.

Structural Applications

Figure 3 may be considered a typical example of *structural* information that can be derived from a rotatory-dispersion curve. It contains the dispersion curves of three isomeric cholestanones, distinguished only by the location of the carbonyl group; it may be noted that these curves differ significantly in either shape or sign. Most importantly, it was observed that these characteristic curves are retained in the presence of many other substituents (esters, acids, alcohols, lactones, and so on) that do not absorb in the same spectral range as the carbonyl group. Consequently, we have now available a tool which can frequently tell us, with less than 1 milligram of recoverable substance, where a keto group (and hence the corresponding hydroxyl function) is located in an unknown steroid. At present, no other physical method affords this information.

The differences in the rotatory-dispersion curves of Fig. 3 were brought about by moving the carbonyl group around the asymmetric framework and thus placing it each time in a distinct asymmetric environment; the change is thus reflected in the dispersion curve. Alternatively, such a change in environment may be produced by keeping the chromophore in the same location but altering the immediate stereochemistry. Thus, reduction of the double bond of the male sex hormone testosterone affords two isomers, 5α- and 5β-androstan-17β-ol-3-one, differing only in the nature of the A/B ring juncture. As shown in Fig. 4, the 5α-isomer exhibits a positive (*A*), and the 5β-isomer, a negative (*B*), Cotton effect. These characteristic rotatory-dispersion features remain unchanged, even if the substituents at C-5 or C-10, or at both positions, in these molecules are replaced by other "nonchromophoric" moieties (CH_2OH, CN, $CH_2CO_2CH_3$, and so on), and this has proved to be very useful in the steroid field for determining the nature of the A/B ring juncture in an unknown 3-keto steroid.

When the carbonyl group is placed next to the ring juncture, then equilibration between the two isomers is possible in the presence of acid or base. This is illustrated in Fig. 5 with the two 15-ketones of the bile acid series, which differ only in the configuration at C-14. The C/D *cis* isomer (*B*), with a negative Cotton effect, is the more stable isomer, and the kinetics of the isomerization can be determined very conveniently on a micro scale by taking advantage (*7*) of the information con-



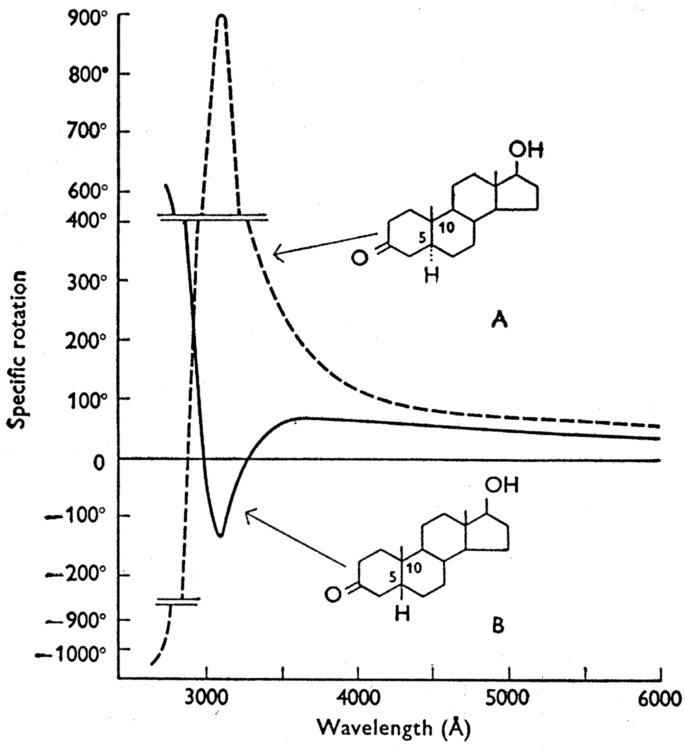


Fig. 3 (left). Optical rotatory-dispersion curves of some isomeric cholestanones. Fig. 4 (right). Optical rotatory-dispersion curves of (*A*) 5α-androstan-17β-ol-3-one (dihydrotestosterone) and (*B*) 5β-androstan-17β-ol-3-one.

