The Use of NMR Spectroscopy for Chiral Discrimination

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"Using NMR Spectroscopic Methods to Determine Enantiomeric Purity and Assign Absolute Stereochemistry," Wenzel, T.J.; Chisholm, C.D., *Progress in NMR Spectroscopy*, (DOI:10.1016/j.pnmrs.2010.07.003).

"Assignment of Absolute Configuration Using Chiral Reagents and NMR Spectroscopy," Wenzel, T.J.; Chisholm, C.D., *Chirality*, (DOI: 10.1002/chir.20889).

Categories of Reagents

- Chiral Derivatizing Agents
- Chiral Solvating Agents
- Metal Complexes
- Liquid Crystals

Chiral Derivatizing Agents
Raban and Mislow (1965)

- Form a covalent bond between an optically pure reagent ((*S*)-CDA) and the compound of interest (Sub)

(*S*)-CDA + (*R*)-Sub = (*S*)-CDA-(*R*)-Sub

(*S*)-CDA + (*S*)-Sub = (*S*)-CDA-(*S*)-Sub

- Resulting compounds are diastereomers
- Signals double in NMR spectrum (Chemical Shift Anisotropy) – areas proportional to percent of each enantiomer

Chiral Derivatizing Agents: Key Criteria if Using to Determine Enantiomeric Excess

- No racemization
- No kinetic resolution
- Need 100% enantiomeric purity of the reagent

Chiral Solvating Agents (Pirkle – 1966)
Metal Complexes (Whitesides and Lewis – 1970)

- Form non-covalent interactions between an optically pure reagent ((*S*)-CSA) and the compound of interest (Sub)

$$(S)\text{-CSA} + (R)\text{-Sub} = (S)\text{-CSA-}(R)\text{-Sub} \quad - K_R$$
$$(S)\text{-CSA} + (S)\text{-Sub} = (S)\text{-CSA-}(S)\text{-Sub} \quad - K_S$$

- Resulting compounds are diastereomers

- K_R and K_S are likely different – causes different time-averaged solvation environments

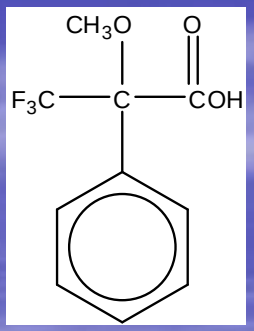
Chiral Solvating Agents and Metal Complexes

- Mix directly in an NMR tube
- Preferable to have fast exchange – NMR spectrum is a time average of bound and unbound forms (CSA + Sub = CSA-Sub)
- High concentration of CSA usually leads to larger discrimination
- Often see enhanced enantiomeric discrimination at lower temperatures
- CSA does not need to be 100% enantiomerically pure

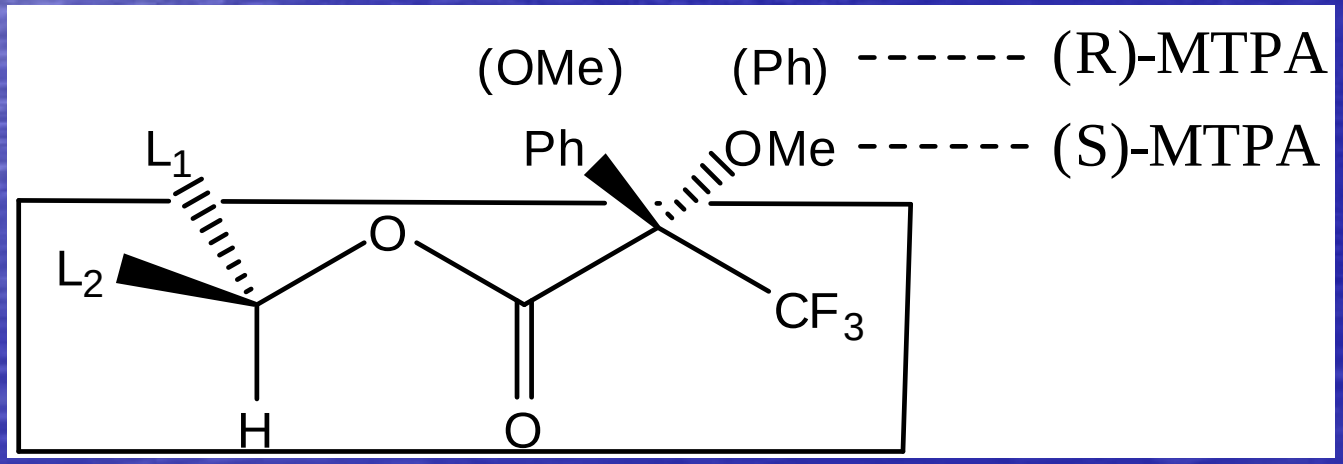
Assigning Absolute Stereochemistry

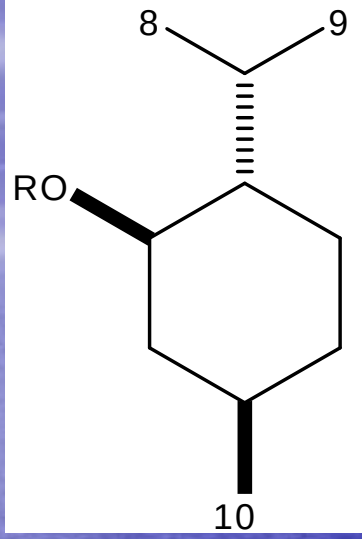
- Mechanism of discrimination is understood and characteristic changes in chemical shifts occur in the spectrum
  - More common with certain families of chiral derivatizing agents
  - Possible with some chiral solvating agents
- Empirical trend
  - Best if use known model compounds as close as possible in structural features to the unknown

Mosher Method: α-methoxy-α-trifluoromethylphenylacetic acid - MTPA (Dale and Mosher – 1973)



- Prepare derivatives with (*R*)- and (*S*)-forms of the reagent (esters of secondary alcohols)
- *Syn-periplanar* arrangement of HC-O-C(O)-C atoms (secondary alcohols)
- Calculate $\Delta\delta^{RS}$ values – negative for L_1, positive for L_2





$\Delta\delta^{RS}$

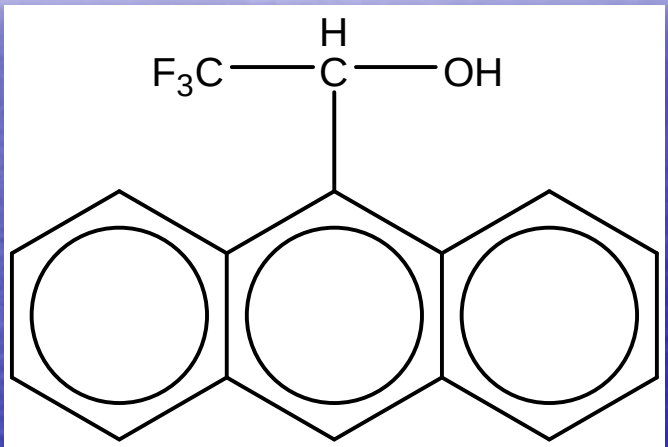
	Me(10)	Me(8)	Me(9)
MTPA	0.07	-0.017	-0.04
MPA	0.05	-0.021	-0.26

$\Delta\delta^{RS}$ depends on:

-Extent of conformational preference/how it influences the shielding

-Degree of shielding (anthryl > naphthyl > phenyl)

2,2,2-Trifluoro-1-(9-anthryl)ethanol (TFAE) (Pirkle's Alcohol)

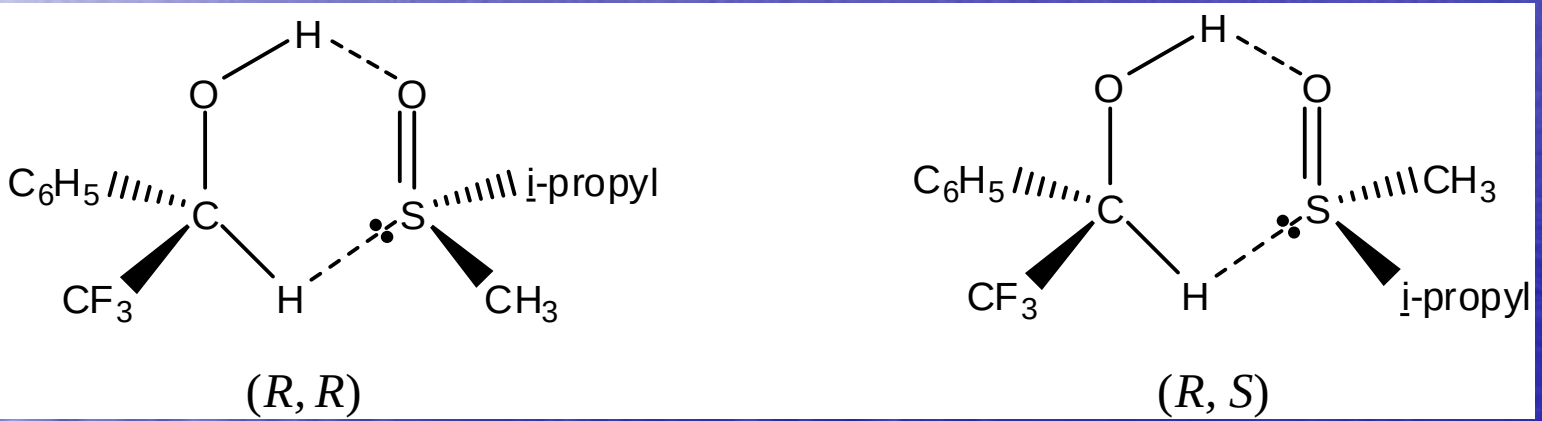


Versatile chiral solvating agent

-Can determine optical purity

-Can assign absolute configurations for certain classes of compounds

Absolute Configurations - TFAE



Sulfoxides

Metal Complexes: Expand Coordination Number or Displace Ligand (Donor/Acceptor Association)

