5.37 Introduction to Organic Synthesis Laboratory

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Appendix 1

Evaluation of *ee* by chiral GC

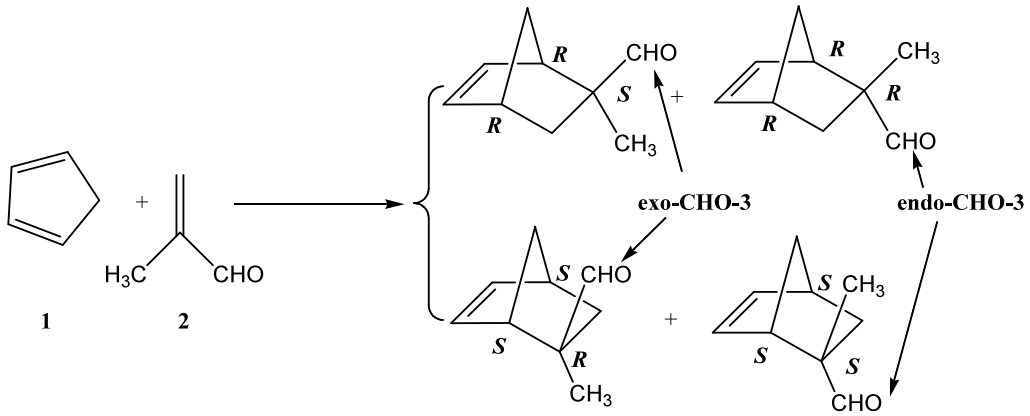
Original :Mircea D. Gheorghiu
Adapted: Mariusz Twardowski

A. Chiral GC.

A cycloaddition of cyclopentadiene to methacrolein, in principle, yields four norbornene adducts: two diastereoisomers, namely **exo-CHO-3** and **endo-CHO-3**, and two enantiomers, ***R*** and ***S*** for each diastereomer..

An achiral cycloaddition (no catalyst or an achiral Lewis acid) yields more ***exo*** diastereoisomer than ***endo*** (see the Table at the bottom of Figure 1). Each diastereoisomer is a racemic mixture (50% ***R***+50% ***S***).

A chiral catalyzed cycloaddition preserves and enhances substantially the amount of the **exo** norbornene derivative, and also favors one enantiomer over the other.



catalyst	solvent	temp	time	exo:endo	R	S
no	THF	RT	8h	5.6:1	50%	50%
BLn* (R,R) from L-Tartaric acid)	CH_2Cl_2	-78 C	24 h	94 : 6	92.4%	7.6%
BLn* (S,S) from D-Tartaric acid)	CH_2Cl_2	-78 C	24 h	92 : 8	11%	89%

Figure 1. Cycloaddition of cyclopentadiene to methacrolein under uncatalyzed and chiral catalyzed conditions (an example selected randomly from previous years undergraduate students results).

The chiral GC traces for a crude sample resulted from the uncatalyzed (Figure 2) and Lewis acid chiral boron catalyzed cycloaddition of cyclopentadiene to methacrolein (Figure 3 and Figure 4) are (traces supplied by Dr Gheorghiu):

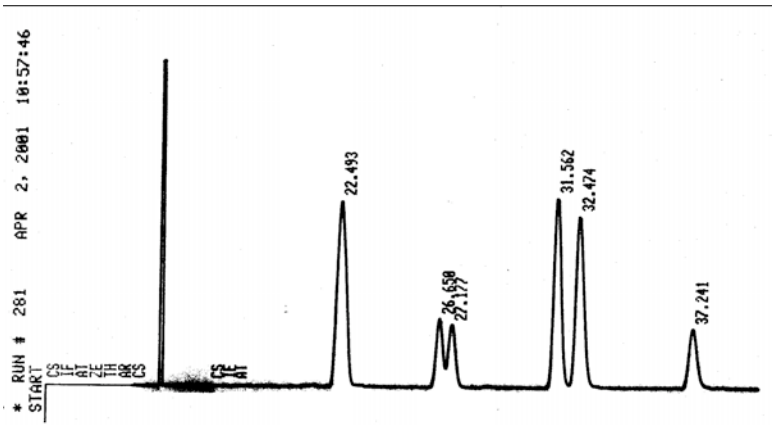


Figure 2. Chiral GC trace of the crude product mixture resulted from cyclopentadiene cycloaddition to methacrolein (run on an α-DEX column).

