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CONFORMATIONAL ANALYSES BY X-RAY CRYSTALLOGRAPHY—II†

PRELOG'S RULE AND THE CONFORMATION OF (−) MENTHYL PHENYLGLYOXYLATE

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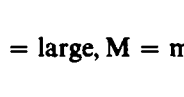
Abstract—The conformation of (−) menthyl *p*-bromophenylglyoxylate has been examined by X-ray crystallographic methods. The main features of the conformation lie in the two CO groups being approximately at right angles to one another, and the ester CO oxygen eclipsing the nearest axial H atom. Prelog's rule is discussed in the light of this result.

THE method of the steric path for the addition to the keto carbonyl of α-ketoesters



(L = large, M = medium, S = small substituents) permitted Prelog[2] in 1954 to perfect a method of easy determination of the absolute configuration of optically active alcohols. Prelog and his coworkers have considered the stereochemical course of reactions between α-ketoesters (II) of asymmetric alcohols (I) and Grignard reagents (Fig 1). They found that one of the two diastereomers (III) pre-

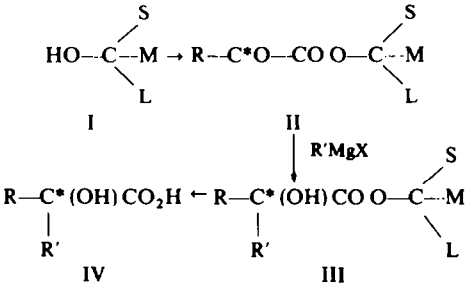


FIG 1

dominated and the stereochemistry of this predominant isomer at C* could be correlated with that of the carbinol atom of the alcohol. They hypothesized that the

† For Part I of this Series, see Ref 1.

Grignard reagent R'MgX would attack C* preferentially from the side on which the smallest substituent lies. This process requires the consideration of the possible conformations of the  group and Prelog has given a rule based on reasonable *a priori* choices of the preferred conformation of $C_6H_5COCOOR$. He suggests placing the two CO group of the α-ketoester in an antiparallel position and one of the bonds C--L, C--M or C--S in this plane as shown in Fig 2. The experimental results

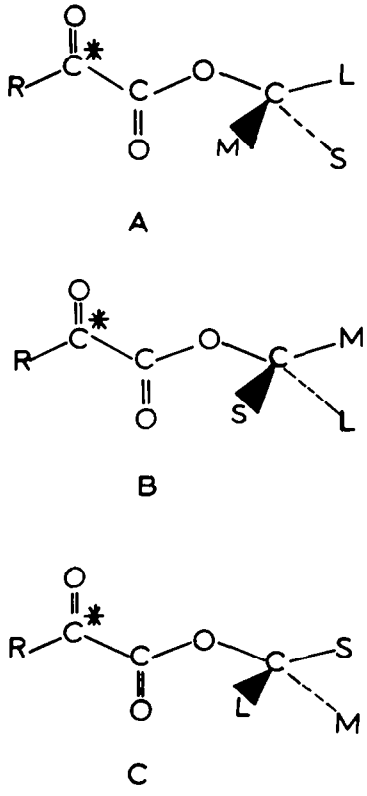


FIG 2.

led Prelog to retain the conformations A or C (Fig 2) as models permitting the preferential attack on C* from the rear. It is important to emphasize the semi-empirical value of Prelog's rule. The great usefulness of this rule is not a proof in itself of the presence of the conformation A or C* (for an analogous discussion of Cram's rule, see Refs 3–5).

It has been thought for a long time,[6] principally because of the results of dipole moment measurements of an ester R--CO_2--R', that simple esters exist in a planar conformation with OR' *cis* in relation to C=O (Fig 3). The rule of Prelog takes this conformation into consideration.

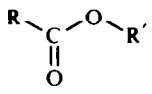


FIG 3.

Mathieson[7] has determined the conformation along the bond O--R' by X-ray crystallographic studies of the acetates of cyclohexanols. For an equatorial ester, he finds an eclipsed position of the CO group with reference to the axial hydrogen (Fig 4).

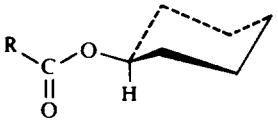


FIG 4.