- Lanthanides – Hard Lewis bases
  - Nitrogen- and Oxygen-containing compounds
- Platinum, Palladium, Rhodium and Silver – Soft Lewis bases
  - Alkenes, alkynes, aromatics, phosphorus-containing, sulfur-containing, alkyl halides

Liquid Crystals
Sackmann, Meiboom, Snyder (1968)

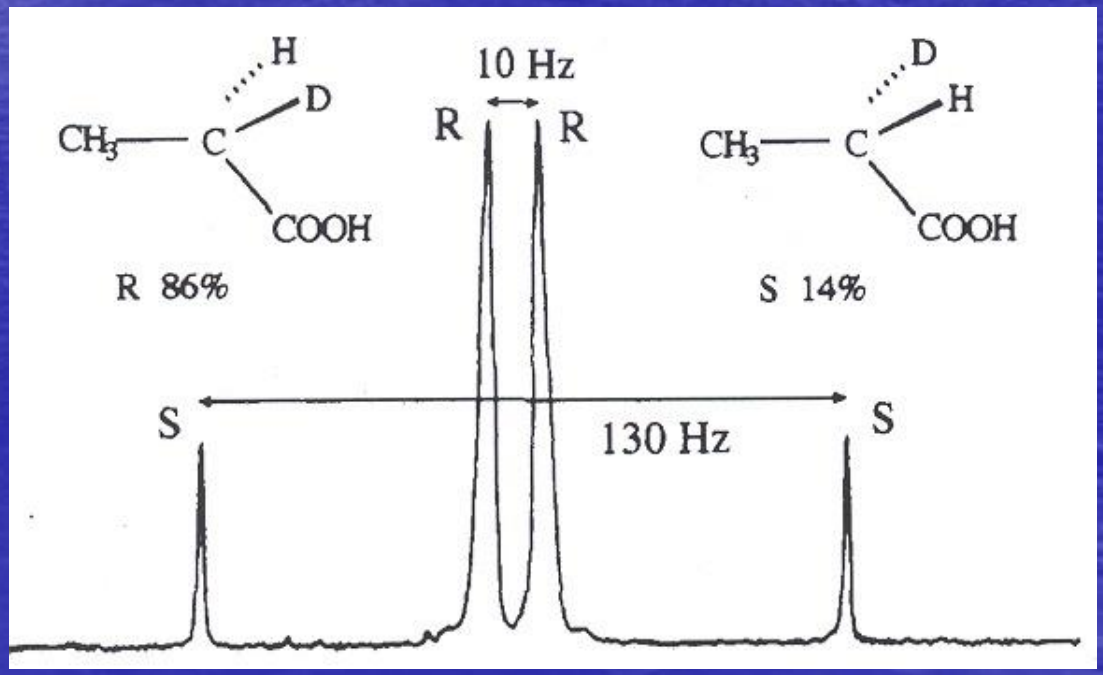
- Forms ordered material in a magnetic field
- Pair of enantiomers have different molecular orientations in the liquid crystal
- Three discrimination mechanisms
  - Chemical shift anisotropy (least useful)
  - Different dipolar coupling constants (^{1}H-^{13}C)
  - Differences in quadrupolar splitting (^{2}H) (most useful)

Quadrupolar Splitting

- Not observed in solution because of rapid tumbling
- Observed in ordered media and extent of splitting depends on orientation relative to the applied magnetic field

2-^{2}H-Propionic Acid

Proton-decoupled deuterium NMR spectrum



Poly(γ-benzyl-L-glutamate) – (PBLG) Incredible Versatility

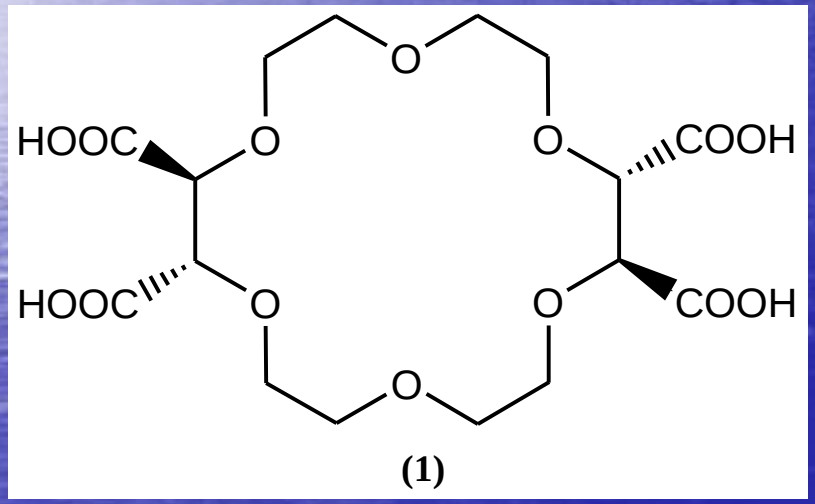
- Only need different packing orders
- Do not need specific interactions between the substrate and the liquid crystal
- Effective for virtually any class of compound
  - Includes aliphatic hydrocarbons
- Especially effective for resonances of nuclei remote to the chiral center

Deuterium Labeling

- Only need deuterium as a signal – better to use achiral reagents so no concern about kinetic resolution or racemization
  - Convert -CO_2H to -CO_2CD_3
  - Add perdeutero benzoyl group (have o-, m- and p-protons as potential probes)
- Provides a single, strong signal (or a few easily assigned signals) for the analysis

Crown Ethers

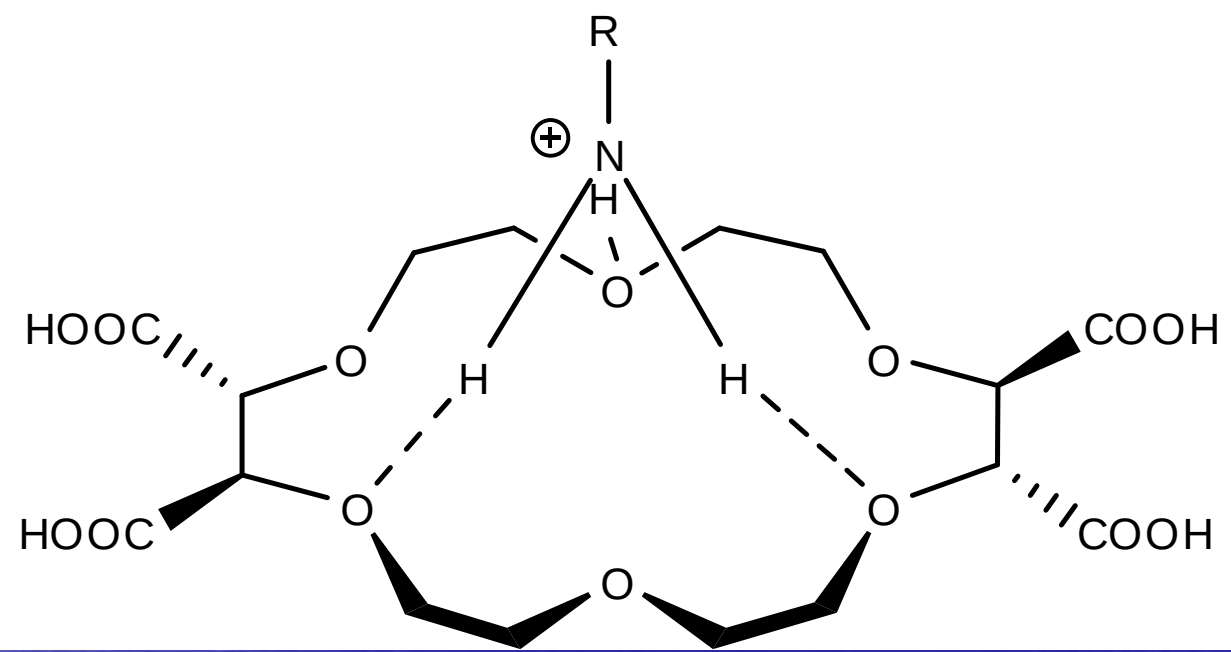
(18-crown-6)-2,3,11,12-tetracarboxylic acid



