ABSOLUTE CONFIGURATION OF GOSSYPOL

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Dedicated to the memory of Dr Karel Bláha, a brilliant chemist and kind friend.

The absolute configuration of the physiologically active (−)-gossypol has been suggested to be M by application of the coupled oscillator theory to its CD.

Gossypol (*I*), first isolated from *Gossypium hirsutum* L. in 1899 by Marchlewski[1] has been shown to have promising antifertility activity in man[2]. Its structure has been elucidated by Adams et al.[3], and the racemate had been resolved by HPLC on a chiral phase by Matlin et al.[4,5], as well as by crystallization or usual column chromatography of a derivative obtained with an optically active base by Huang et al.[6]. Since only the (−)-enantiomer shows antifertility activity in male rats[7] it is important to determine its absolute configuration, which could now be achieved by chiroptical methods. X-ray diffraction data are available from two laboratories[8,9], from which follows that the two naphthalene moieties are twisted by a torsional angle of 68°, or 79°, resp., so the two chromophoric units are electronically decoupled and exciton theory[10] can be applied in order to determine absolute configuration.

The CD-spectra of both enantiomers of *I* (in chloroform) have been published[11]; above 300 nm two strong Cotton effects of opposite signs are observed at 377 and 338 nm. The corresponding UV-maximum (in the same solvent) is in between, viz. at 364 nm, and very intense, a typical situation for Davydov splitting[10]. In order to determine the direction of the electric transition moments for this first intense absorption Streitwieser's corrections[12] have been applied; the aldehyde group as well as all phenolic OH-groups have been included into the π-system, but only the canonical structure shown in formula *I* has been considered. Fifteen MO's have thus been obtained, and the first three

excited one-electron configurations have energies of approximately 0.9, 1.2, and 1.5β, resp. With this relatively large difference in energy between the first and the second excited configuration it seems not necessary to involve configurational interaction—at least not at this level of approximation,which is, however, sufficient for our purposes. The center of the corresponding transition dipole (approx. 4 Debye) is close to C(1) of the naphthalene system, and the vector is inclined by approx. 70° towards the pivot bond between the two naphthalene units, i.e. nearly parallel to the short axis of the chromophore. Assuming P-configuration for the gossypol molecule (Fig. 1) and a halfband width of 3 000 cm^{-1} one calculates $\Delta\varepsilon_{max}$-values of $+11.3$ and -11.2 for maxima at 395 and 340 nm. This is a very good agreement for such a crude approximation with the published CD-values[11] of $(+)$-gossypol, which has thus the P-configuration.
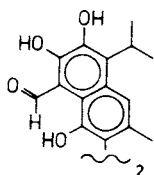
This result is neither very sensitive to the direction of the first electric transition moment vector, nor to midpoint (the position in the point-dipole approximation). The measured CD-couplet is not conservative; one obvious reason for this can be that the Cotton effect for the $n-\pi^*$ transition has opposite
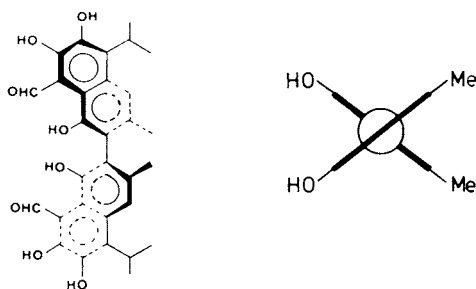

Fig. 1

Two projections of P-gossypol (I). Left: from top of molecule. Right: along the pivot bond (only the two substituents in o,o'-position are shown)

sign to the CD of that branch of the couplet with which it overlaps. The physiologically active (−)-gossypol is thus the (*M*)-enantiomer.

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