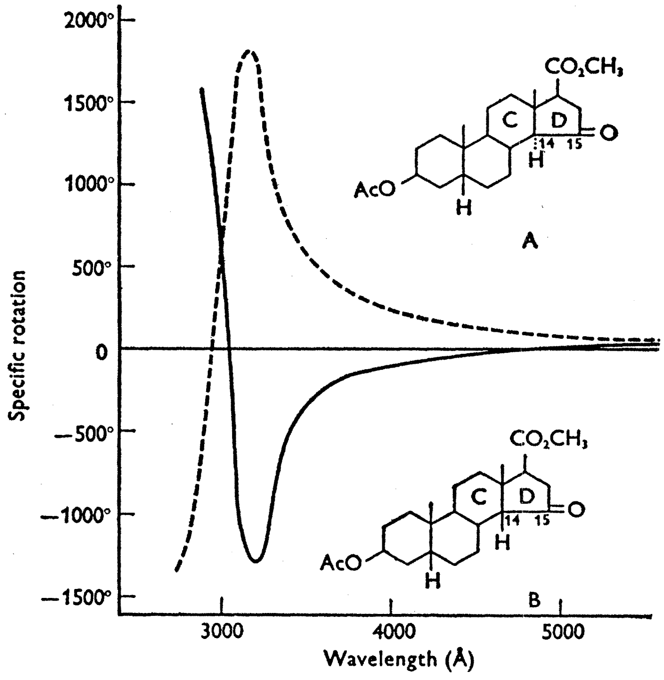
tained in Fig. 5. It may be noted that the rotations of the two isomers are rather similar at the conventional sodium D line in the visible (5890 A), while in the ultraviolet near 3200 A this difference in specific rotation amounts to over 3000 degrees. All that is necessary, therefore, is to measure the rate of change in rotation at some convenient wavelength in the ultraviolet and calculate from these data the kinetics and position of equilibrium.

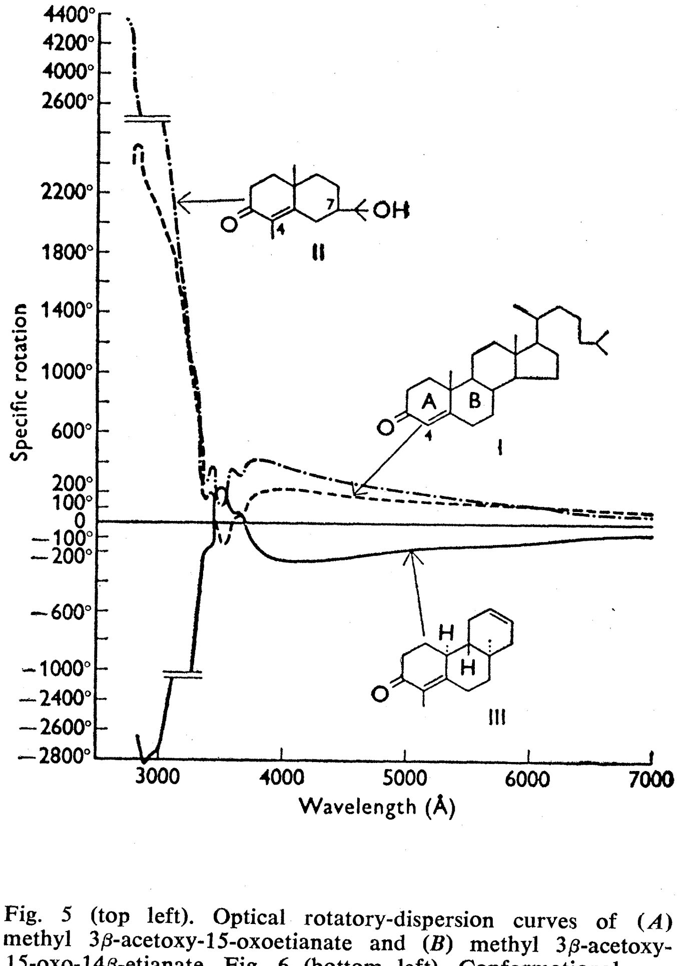
The rotatory-dispersion curves in Figs. 3, 4, and 5 represent typical examples from the steroid series of structural, stereochemical, and analytical-kinetic applications of dispersion measurements. That these generalizations from the steroid group are, in fact, of much wider scope was then demonstrated (*8*) by a process of dissection, through which it was found that only the immediate asymmetric bicyclic environment around the carbonyl group is responsible for the characteristic rotatory-dispersion features. This conclusion led immediately to the two most important applications of rotatory dispersion—the assignment of absolute configurations and the detection of conformational alterations.

Conformational Analysis

The use to which this tool can be put in conformational analysis is illustrated in Fig. 6. *Trans*-10-methyl-2-decalone (I) represents the bicyclic analog of a 5α-3-keto steroid (for example, *A* in Fig. 4), and its conformation can be defined unambiguously as the all-chair form IA (Fig. 6). The rotatory-dispersion curve of this ketone I proved to be practically identical with that of steroid *A* in Fig. 4.