Klyne[8a, b] successfully used these results to interpret the CD of steroid esters.[8c] The conformations used by Prelog (Fig 2) for glyoxylates are *not* of the type found in simpler esters by Mathieson. Indeed, the conformation found by Mathieson gives the *incorrect* prediction in an asymmetric synthesis.

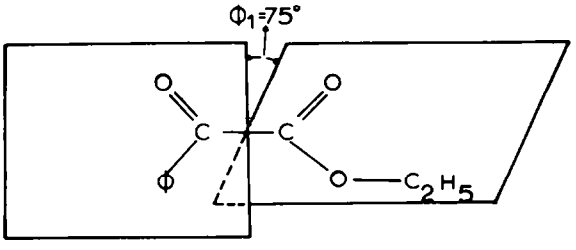
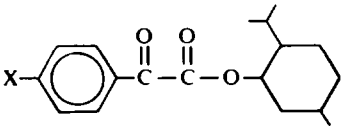


FIG 5.

The more closely analogous ethyl α-ketoesters were studied in 1968[9] by IR and dipole moment measurements. It appears that ethyl phenylglyoxylate exists in a conformation where the two carbonyls have been rotated by 75° from *cis*-coplanarity with one another (Fig 5).

It seemed interesting to examine the conformation of (−)menthyl *p*-bromophenylglyoxylate (hereafter referred to as PBGM; see Fig 6) by X-ray crystallographic methods in order to see whether, in this molecule, a good model for Prelog's asymmetric synthesis, one would again find the two characteristics discovered in the more simple cases by other methods: the conformation of Mathieson (Fig 4) and the twisting of the carbonyls (Fig 5).



1: X = Br
2: X = H

FIG 6.

PBGM crystallized from methanol at room temperature. The crystals are triclinic, space group $P\bar{1}$ with *four* molecules in the unit cell. The cell constants at room temperature (28° ± 1°) are: a = 10·152(4)Å, b = 19·661(3)Å, c = 9·220(3)Å, α = 92·45(3)°, β = 102·74(4)°, γ = 93·11(4)°. The measured density is 1·30 g/cm^3; the calculated density on the basis of four molecules in the cell is 1·36 g/cm^3.

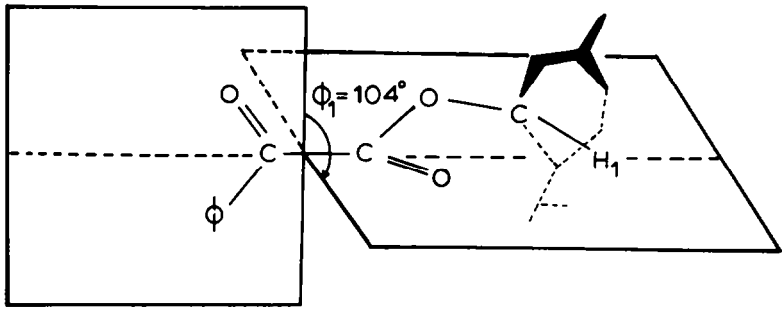


FIG 7.

Using a GE-XRD-6 diffractometer equipped with a single crystal orienter and scintillation counter, three dimensional intensity data involving 6813 independent reflections were measured to the limit 2θ = 140° for CuKα_1 (=1·5405Å) radiation. The stationary crystal–stationary counter technique was used for measuring the intensities and Ni-Co balanced filters were used for monochromatization. The crystal