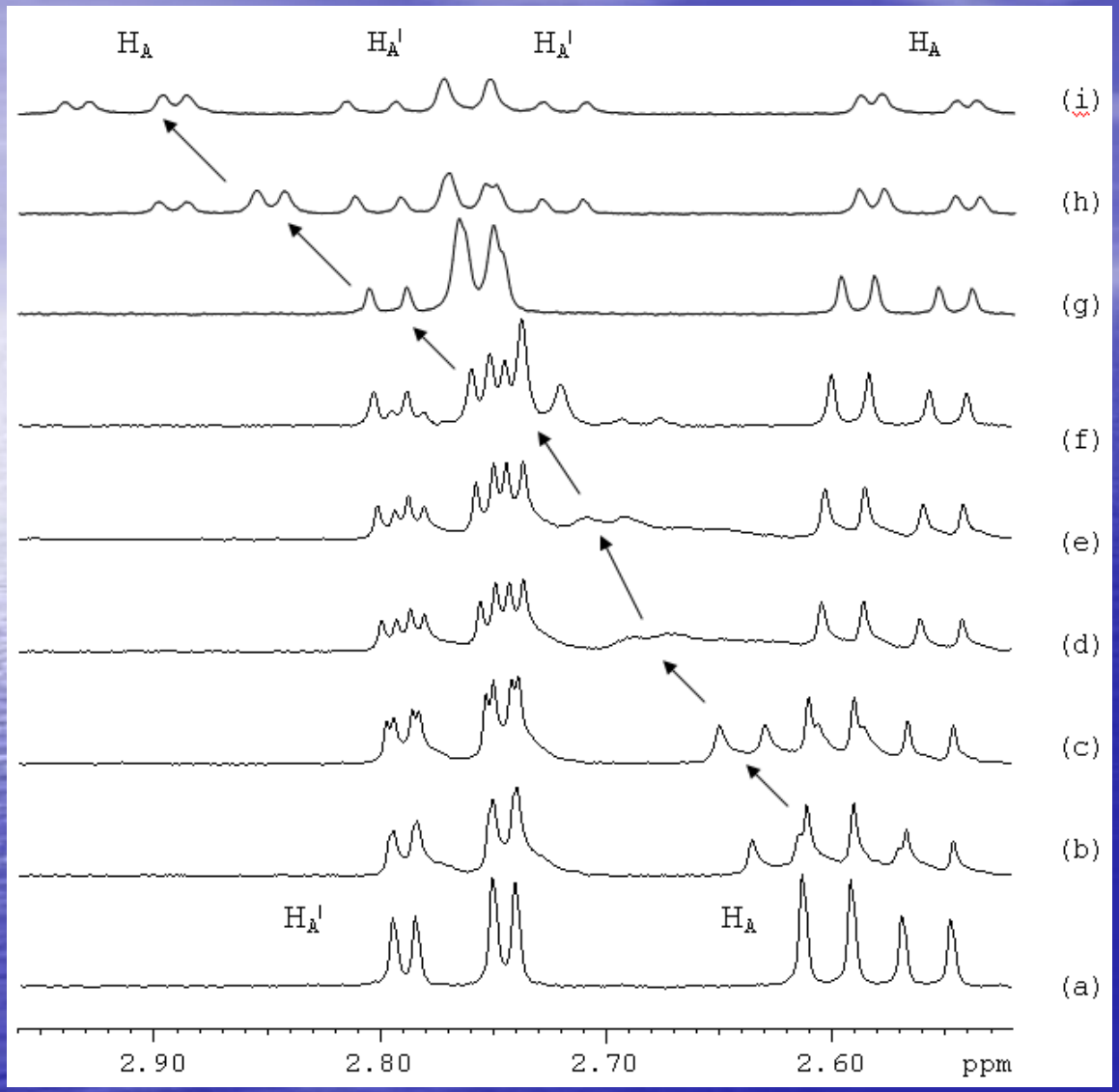
(1)

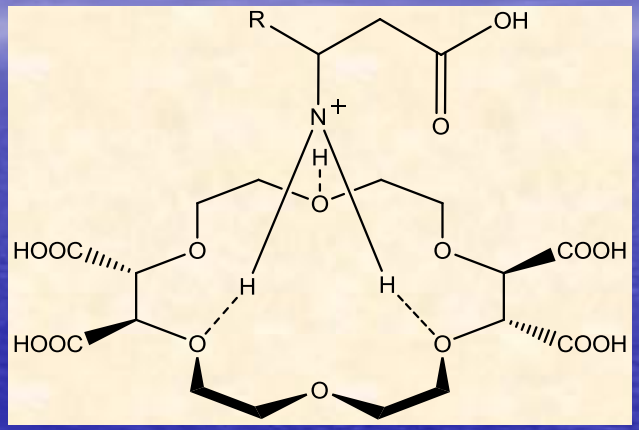
Commercially Available

Association of Primary Amines



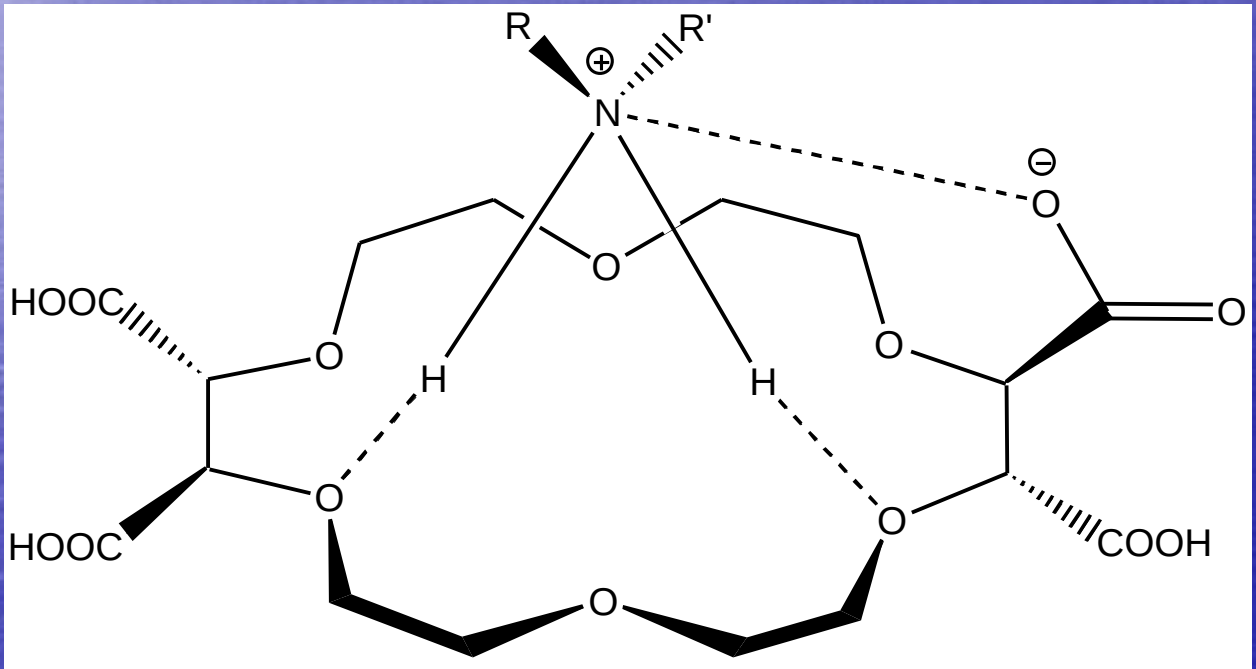
Wenzel, T. J.; Freeman, B. E.; Sek, D. C.; Zopf, J. J.; Nakamura, T.; Yongzhu, J.; Hirose, K.; Tobe, Y, *Analytical and Bioanalytical Chemistry*, **2004**, *378*, 1536-1547.
Wenzel, T. J.; Thurston, J. E., *Tetrahedron Letters*, **2000**, *41*, 3769-3772.
Wenzel, T. J.; Thurston, J. E., *Journal of Organic Chemistry*, **2000**, *65*, 1243-1248.



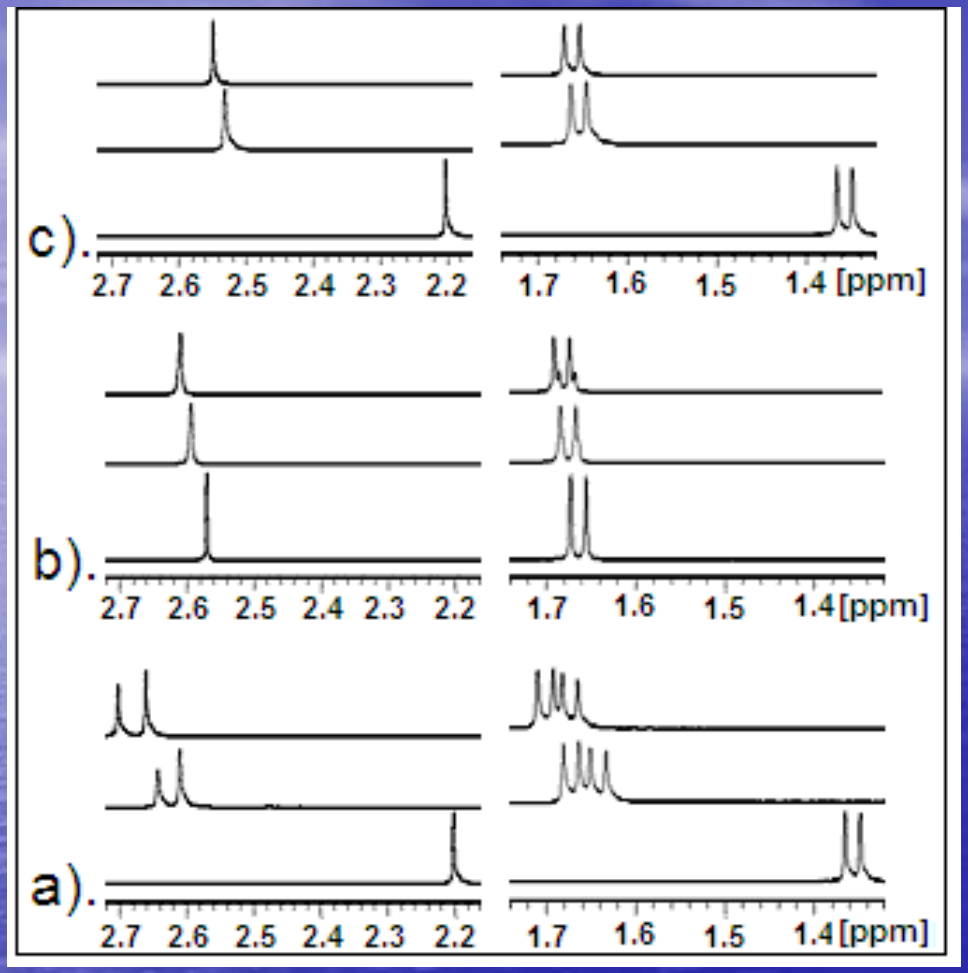


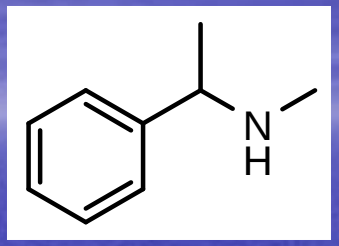
Wenzel, T.J.; Bourne, C.E.; Clark, R.L., *Tetrahedron: Asymmetry*, **2009**, *20*, 2052-2060.
Chisholm, C.D.; Fülöp, F.; Forró, E.; Wenzel, T.J., *Tetrehedron: Asymmetry*, **2010**, *21*, 2289-2294.