A considerably more difficult situation prevails in the isomeric *cis*-10-methyl-2-decalone (II in Fig. 6), where two all-chair conformations (IIA and IIB) have to be considered. Of these, IIA is called the steroid conformation, since steroids are frozen in this conformation by virtue of the additional ring fusions. Since we had already established (*8*) that the more distant rings in the steroid series do not play an important part insofar as the typical shape of the rotatory-dispersion curve of a given ketone is concerned, the negative Cotton effect of steroid *B* in Fig. 4 will thus serve as a suitable reference curve for the steroid conformation of the bicyclic ketone II in conformation IIA (Fig. 6). It may be seen that in the nonsteroid conformation IIB, the





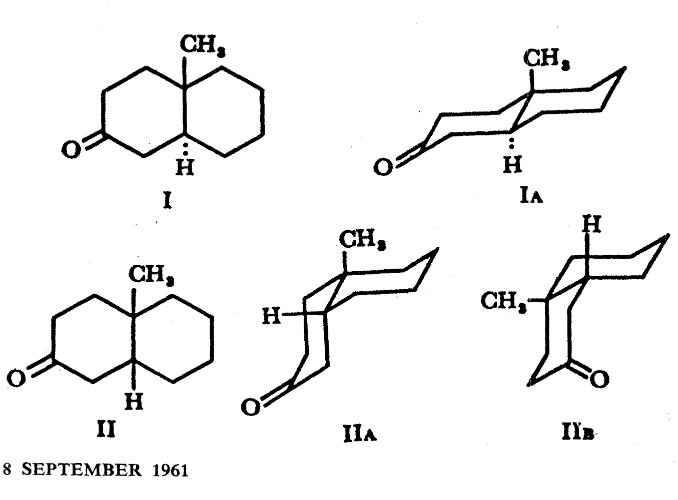


Fig. 5 (top left). Optical rotatory-dispersion curves of (*A*) methyl 3β-acetoxy-15-oxoetianate and (*B*) methyl 3β-acetoxy-15-oxo-14β-etianate. Fig. 6 (bottom left). Conformational representations of (I) *trans*-10-methyl-2-decalone and (II) *cis*-10-methyl-2-decalone. Fig. 7 (right). Optical rotatory-dispersion curves of (I) Δ^4-cholesten-3-one; (II) carissone; and (III) (—)-1,14-dimethyl-2-oxo-$\Delta^{1(11),9}$-decahydrophenanthrene.

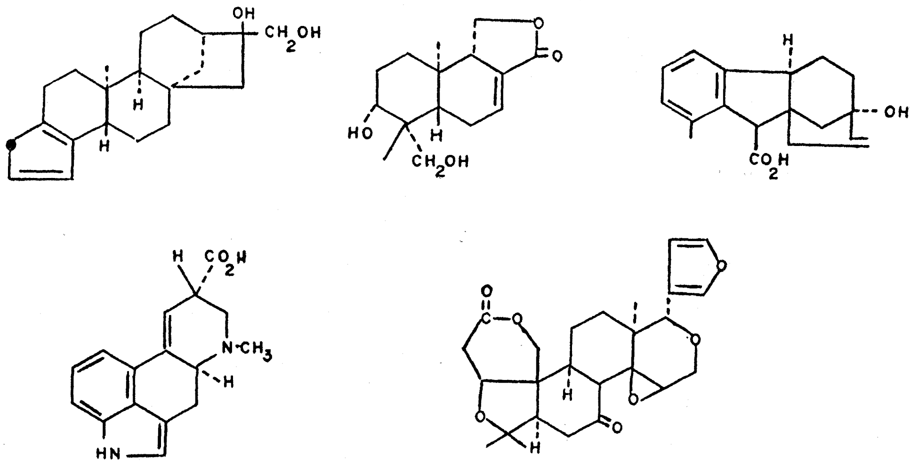


Fig. 8. Configurations of various compounds, established through optical rotatory-dispersion analysis: (top left) cafestol; (top middle) iresin; (top right) allogibberic acid; (bottom left) lysergic acid; (bottom right) limonin.

carbonyl group is in a different asymmetric environment, and its rotatory-dispersion curve would be expected to be quite distinct from that of the steroid model. When ketone II was synthesized (*8*) in optically active form and when its rotatory-dispersion curve was measured, the curve proved to be very similar to that of the steroid *B* in Fig. 4. One can deduce, therefore, that ketone II exists in the steroid conformation IIA—a conclusion which, a priori, was not self-evident. At the present time, rotatory dispersion is the only physical method that has shed any light on the conformation of such a decalone in solution.