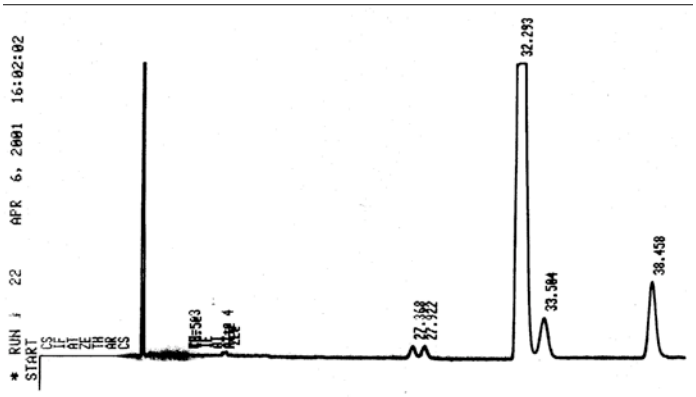


Figure 3. Chiral GC trace of the crude product mixture resulted from the cyclopentadiene cycloaddition to methacrolein in the presence of the chiral boron catalyst synthesized from the L-tartaric acid precursor (run on an α-DEX column).

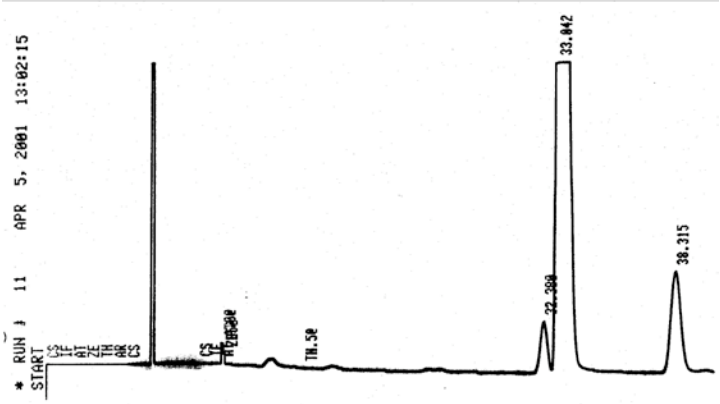


Figure 4. Chiral GC trace of the crude product mixture resulted from the cyclopentadiene cycloaddition to methacrolein in the presence of the chiral boron catalyst synthesized from the D-tartaric acid precursor (run on an α-DEX column).

The separation capacity of the chiral capillary Supelco β-DEX™ 225, used in this experiment has been done with the enantiomers of citronellal (Aldrich, (*R*)-(+)- 90% purity and (*S*)-(-)- 98% purity). The traces are presented in Figure 5 and Figure 6

respectively. The *ee* for (*R*)-(+)-citronellal is 80.4%, while for (*S*)-(-)-citronellal is 91.4%.

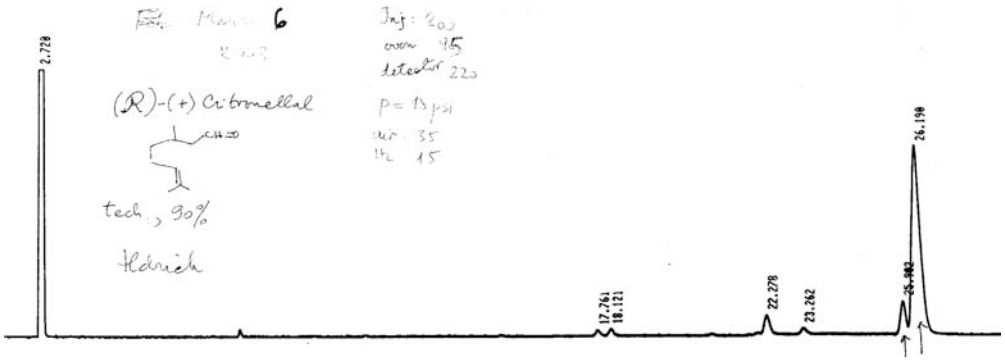


Figure 5. (*R*)-(+)-citronellal (oven 95°C, detector 220°C, injection 200°C).

