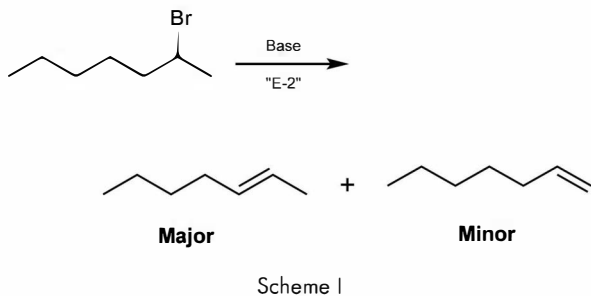


The Discovery-Oriented Approach to Organic Chemistry. 5. Stereochemistry of E2 Elimination: Elimination of *cis*- and *trans*-2-Methylcyclohexyl Tosylate

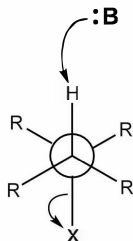
Marcus E. Cabay, Brad J. Ettl, Adam J. Tuite, Kurt A. Welday, and Ram S. Mohan

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The E2 elimination, used to synthesize alkenes, is one of the most important reactions in organic chemistry and is discussed in considerable detail in a sophomore organic course. An E2 reaction requires (i) a base and (ii) a substrate with a carbon bearing a leaving group and an adjacent carbon atom bearing a hydrogen atom. Product distribution is typically governed by alkene stability: the more highly substituted alkene is usually the major product (Scheme I).



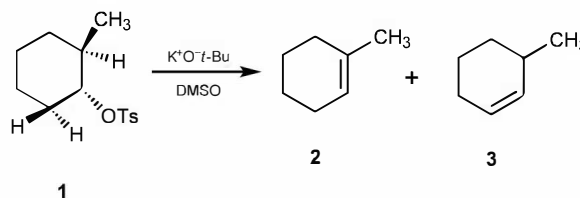
The stereochemistry of the E2 elimination is also discussed in detail in most sophomore organic texts. It is emphasized that the E2 reaction requires an anti-periplanar arrangement of the leaving group and the proton being abstracted:



Another factor that controls product formation is the steric bulk of the base. If the base used is bulky or the proton being abstracted is sterically hindered, the less substituted alkene is frequently formed. However, all the experiments found in currently used laboratory texts utilize aliphatic alkyl halides to illustrate the E2 elimination (1). The products of these reactions do not allow a student to draw any conclusions about the stereochemistry of the E2 elimination.

It is well recognized that the discovery approach to learning is far more effective than cookbook laboratory experiments (2). We have developed a discovery-oriented lab experiment that illustrates the stereochemistry of the E2 elimination. The experiment involves the elimination reaction of *trans*-2-methylcyclohexyl tosylate **1** using potassium

tert-butoxide in dimethyl sulfoxide (DMSO) as the solvent (Scheme II) (3).

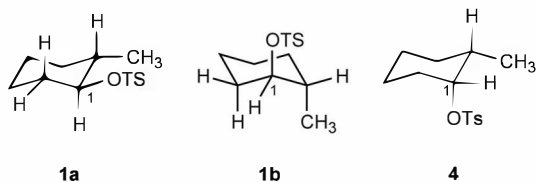


Scheme II

The products of the reaction are analyzed by GC and NMR spectroscopy. On the basis of the Saytzeff rule, students will be tempted to speculate that the major product of the reaction will be 1-methylcyclohexene **2** and the minor product will be 3-methylcyclohexene **3**. However, owing to the stereochemical requirement of the E2 reaction, 3-methylcyclohexene is the only observed product of the reaction. The products of elimination are easily analyzed by ¹H NMR spectroscopy and this is, in itself, an educative exercise. However, product identification can also be easily done using GC, since both 1-methylcyclohexene and 3-methylcyclohexene are commercially available. Thus this discovery lab is also suitable for schools that do not have access to an NMR spectrometer.

Students are told to consider the possibility that the base used is bulky and hence steric factors can come into play. The experiment is then repeated with *cis*-2-methylcyclohexyl tosylate **4** and potassium *tert*-butoxide. Interestingly enough, a 70:30 mixture of 1-methylcyclohexene and 3-methylcyclohexene is observed. This indicates that the observed product distribution cannot be attributed to steric bulk of the base. The stereochemical requirement that the tosylate group and hydrogen being abstracted be anti-periplanar to each other is the most important factor in determining product composition. Thus a *trans*-diaxial relationship between the proton being abstracted and the tosylate group is required on the cyclohexane ring. The ¹H NMR spectra of the tosylates clearly reveal their major conformations. The C-1 proton adjacent to the tosylate group in the *trans* isomer exhibits a classic triplet of doublets for an axial hydrogen, indicating that the major conformation is **1a**, with the tosylate in the equatorial position (see structures below). The formation of 3-methylcyclohexene must then take place via the less stable conformation **1b** in which the tosylate group has a diaxial relationship with the C-6 hydrogen. In the *cis* isomer **4**, the C-1 signal in the ¹H NMR spectrum has a narrow line width indicating that the OTs is in the axial position. The formation of the more stable

alkene 1-methylcyclohexene can take place via this conformation, since the required diaxial relationship is already present.



The experiment can be carried out in two 3-hour labs. Students work in pairs and complete the preparation of the tosylates from the corresponding alcohols in the first lab. In the second lab, one student in each pair carries out the elimination of the *trans* tosylate and the other carries out the elimination of the *cis* tosylate. Product(s) are analyzed by NMR spectroscopy and GC.

The starting materials, *trans*-2-methylcyclohexanol (\$144 for 25 g) and *cis*-2-methylcyclohexanol, (\$28 per g) are relatively expensive. The synthesis of the *cis* alcohol by stereoselective hydride reduction of 2-methylcyclohexanone has been reported in the literature (4). The *trans* isomer can be synthesized by hydroboration–oxidation of 1-methylcyclohexene. An improved procedure for hydroboration–oxidation that is suitable for undergraduate laboratories has previously been reported (5). Thus the costs associated with this experiment can be reduced substantially if the starting materials are synthesized in bulk in the lab. Alternatively, the synthesis of the alcohols can be included as part of the experiment, making this a three-week lab.

Hazards

Pyridine is harmful and has a foul odor. Long-term exposure can cause sterility in males. It should be handled in the hood with gloves. Dimethyl sulfoxide is toxic and should be dispensed in the hood. Diethyl ether and pentane are

highly flammable. No flames should be present in the lab. *p*-Toluenesulfonyl chloride is corrosive and has an unpleasant odor. Potassium-*tert*-butoxide is caustic.

Acknowledgments

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Supplemental Material

Experimental details and CAS registry numbers and sources of required chemicals are available in this issue of *JCE Online*.

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