Absolute Configuration

The determination of absolute configuration—that is, the differentiation between mirror-image representations—has been of concern since the earliest days of stereochemistry. The only direct procedure is that of x-ray analysis (*9*), but until now this has been used in only a very few instances. What is really needed is a quick method which permits the establishment of the absolute configuration of a given molecule by relating it to another reference compound whose absolute configuration has been settled directly or indirectly (through various chemical transformations) by the x-ray method. It is in this area of stereochemistry that optical rotatory-dispersion measurements have filled a very important need.

In principle, the approach (*8*) is quite simple and is based on the premise employed in Fig. 6 for examining the conformation of *cis*-10-methyl-2-decalone. Since we have shown that the characteristic shape of a rotatory-dispersion curve is governed by the bicyclic stereochemical (and conformational) environment of the chromophore —in the present instance, the carbonyl group—and since additional nonchromophoric substituents do not interfere, then all that is necessary is to compare the rotatory-dispersion curve of the unknown compound with that of a known reference substance, possessing the same chromophore, in a similar environment.

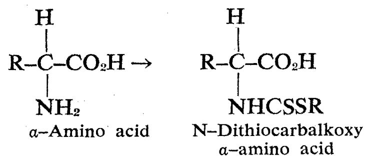
The absolute configuration of the steroids is known (*10*), and their rotatory-dispersion curves, therefore, can be used for such reference purposes. A typical example is reproduced in Fig. 7, with the rotatory-dispersion curves of the steroid Δ^4-cholesten-3-one (I) and the sesquiterpene carissone (II). The hydroxy-isopropyl substituent at C-7 of carissone represents a nonchromophoric substituent, as does the extra methyl group at C-4. This latter point was established (*8*) in a separate experiment in which it was noted that the rotatory-dispersion curve of Δ^4-cholesten-3-one (I) was not altered in any of its essential details by the addition of a methyl function at C-4. Consequently, the carbonyl chromophore in the steroid I of known absolute configuration and the sesquiterpene carissone (II) are found in identical bicyclic environments, and as their rotatory-dispersion curves are very similar in shape and sign, there is no question but that the absolute configuration of carissone is that represented in stereoformula II, rather than its mirror image. The third substance in Fig. 7, the tricyclic ketone III, also has the same relative stereochemical environment in rings A and B as the steroid I. Its rotatory-dispersion curve, however, is essentially of mirror-image type, and from this it follows that, in terms of its absolute configuration, ketone III belongs to the antipodal series.

Various refinements of this approach have been introduced recently, including semiempirical generalizations that often make it possible to predict the sign of the Cotton effect of an unknown ketone without requiring the rotatory-dispersion curve of a reference compound. These generalizations have already been reviewed elsewhere (*2*, chaps. 9, 10, 13). Suffice it to say that by the approach illustrated in Fig. 7, or its extensions (*2*, chaps. 9, 10, 13), the absolute configurations of a wide variety of very complicated natural products have been established very quickly. A few typical examples are listed in Fig. 8, and it is quite obvious that to arrive at the same conclusions by any other classical approach would have required a tremendous effort.

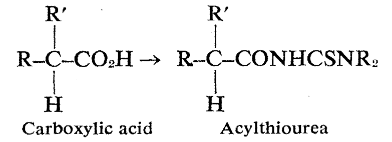
Recent Studies

Most of the discussion up to this point has centered on the carbonyl chromophore, largely because most of our original work was focused on it by virtue of its abundance and its favorable spectral characteristics. Lately, our attention, as well as that of other investigators, has centered on other chromophores, and a very substantial amount of progress has already been achieved. Examples of chromophores recently studied are dithiocarbamates and xanthates (*11*), disulfides and diselenides (*12*), phthalimides (*13*), acylthioureas (*14*), and osmates (*15*). This partial list is important not only because it illustrates the range of different chromophores that may give rise to Cotton-effect curves but even more significantly because it includes derivatives of important nonchromophoric functional groups.