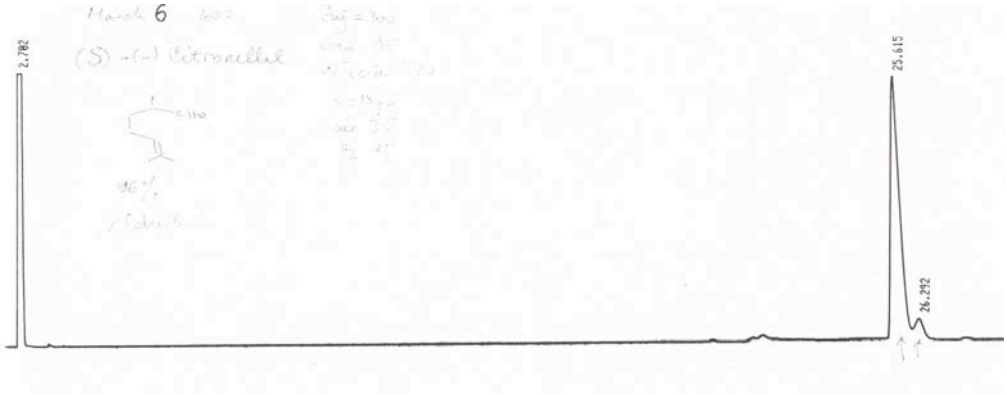


Figure 6. (*S*)-(-)-citronellal (oven 95°C, detector 220°C, injection 200°C).

Asymmetric cycloadditions:

The enantiomeric excess (***ee***) is defined as follows:

$$ee(\%) = \frac{|I_R - I_S|}{I_R + I_S} \times 100$$

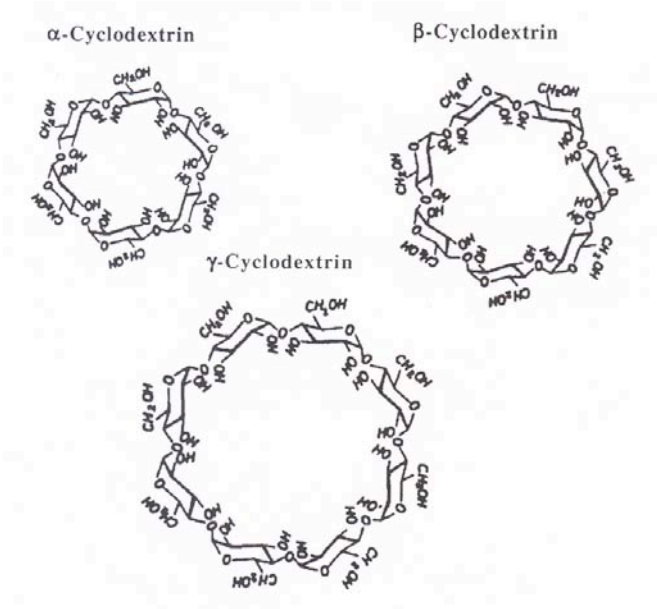
$\mathbf{I_R}$ (or $\mathbf{I_S}$) is the intensity (%) of the respective peak in the GC output. The Table from the bottom of Figure 1, provides the actual ***ee*** values calculated for the cycloadditions carried out with the chiral boron catalyst resulted from the precursors of tartaric acids enantiomers.