Association of Secondary Amines



In methanol

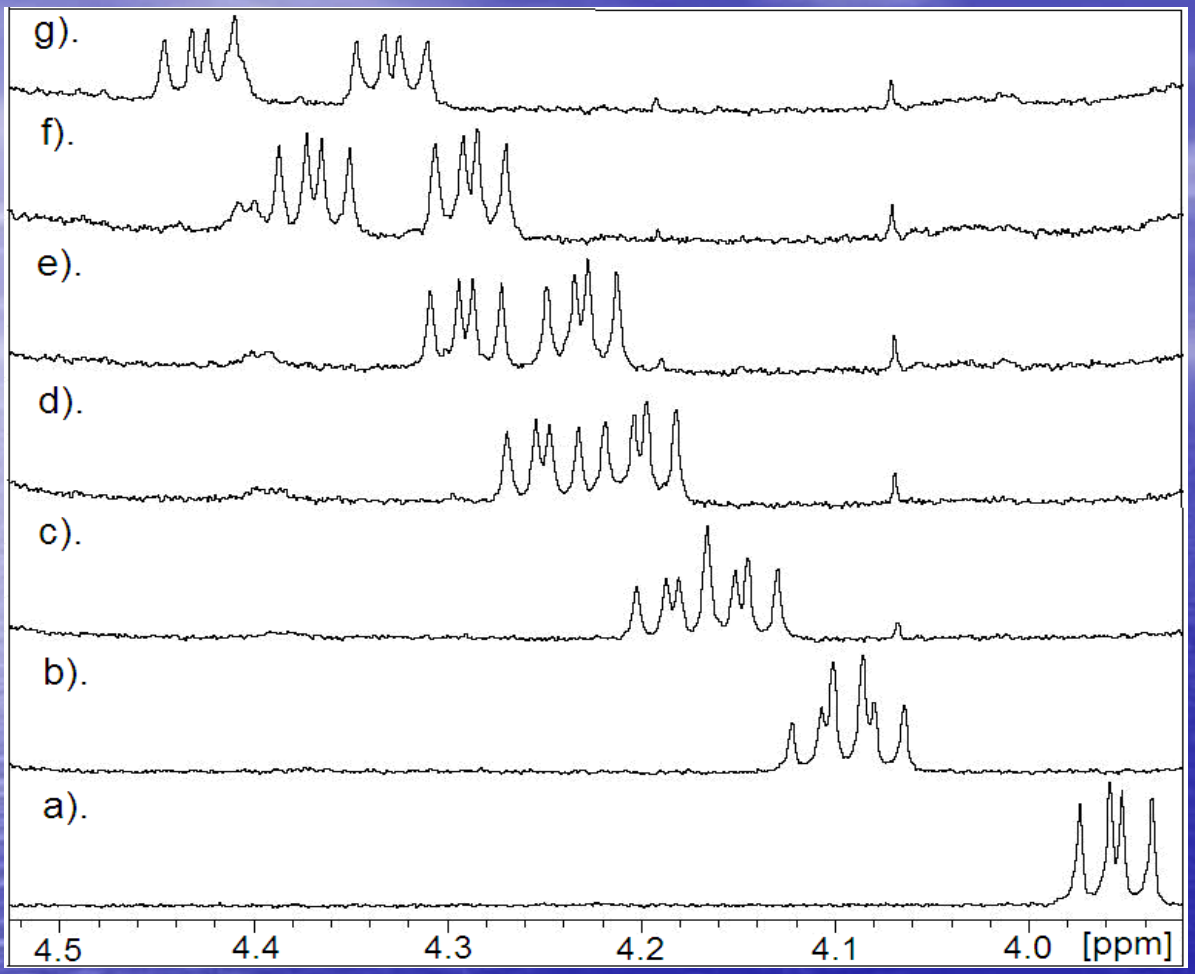


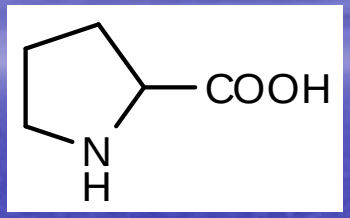


Dimethylbenzylamine

The *C*-methyl and *N*-methyl resonances (400 MHz) of (a) **3** (10 mM) with increasing concentrations of **1** (0, 5, and 10 mM), (b) the hydrochloride salt of **3** (10 mM) with increasing concentrations of **1** (0, 20, and 40 mM), and (c) **3** (10 mM) with increasing concentrations of L-tartaric acid (0,5, and 10 mM)

Lovely, A.E.; Wenzel, T.J., *Organic Letters*, **2006**, *8*, 2823-2826.

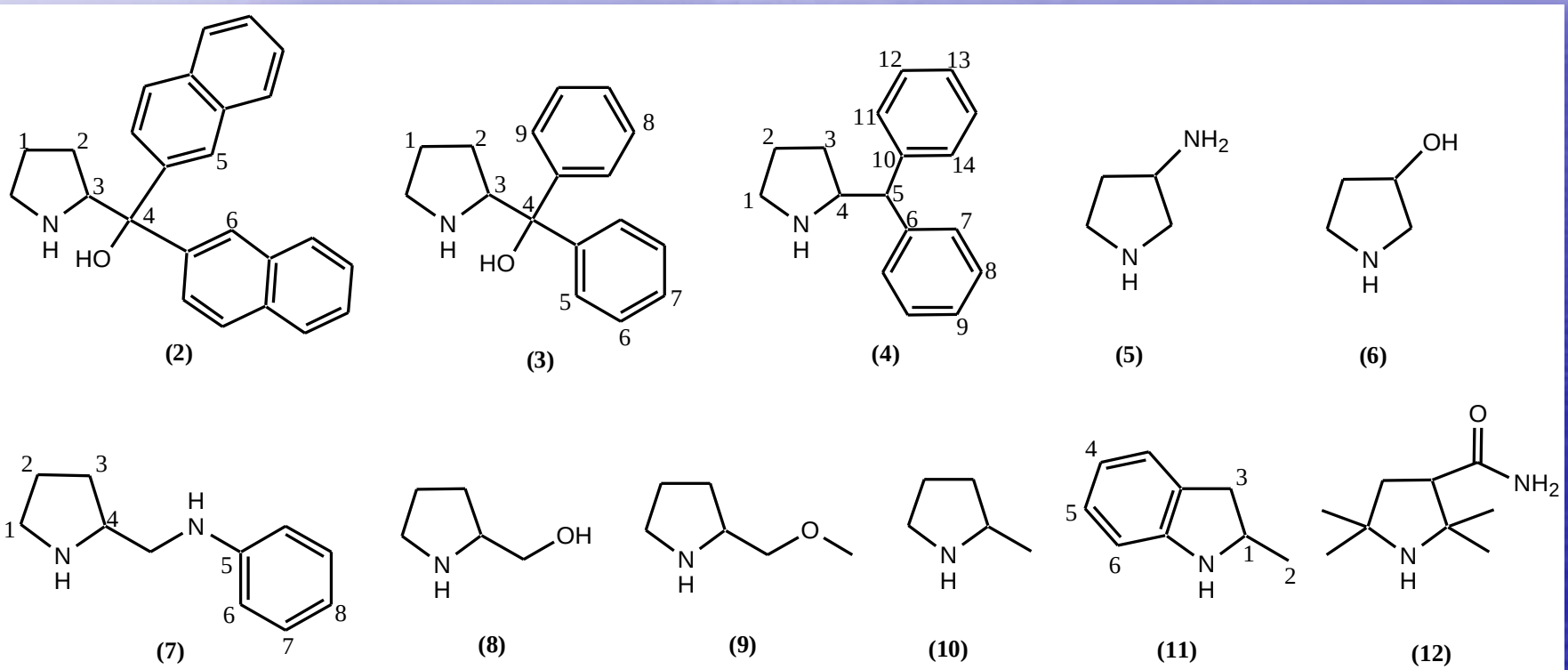




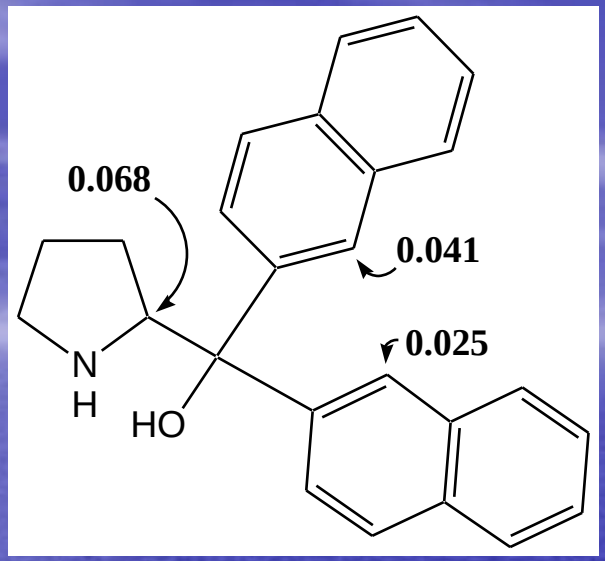
^{1}H NMR spectrum (400 MHz) of the methine resonance of **8** (10 mM) in methanol-d4 with **1** at (b) 5 mM, (c) 10 mM, (d) 15 mM, (e) 20 mM, (f) 30 mM, (g) 40 mM.

