

Moffitt W, Woodward R B, Moscovitz A, Klyne W & Djerassi C. Structure and the optical rotatory dispersion of saturated ketones.

*J. Amer. Chem. Soc.* 83:4013-18, 1961. [Dept. Chem., Harvard Univ., Cambridge, MA; Sch. Chem., Univ. Minnesota, Minneapolis, MN; Dept. Chem., Westfield Coll., Univ. London, England; and Dept. Chem., Stanford Univ., CA]

The octant rule provides a means of predicting the sign of the 'Cotton effect' of organic carbonyl-containing compounds by measuring their optical rotatory dispersion or circular dichroism, thus leading to the determination of the absolute configuration or conformation of a molecule. [The SC<sup>2</sup> indicates that this paper has been cited in over 600 publications since 1961.]

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"Even though optical rotatory dispersion was known for over 100 years, prior to 1950 it had not found any application to structural or stereochemical studies of organic molecules. In 1952, my research group started a systematic investigation of the optical rotatory dispersion of steroid ketones and showed that the sign and/or shape of the resulting 'Cotton effect' curve could be associated with the location of the carbonyl chromophore in the steroid nucleus. Since only submilligram quantities of recoverable material were required, this prompted us to undertake a much more extensive study of optical rotatory dispersion applications in organic chemistry. In general we found<sup>1</sup> that the bicyclic environment of the steroid ketone played the dominant role and one could thus use steroid ketones as templates for determining the absolute configuration of a wide variety of natural products (notably terpenoids) whose absolute configuration had not been established earlier. We then turned to a study of the effect of extranuclear substituents such as alkyl and halogen.<sup>1</sup> With the latter, we found<sup>2</sup> that an  $\alpha$ -substituted axial chlorine, bromine, or iodine atom has a predictive effect which lends itself to the determination of the absolute configuration or conformation of a cyclic ketone without recourse to any reference compound of known absolute configurations. This represented a major advance in stereochemistry and was called by us<sup>1,2</sup> the 'axial  $\alpha$ -haloketone rule.'

"Shortly thereafter, A. Moscovitz and the late W. Moffitt<sup>3</sup> at Harvard University conducted

theoretical studies on the light absorption of the carbonyl chromophore located in an asymmetric environment. The late R.B. Woodward, also at Harvard, was familiar with our studies and during one of my visits to Harvard organized a discussion among the four of us. The late W. Klyne of the University of London, who had collaborated with me on the axial haloketone rule, joined us on a subsequent occasion and these discussions rapidly led to the conclusion that our empirically derived axial haloketone rule was in fact readily accommodated in a more general 'octant rule' based on Moscovitz's and Moffitt's theoretical studies.<sup>3</sup> These studies suggested the existence of three nodal and symmetry planes associated with the relevant orbitals of the carbonyl group which divided the space occupied by a cyclic ketone into eight octants. Location of a given substituent in each of these octants then leads to a predicted sign of the Cotton effect and thus to an *a priori* determination of the absolute configuration or conformation of a molecule, just as we had accomplished earlier with the more specialized  $\alpha$ -haloketone rule.<sup>2</sup>

"Our Citation Classic paper had an important personal as well as a general consequence. Personally, it led to collaboration between Moscovitz (now at the University of Minnesota) and my group which has continued off and on for 20 years. In a more general context, it stimulated a very wide use of optical rotatory dispersion and subsequently of the phenomenologically related circular dichroism to which the octant rule could be applied without modification. The absolute configurations of numerous organic molecules were first established by the octant rule, as well as many subtle conformational effects. Indeed, the octant rule has proved very useful even in predicting the rotational behavior of isotopes such as deuterium and <sup>13</sup>C.<sup>4</sup>

"In addition to these practical applications, numerous theoretical studies were prompted by our paper. Most of them focused on the ambiguity introduced by the third nodal plane (to whose uncertainty we had already alluded in our original paper) and numerous subsequent studies<sup>5</sup> have considerably clarified the subtleties of the octant rule. The elaboration and wide application of this rule is one of the key factors why optical rotatory dispersion and later circular dichroism have become the most important chiroptical methods in organic chemistry."

1. Djerassi C. *Optical rotatory dispersion. Application to organic chemistry*. New York: McGraw-Hill, 1960. 293 p.
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3. Moffitt W & Moscovitz A. Optical activity in absorbing media. *J. Chem. Phys.* 30:648-60, 1959.
4. Barib G & Djerassi C. Circular dichroism of molecules with isotopically engendered chirality. *Tetrahedron* 37:4123-42, 1981.
5. Hansen A E & Bouman T D. Natural chiroptical spectroscopy: theory and computations. *Advan. Chem. Phys.* 44:545-644, 1980.