When the chiral catalyst precursor is derived from the (2***R***,3***R***)-tartaric acid (natural), the Diels-Alder adduct **exo-CHO-3** has the ***R*** configuration. The ***S*** enantiomer of the **exo-CHO-3** is formed when the catalyst is derived from (2***S***,3***S***)-tartaric acid.

Chiral chromatography[1]

Although chiral gas chromatography was invented by Gil-Av[2] in 1966, it became commercial after 1978 when Harada[3] introduced cyclodextrines as chiral separation agent, which nowadays became the most common chiral separating agent.

Cyclodextrin (CD) is the chiral component in the stationary phase of a DEX capillary column. Cyclodextrins are cyclic oligomers obtained by the partial degradation of starch followed by enzymatic coupling of the glucose units into homogeneous structures of different molecular sizes. The most widely characterized are three cyclodextrines, namely α-, β-, and γ-cyclodextrines containing 6, 7 and 8, respectively, units of glucose. D(+)-glucose is linked through α(1-4) glycosidic bonds.



The shape of the oligomer is toroidal with a larger circumference of the top mouth than the base. The size of the torus-shaped cavity of β-CD is 6.0-6.5 Å. You will run chiral GC on a capillary column[4] Supelco β-DEX™ 225. The stationary phase is formed from heptakis(2,3-di-O-acetyl-6-O-tert-butyldimethylsilyl)-β -cyclodextrin embedded in siloxane matrix SPB™-20 poly(20% diphenyl / 80% dimethylsiloxane). The column has 30m x 0.25mm ID, 0.25μm film.

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[1] For more details consult: Beesley, T. E.; Scott, R. P. W. *Chiral Chromatography*; Wiley: New York, 1998.

[2] Gil-Av, D.; Feibush, B.; Charles-Siegies, R. *Tetrahedron Lett*. **1968**, 1009.

[3] Harada, A.; Furue, M.; Nozakura, S. L. *J. Polymer. Sci*. **1978**, *16*, 189.

[4] Capillary column is used in more than 80% of GC applications.

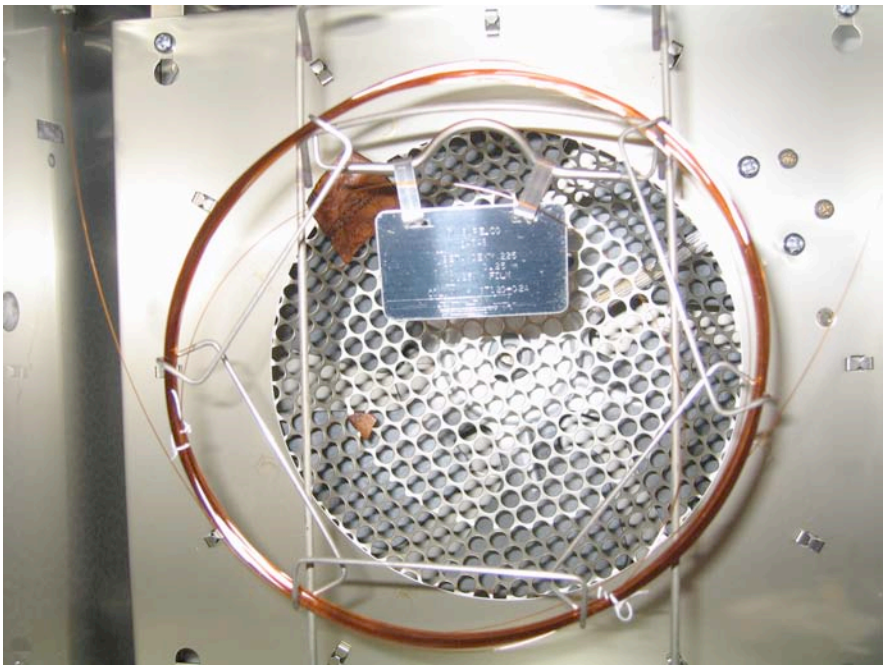

Figure 7. β-DEX™ 225 capillary column in the oven of HP 9890A GC.