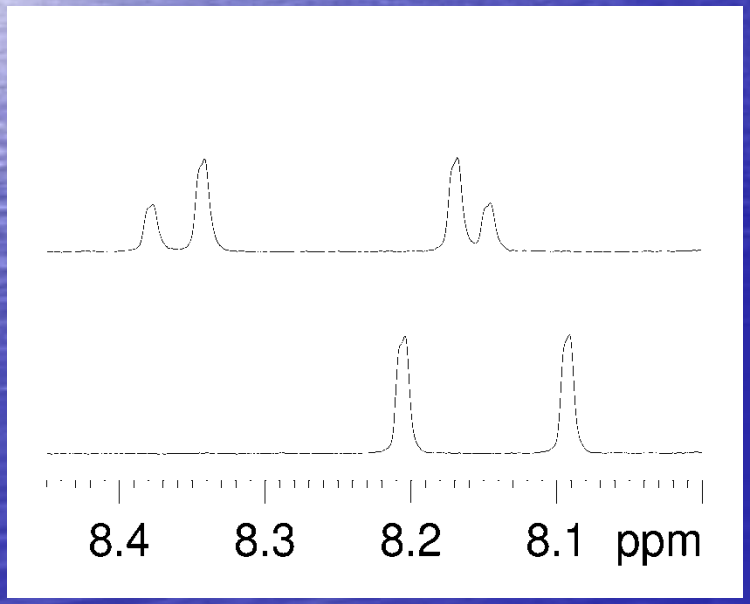
Lovely, A.E.; Wenzel, T.J., *Organic Letters*, **2006**, *8*, 2823-2826.

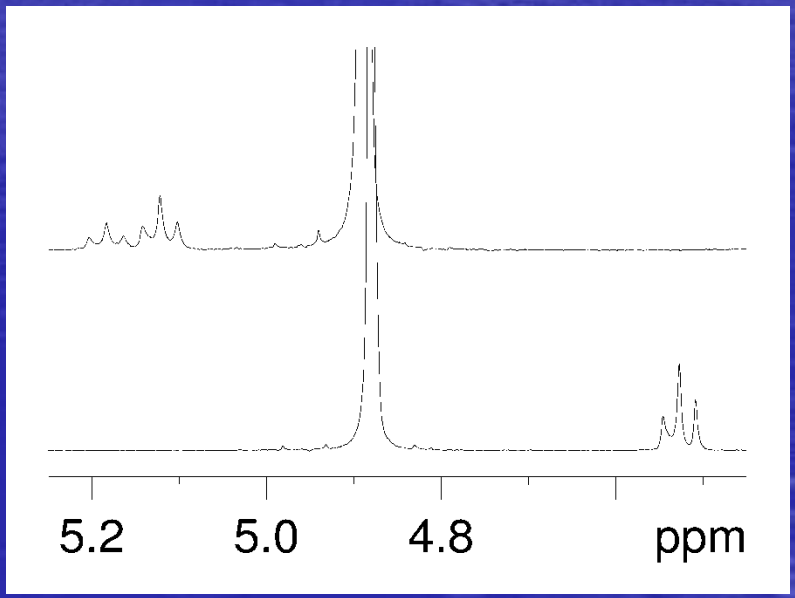
Pyrrolidines



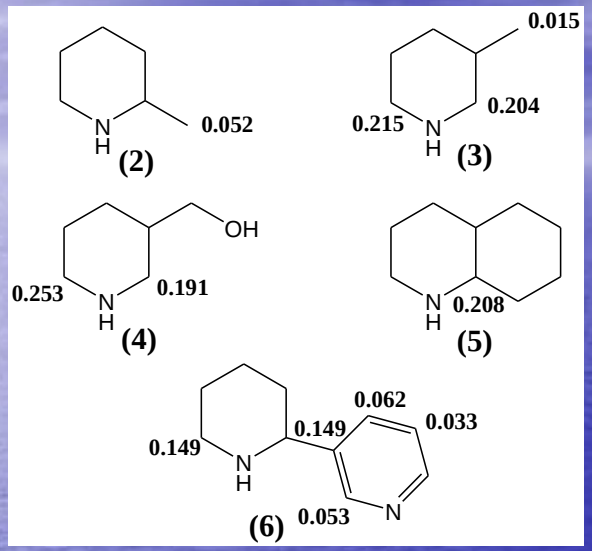
Lovely, A.E.; Wenzel, T.J., *Tetrahedron Asymmetry*, **2006**, *17*, 2642-48

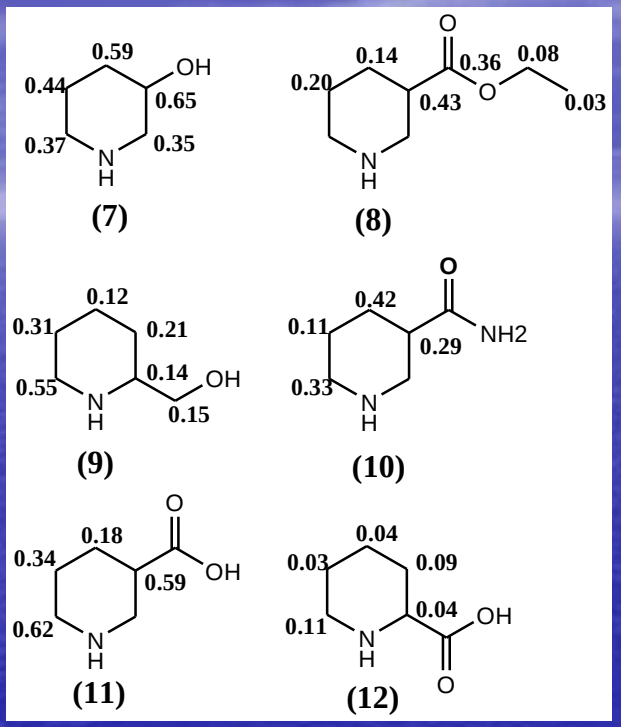

0.068
0.041
0.025
N
H
HO

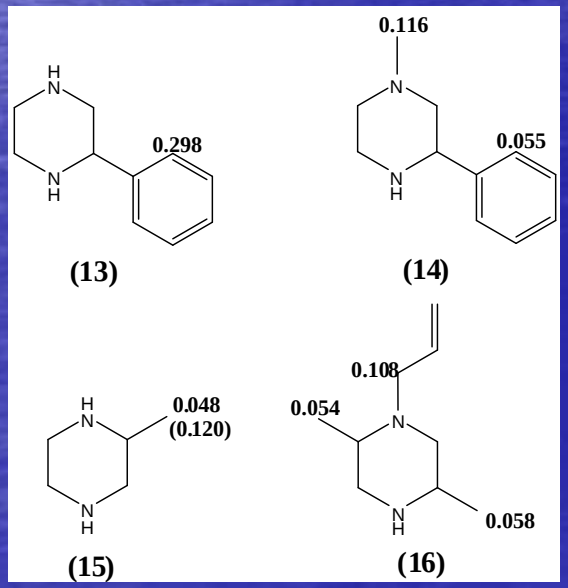

8.4
8.3
8.2
8.1
ppm


5.2
5.0
4.8
ppm

Piperidines and Piperazines

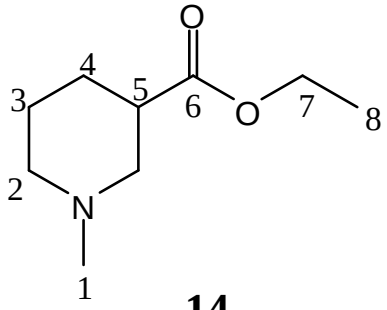






Lovely, A.E.; Wenzel, T.J., *Journal of Organic Chemistry*, **2006**, *71*, 9178-82.

Tertiary Amines



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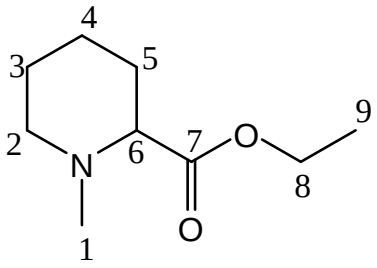

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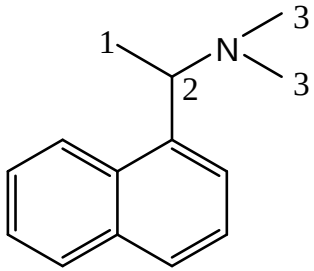

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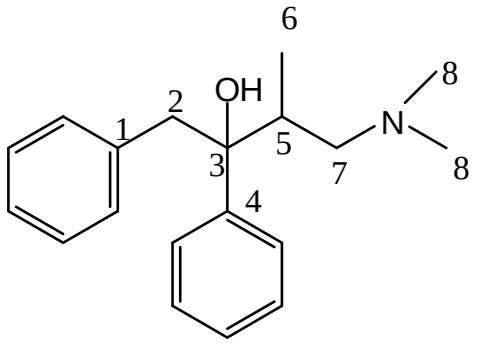

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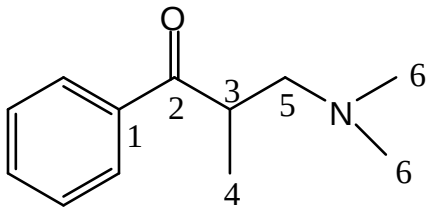

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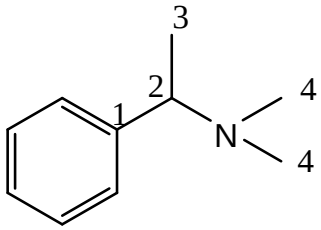

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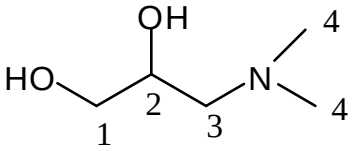

