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THE STEREOCHEMISTRY OF THE MICHAEL ADDITION REACTION. THE SYNTHESIS OF TRANS -3, 5 - DIMETHYLCYCLOHEXANONE*

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The 1, 4- addition of a Grignard reagent to an α, β-unsaturated ketone appears to be an ordinary Michael type addition, except that it is irreversible and the product obtained from the reaction will be governed by kinetic control.[1] The Michael reaction in general has not been studied very much with respect to the stereochemistry of the product, which may often result from thermodynamic, rather than kinetic control.[2-4] The stereochemical result of kinetic control has been explained on the basis of attack of the nucleophile perpendicular to the olefinic bond, and from the least hindered side of the molecule.[1-4]

In connection with other work, we recently had occasion to require large quantities of trans -3, 5-dimethylcyclohexanone. Since the cis isomer is the thermodynamically stable one, the trans isomer is not obtained in good yield by methods leading to a thermodynamically controlled product, but it has been obtained by two other methods, both of which are laborious and give rather poor overall yields.[5]

Among the methods we considered for synthesis of the desired com-

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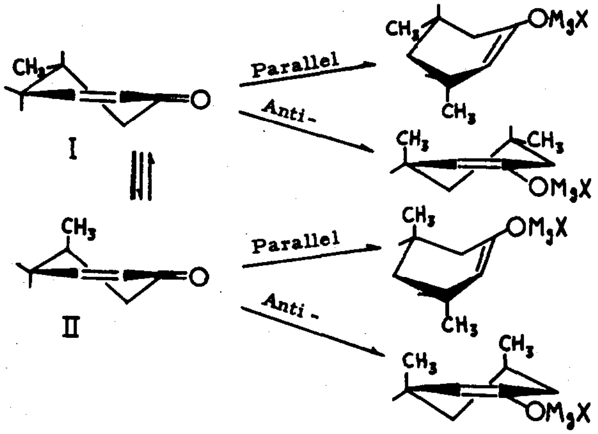
pound was the Michael addition of methyl magnesium iodide to the readily available 5-methyl-2-cyclohexenone.[6] It was not clear a priori, however, that the trans isomer would be obtained. Our analysis of the situation was as follows: the cyclohexenone molecule may be presumed to exist as an equilibrium mixture of forms containing equatorial (I) and axial (II) methyl groups respectively.[*] In order for the incoming reagent to bond to the terminal carbon of the conjugated system, it is essential that it overlap with the component of the anti-bonding pi orbital at that carbon, i.e., it must come in approximately perpendicular to the plane of the double bond. This means that there are two conformations of the cyclohexenone, each of which has two possible reation paths available to it, which lead to four different transition states and two different products. In determining which of these paths will be followed preferentially, it is not sufficient to say that the reagent will attack from the least hindered side, as the methyl group offers no significant hindrance to three of the four available reaction paths.



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[*] The molecules can also undergo some flexing which might be considered as boat ⇌ chair interconversions. The geometric changes and energies involved are small however, and have no bearing on the present problem.

The determining factor as far as the stereochemical outcome of the reaction hinges on the relative energies of the transition states which result from the four reaction paths. The nature of the equilibrium between the starting conformations is irrelevant (Curtin-Hammett Principle)[7]. The relative energies of the transition states can be estimated by examining the starting conformations and the products (a method sometimes referred to as the Evans-Polanyi Principle[8]), which was done in the following way.

Addition of the reagent to the terminal double bond leads to an enolate ion, which has the conformational features of a cyclohexene. While cyclohexenes do not represent conformationally well-studied systems, it is clear that they do possess forms which can be referred to as boats and chairs, and in the absence of unusual interactions the chair form is more stable than the boat by a considerable amount, of the order of 2-3 kcal/mole[9]. If we label the available reaction paths as parallel or anti-parallel depending on the relation of the incoming reagent to the axial hydrogen on the adjacent carbon in the transition state[10], it can be seen that parallel attack leads to a cyclohexane in which the ring is in a boat form, while anti - parallel attack leads to the corresponding chair form. Clearly the reaction paths leading to the chair forms will be very much preferred over those leading to the boat forms, in the absence of other interactions. The fact that the boat can attain the chair form by a subsequent pseudo-rotational motion without crossing an energy barrier is of no help, because the boat must be (approximately) generated in the transition state, and the subsequent energy changes will not affect the stereochemistry of the reaction. With conformation I, anti-parallel attack leads to a quite comfortable transition state, the only difficulty sterically appearing to be between the incoming methyl and hydrogen at C5. On the other hand, anti-parallel attack on conformation II will yield a transition state in which there is serious interference between the two methyl groups. Hence the prediction is clear cut, and is that the reaction should proceed to give the transition state that would result from anti-parallel attack on conformation I, which in turn will lead to the trans isomer as the reaction product.

When the Michael addition of methyl magnesium iodide (1.1 moles) to 5-methyl-2-cyclohexenone (1 mole) was carried out in ethyl ether with the aid of cuprous chloride[11] (1 mole per cent), the 3,5-dimethylcyclohexanone was obtained in a yield of 55 to 65%. The product was indentified by means of the 2,4-dinitrophenylhydrazone, m.p. 109.5 - 110.5°, and by the infrared spectrum, which was characteristic of the *trans* and showed the presence of no *cis* isomer.[5] Vapor phase chromatography, and comparison with authentic samples showed that the ketone contained 94 - 96% of the *trans* isomer, and 4 - 6% of the *cis* isomer.

We believe that the type of analysis given here is generally applicable to kinetically controlled Michael addition reactions, and it should be of predictive value.

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