Stereospecific Friedel–Crafts Reactions: Alkylation with a Cyclic Ether

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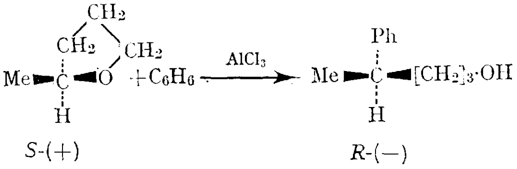
RECENTLY, we reported that the alkylation of benzene by γ-valerolactone in the presence of aluminium chloride to produce γ-phenylvaleric acid occurs with a high degree of inversion of configuration.[1] This was the first observation of a stereospecific Friedel—Crafts reaction.[2] Results indicated that the reaction proceeds through ion-pairs, and that much of the stereospecificity was due to the cyclic nature of the substrate and the enforced proximity of the leaving group. We suggested that stereospecificity may be general for Friedel–Crafts reactions of cyclic compounds. Subsequently, it was reported that alkylation with propene oxide occurs with at least 95% inversion in a Friedel–Crafts reaction.[3] Since epoxides may be a typical substrates we have now demonstrated that Friedel–Crafts alkylations by other cyclic ethers are, in fact, also stereospecific reactions. Thus, the alkylation of benzene by (*S*)-(+)-2-methyltetrahydrofuran with aluminium chloride gives (*R*)-(−)-4-phenylpentan-1-ol. The reaction occurs with at least 35% net inversion of configuration. The starting material is not racemized appreciably during the reaction.



This reaction proceeds in reasonable yield (>50%) with *ca.* 1·25 equivalents of aluminium chloride in benzene solvent at 20—30°. Although the stereochemical result may occur because of the heterogeneous nature of the reaction medium under these conditions, we have demonstrated previously that heterogeneity is not required for stereospecificity in reactions of lactones,[1] and we believe that this reaction is similar. The structure of the product was determined by its n.m.r. and i.r. spectral characteristics, elemental analysis, and identity with authentic material. The rotations were obtained on material which had been purified by v.p.c. and gave correct elemental analysis, n.m.r., and i.r. Thus, the possibility of contamination by optically active impurities is extremely small. The absolute configurations and maximum rotations of starting material[4] and product[5] are known.

The stereochemistry of the Friedel–Crafts reaction is in marked contrast to the essentially complete racemization observed with acyclic ethers.[6] As in the case of lactones, it appears likely that the reaction proceeds through ion pairs since the starting material does not experience extensive racemization. The reaction is exceedingly sensitive to small amounts of water, and consequently we have not yet been able to control the extent of reaction or stereospecificity with sufficient reproducibility to study the mechanism completely. Nevertheless, it is clear that this reaction bears great similarity to the reaction of lactones. Consequently, we believe that stereospecificity is likely to be the usual course in Friedel–Crafts reactions of cyclic compounds.

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[2] See "Friedel-Crafts and Related Reactions," ed., G.A. Olah, Interscience, New York, 1963, for a general review.

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[5] See ref. 1, footnotes 11—17.

[6] R. L. Burwell, jun., L. M. Elkin, and A. D. Shields, *J. Amer. Chem. Soc.*, 1952, **74**, 4570.