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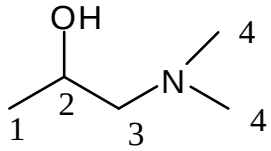


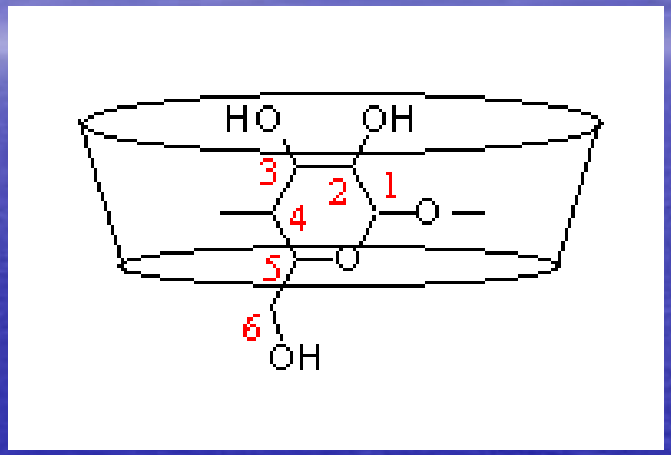
21

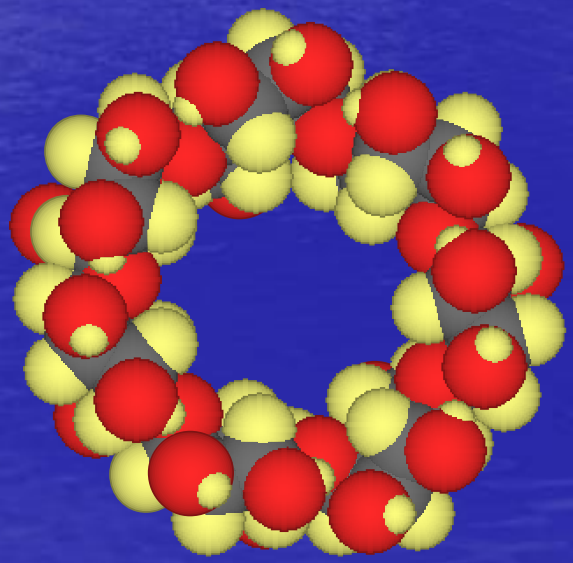
^{1}H – Discrimination usually small
^{13}C – Baseline discrimination

Lovely, A.E.; Wenzel, T.J., *Chirality*, **2008**, 20, 370-378

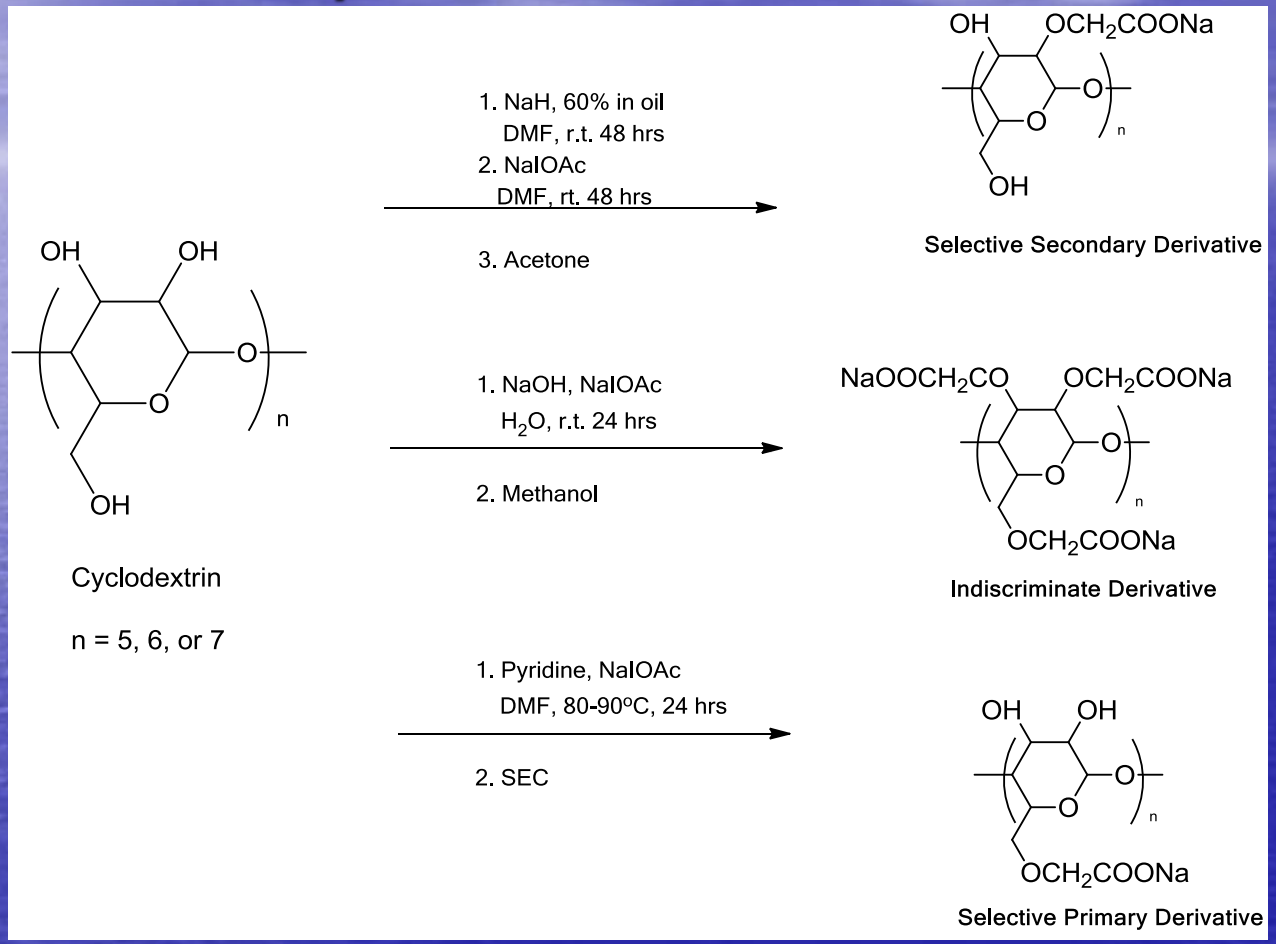
Cyclodextrins

- Cyclic oligosaccharides
- Glucose units
  - 6 – α
  - 7 – β
  - 8 – γ
- Water-soluble





Carboxymethylated Cyclodextrins Synthetic Schemes



Dignam, C.F.; Randall, L.A.; Blacken, R.D.; Cunningham, P.R.; Lester, S.-K.G.; Brown, M.J.; French, S.C.; Aniagyei, S.E.; Wenzel, T.J., *Tetrahedron Asymmetry*, **2006**, *17*, 1199-1208.

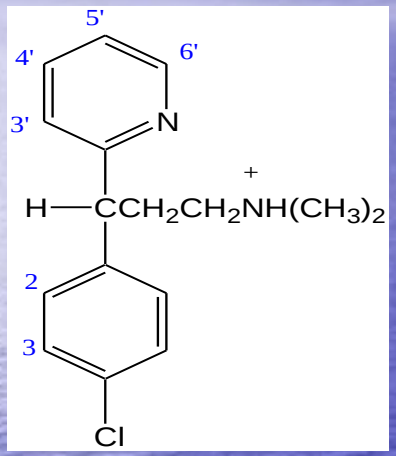
Wenzel, T. J.; Amonoo, E. P.; Shariff, S. S.; Aniagyei, S. E., *Tetrahedron: Asymmetry*, **2003**, *14*, 3099-3104.

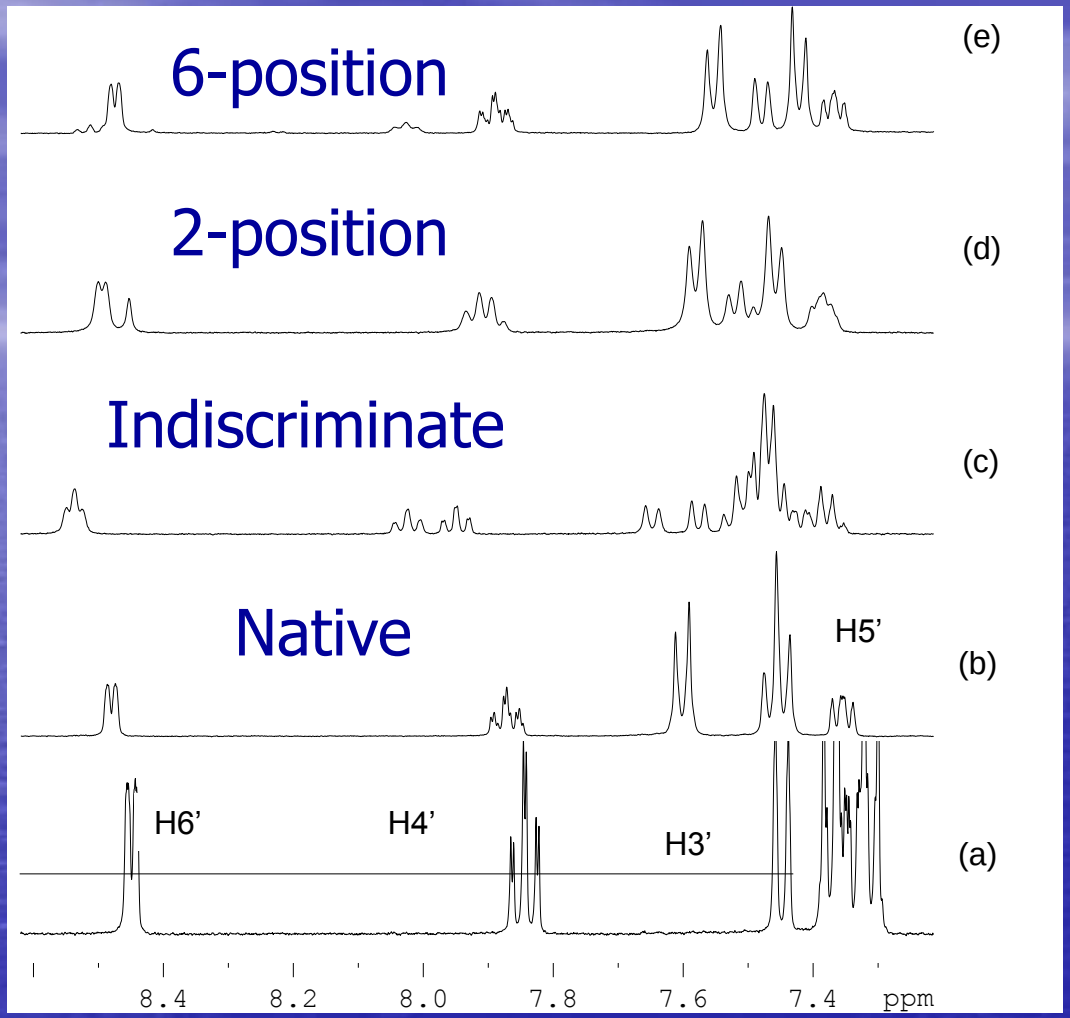
Smith, K. J.; Wilcox, J. D.; Mirick, G. E.; Wacker, L. S.; Ryan, N. S.; Vensel, D. A.; Readling, R.; Domush, H. L.; Amonoo, E. P.; Shariff, S. S.; Wenzel, T. J., *Chirality*, **2003**, *15*, S150-S158.