Presently, cyclodextrines are the most effective stationary phase for GC separation of stereoisomers. This effective chiral characteristics of β-CD is the result of its 35 stereogenic centers. More than 30% of the known chiral separations have been carried out on β-DEX. Because β-CD is polar, the more polar materials are eluted much later. The oven the column temperatures is constant to ±0.2°C.

Detector: the GC separation is monitored by the flame ionization detector (FID, apropos this acronym is not the NMR FID, e.g. the free induction decay) which is used in more than 90% of chiral GC. The FID was invented in 1958 by Harley and Pretorious[5] and independently by McWiliams and Dewer[6] and is considered a "universal" detector (because has diverse and comprehensive response). By burning (oxidation) of the column exit organic compound (the solute) ions and electrons are generated by thermionic emission from the oxidized fragments. The ionization process produces about one ion per $5x10^4$ molecules, a highly inefficient process. However, enough (!) to be collected by a potential of 110 or 220 volts applied between the jet and the electrode (see Fig. XX). These ions are producing a very small current of ca. 1-2 x 10^{-12} amperes, with a noise level of 10^{-14} amperes.

[5] Harley, J.; Nel, W.; Pretoriuos, V. *Nature* (London) **1958**, *181*, 177.
[6] McWilliams, G.; Dewer, R.A., *Gas Chromatography*, Desty, D.H. Ed. Butterworths: London, 1958

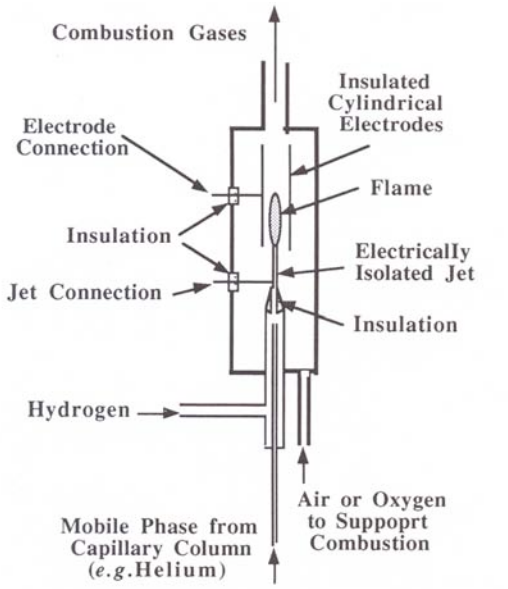

Figure 8. Schematics of the FID.

Within the FID detector H_2 and air is mixed with the exiting organic compounds from the capillary column carried by He. The burning occurs at a small jet placed very close to a cylindrical electrode. The resulting current is amplified and sent to the recorder. FID is not detecting CS_2, CO, etc. but detects all the other carbon containing solutes.

Syringe.

The syringe, Pressure Lok® mini-injector, that you are going to use for chiral GC has several features; (i) its capacity is 0.01μL, (ii) it has a plunger-within-a-needle, that is has a precisely measurable (0.01μL) groove ring in the wire plunger. **Please handle the syringe carefully in order not to bend the plunger or break it.**

How to operate the GC.

1. The red **NOT READY LIGHT** must be off.

Figure 9. Keyboard of GC HP-5890A.

2. Verify or ask the TA if the following parameters are set correctly:
   - oven temperature (should be isothermally set at **80°C**)
   - injection port temperature (should be set at **200°C**)
   - detector temperature (should be set at **250°C**)
   - pressure of the He (carrier) 16 psi. **Do not touch any valve related to air and hydrogen flow.**

Figure 10. Column head pressure gauge (should read 16 psi).

Preparing sample for the GC injection:

A. The solvent chosen is CH_2Cl_2 because of its low boiling point. Make the sample in a vial with a concentration of 30-40mg/mL in CH_2Cl_2 and transfer about 0.5 mL into a culture tube (6x50mm).