For instance, α-amino acids do not absorb in a convenient region of the ultraviolet, and thus they show only plain rotatory-dispersion curves, but their readily prepared N-dithiocarbalkoxy derivatives (dithiocarbamates) exhibit strong Cotton effects. In fact, the sign of the Cotton effect can be related directly (*11*) to the absolute configuration of the asymmetric center, members of the L-series showing a positive Cotton effect and of the D-series, a negative one.


$$R\text{-}\overset{H}{\underset{NH_2}{C}}\text{-}CO_2H \rightarrow R\text{-}\overset{H}{\underset{NHCSSR}{C}}\text{-}CO_2H$$

Similarly, carboxylic acids do not absorb above 2100 A, but their derived acylthioureas (*14*) contain a low-intensity absorption maximum near 3400 A. It is not surprising, therefore, that such thiourea derivatives should yield Cotton-effect curves, and that the sign of these Cotton effects can be used for deducing the absolute configuration of the α-asymmetric center of the parent carboxylic acid.


$$R\text{-}\overset{R'}{\underset{H}{C}}\text{-}CO_2H \rightarrow R\text{-}\overset{R'}{\underset{H}{C}}\text{-}CONHCSNR_2$$

Olefins are essentially transparent above 2000 A, but they react readily with osmium tetroxide to form osmate esters. These esters, notably their dipyridyl complexes, have been found (*15*) to exhibit strong Cotton effects in a very convenient region of the spectrum, and as these osmates can be prepared on a micro scale, there is now available a means of studying certain structural and stereochemical features of olefins in terms of anomalous optical rotatory-dispersion curves.

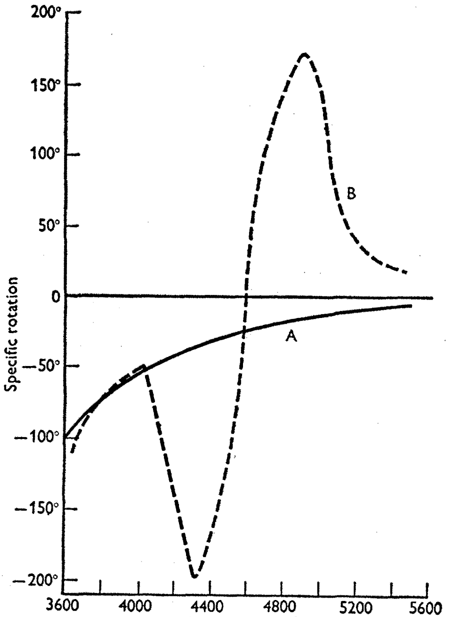


Fig. 9. Optical rotatory-dispersion curve of poly-α, L-glutamic acid at *p*H 4.9. *A*, Polypeptide without dye; *B*, polypeptide-acriflavine complex. [Redrawn from Blout and Stryer (*17*) with permission]

Conformation of Polypeptides and Proteins

One very exciting area of application of optical rotatory dispersion which has not yet been mentioned is represented by the determination of conformation of polypeptides and proteins. This has been reviewed recently in great detail by E. R. Blout (*2*, chap. 17), one of the experts in this field, and only brief reference will be made to it here. The hydrogen-bonded α-helix structure of proteins, initially proposed by Pauling and Corey, is now generally accepted. One of the most effective ways of studying such a conformational feature has been by optical rotatory dispersion, even though such curves have until recently been of the plain type. Specifically, it was found that the plain curves of polypeptides in a random conformation follow a simple Drude equation, while this is not true of the helical conformation, and the consequent mathematical generalization, largely attributable to W. Moffitt, has proved to be very useful in this biochemical area. As an illustration of the use to which this information can be put, Goodman and his collaborators (*16*) have demonstrated by such rotatory-dispersion measurements that the critical range where synthetic polypeptides of γ-methyl glutamic acid shift from the random to the helical structure falls between the hepta- and the nonapeptide.

Two important recent observations by Blout and his collaborators indicate that anomalous optical rotatory dispersion with experimentally determined Cotton effects will play an increasingly significant role in the polypeptide and protein fields. In the first paper (*17*) it was noted that while poly-α, L-glutamic acid exhibits only a plain rotatory-dispersion curve (*A* in Fig. 9), its complex with the optically *inactive* dye acriflavine now shows a Cotton effect (*B* in Fig. 9) centered around the 4570-A absorption band of the dye. Such Cotton effects are observed with the dye-polypeptide complex only when the polypeptide is in the helical, rather than the random, conformation. The complexes thus offer a strikingly simple approach to the study of helical conformations as well as to the determination of the "handedness" of the helix by means of anomalous rotatory dispersion. Of even more general applicability is the observation (*18*) that Cotton effects of polypeptides and proteins may be determined *directly* in the 2100- to 2300-A region with the new automatically recording Rudolph spectropolarimeter, and this development points toward the most significant contribution that improved instrumentation can make.

Future Prospects

As spectropolarimeters are designed that can either handle strongly absorbing systems or else permit greater penetration into the ultraviolet region, more and more classes or organic compounds will fall within the scope of the type of anomalous optical rotatory-dispersion analyses that have been covered in this article—analyses that have been responsible for the suddenly revived interest in optical rotatory dispersion and its widespread use in organic chemical and biochemical research problems.

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