Degree of CM Substitution

	2-position	6-position	Indiscriminate
α-CD	3	2	7
β-CD	4	1	9
γ-CD	4.5	2	8

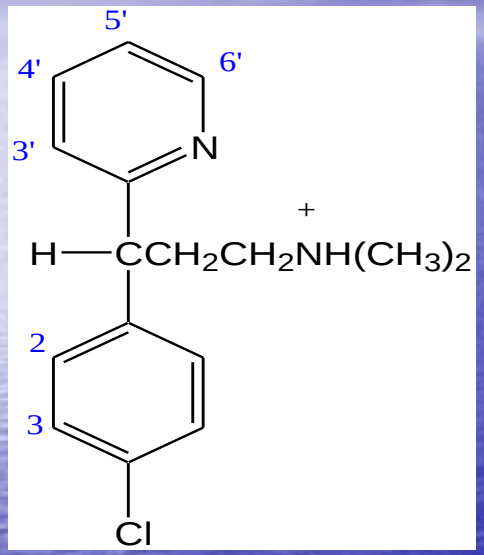
α-CDCM

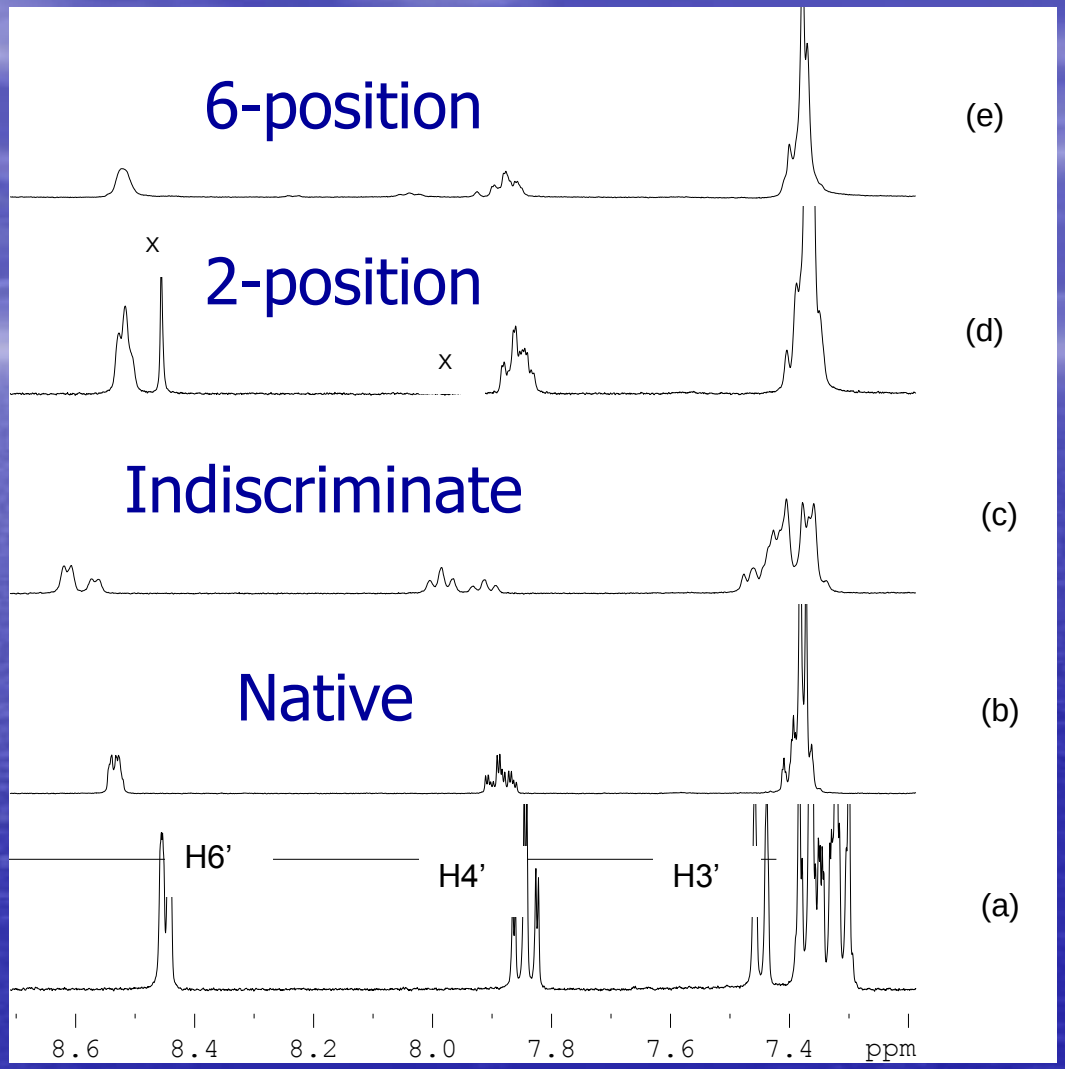




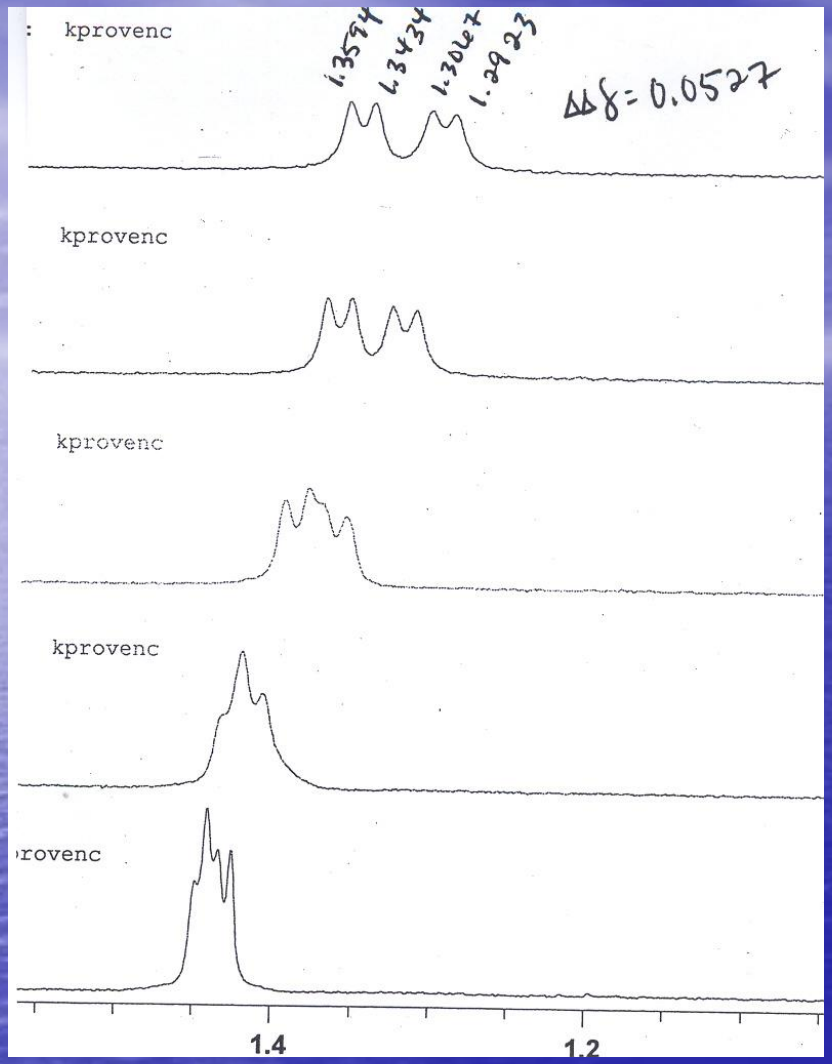
^{1}H NMR (400 MHz, D_2O) of (a) 10 mM chlorpheniramine with 10 mM (b) α-CD, (c) α-CDCM-Ind, (d) α-CDCM-2 and (e) α-CDCM-6.