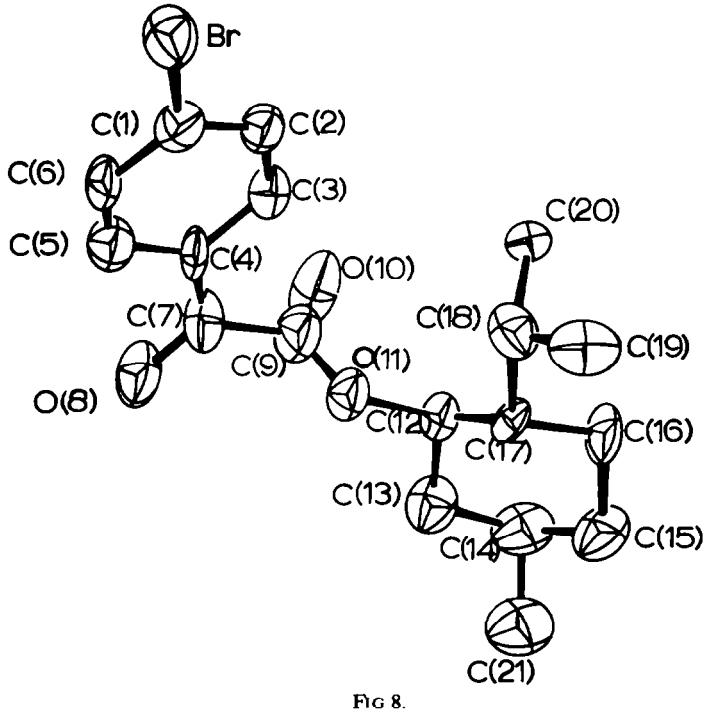


FIG 8.

structure was solved by the heavy-atom method and refined by applying Fourier and least-squares methods. The conventional agreement index R now has a value of 0·06. The details of the structure analysis will be reported elsewhere. The absolute configuration of the molecule was also determined using anomalous dispersion of the Br atoms for the CuKα radiation, and as expected, is as shown in Fig 9.

It is important to emphasize that there are *four* independent molecules in the cell, not related by any symmetry operation. The overall conformations of the four independent molecules are similar. However, there are some minor conformational differences between the individual molecules. The main results of this analysis are summarized in the following perspective view (Fig 7) and illustrated in Figs 8 and 9.

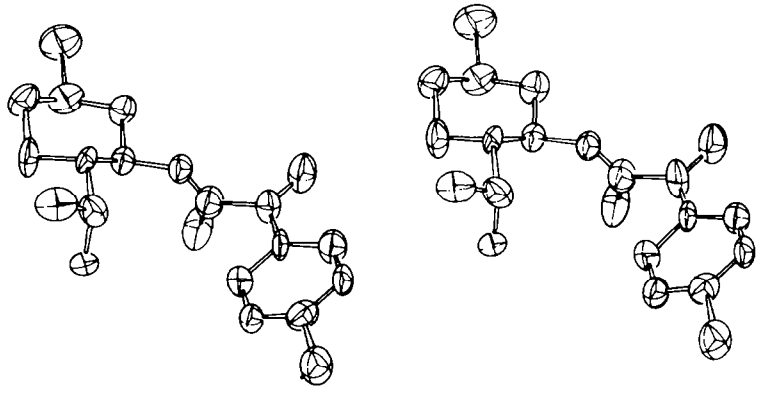


FIG 9. Stereodiagram.

The important conformational features are:

(a) The phenyl is coplanar with the keto CO.
(b) The angle θ between the planes of the two CO groups varies between $+92°$ and $+111°$, with an average of 104°.
(c) The axial hydrogen H(12) practically eclipses the closer CO.

The position of H(12) was inferred from the positions of the carbons attached to C(12).

According to this model, it is interesting to consider the steric hindrance of the two sides of the keto CO of PBGM. Apparently, the isopropyl hinders the two sides about equally. The ester CO clearly finds itself on the front position (Fig 7). Under these circumstances, it is difficult to make an *a priori* choice on the direction of the preferential attack.

The conformation of PBGM deduced from data cited earlier is in accord with the results of the X-ray crystallographic studies. It is probable that the conformation obtained from X-ray studies equally represents that of PBGM in solution, especially since there are four independent molecules in the unit cell and *all* of them have very similar conformations. The average angle between the carbonyls is 104° as contrasted to 75° for the ethyl-bromophenylglyoxylate.[9]

Despite the great generality of Prelog's rule and the success recently encountered by Weill-Raynal and Mathieu[10] in its utilization (by a semi-empirical analysis postulating a variable equilibrium in conformations A, B, C), it is dangerous, as shown

here, to deduce the conformation of the ketoesters from the results of asymmetric syntheses.

It is a pleasure to express our indebtedness to Prof. D. Harker for many invaluable discussions and for his keen interest in this work. We are thankful to Miss Natalie Varco for her excellent technical assistance.

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