B. Cleaning the syringe. Before using, the syringe is flushed with CH_2Cl_2, and heated at 370°C in the syringe cleaner (see Figure 12). Insert the syringe needle when the plunger is retracted all the way. After the needle is in the hot chamber push the plunger all the way out. Keep for ca 3 minutes and before extracting the needle, retract the plunger all the way. Let the syringe cool. **Please handle the syringe carefully in order not to bend or snap the plunger.**

Figure 11. "Burning" the syringe barrel.

C. Extracting the sample. Insert the syringe needle into the solution of the Diels-Alder adduct dissolved in CH_2Cl_2. Push the plunger all the way out, avoiding hitting the bottom of the sample container and then pull it back. Do these movements for 2-3 times more. Retract the plunger, take the needle out of the solution and wipe the exterior of the needle gently with a Kimwipe. Now you are ready to inject.

Injection. Carefully insert the clean needle into the septum of the injection port ca 90% of the length of the needle. Push the plunger down quickly. Hit **RUN** on the GC keyboard. Pull the plunger back all the way. Extract the needle from the septum carefully.

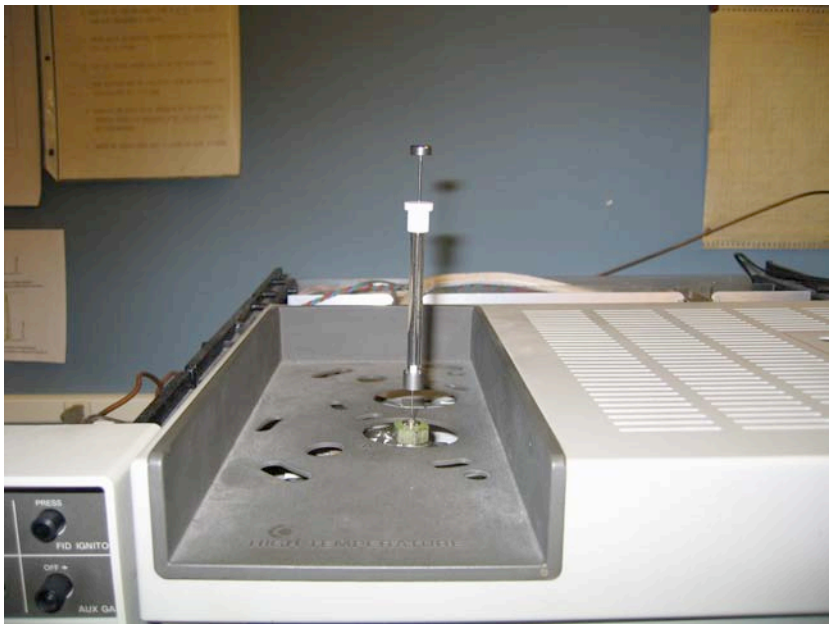

Figure 13. Injection of the sample

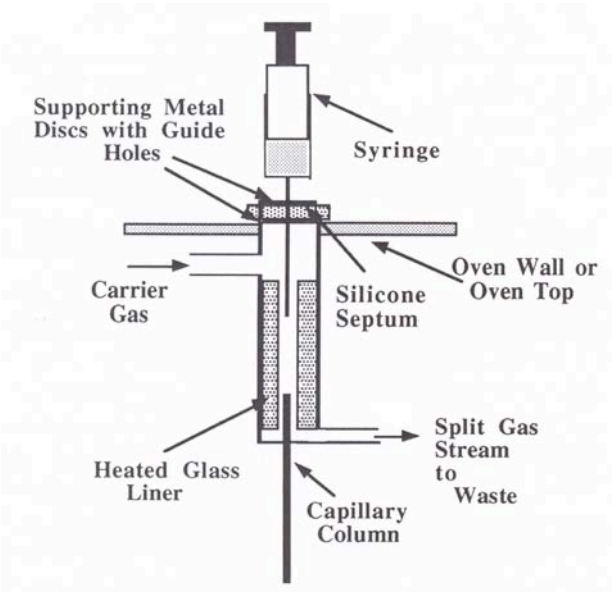

Figure 14. Schematics of the split-flow injection port.

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