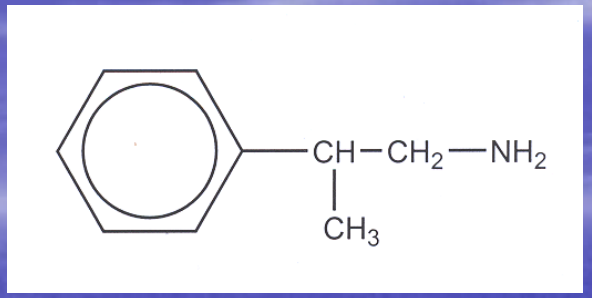
β -CDCM





^{1}H NMR (400 MHz, D2O) of (a) 10 mM chlorpheniramine with 10 mM (b) β -CD, (c) β -CDCM-Ind, (d) β -CDCM-2 and (e) β -CDCM-6. Impurities marked by "x"

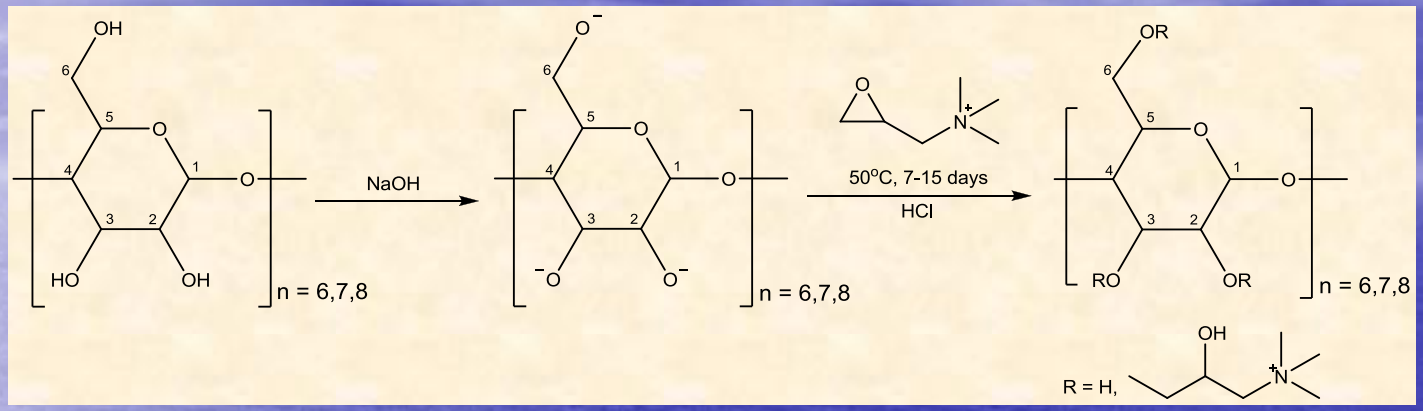


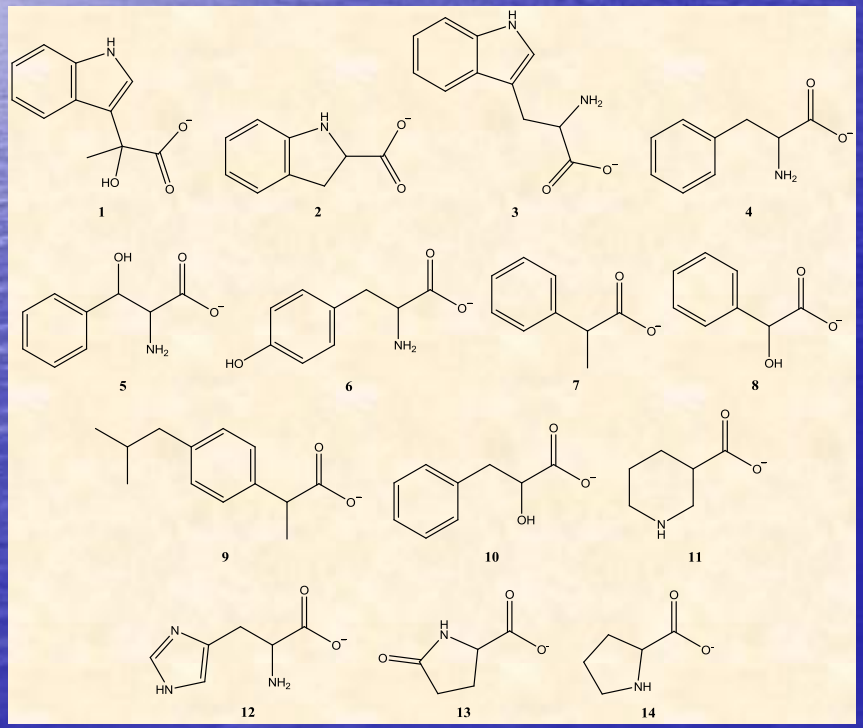


- β-methylphenethyl-amine HCl (10 mM)
- β-CM-CD-Ind (20 mM)
- Yb(III) – (2-8 mM)

K.A. Provencher, T.J. Wenzel, *Tetrahedron Asymmetry*, **2008**, *19*, 1797-1803
Provencher, K.A.; Weber, M.A.; Randall, L.A.; Cunningham, P.R.; Dignam, C.F.; Wenzel, T.J., *Chirality*, **2010**, *22*, 336-346.

Cationic Cyclodextrins



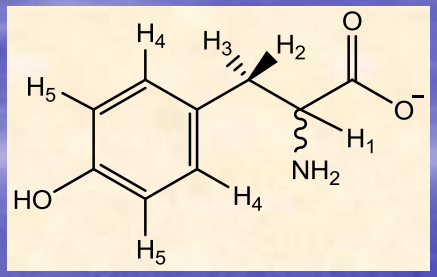


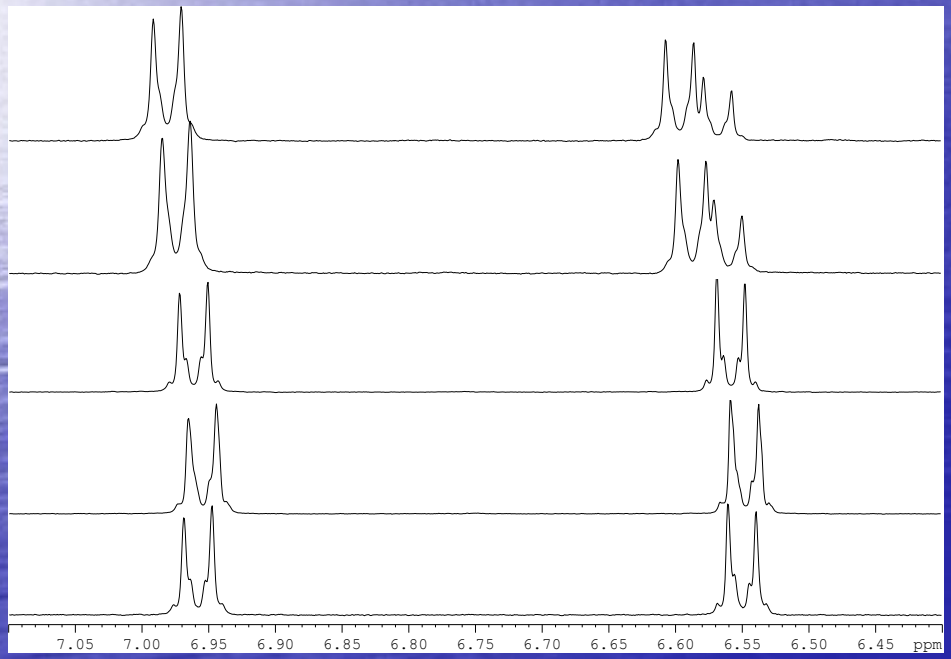
DS = 0.7, 1.1, 1.5, 3.0

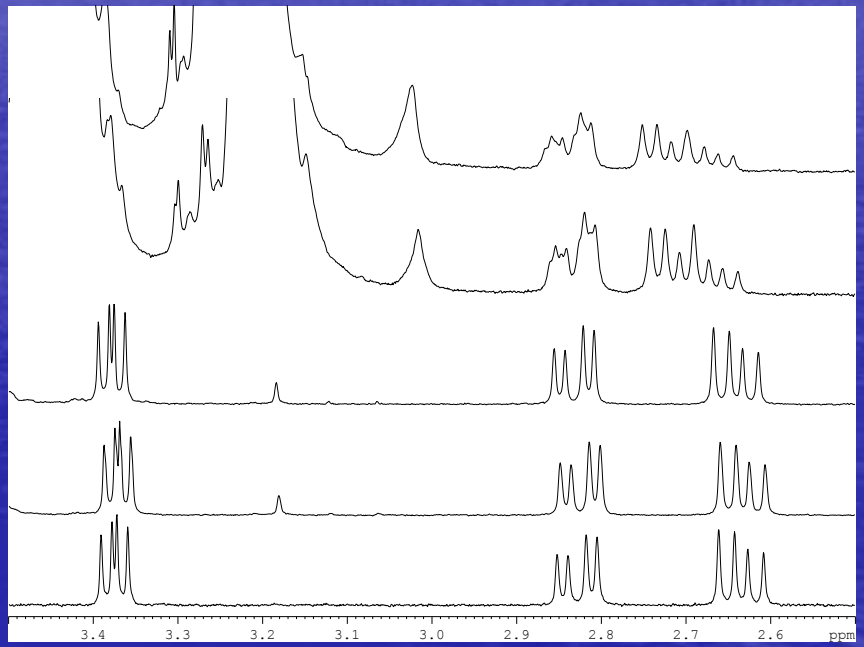
DS = 1.5 the best

C.D. Chisholm, T.J. Wenzel, *Tetrahedron Asymmetry*, in press

Tyrosine with α-CD-GTAC

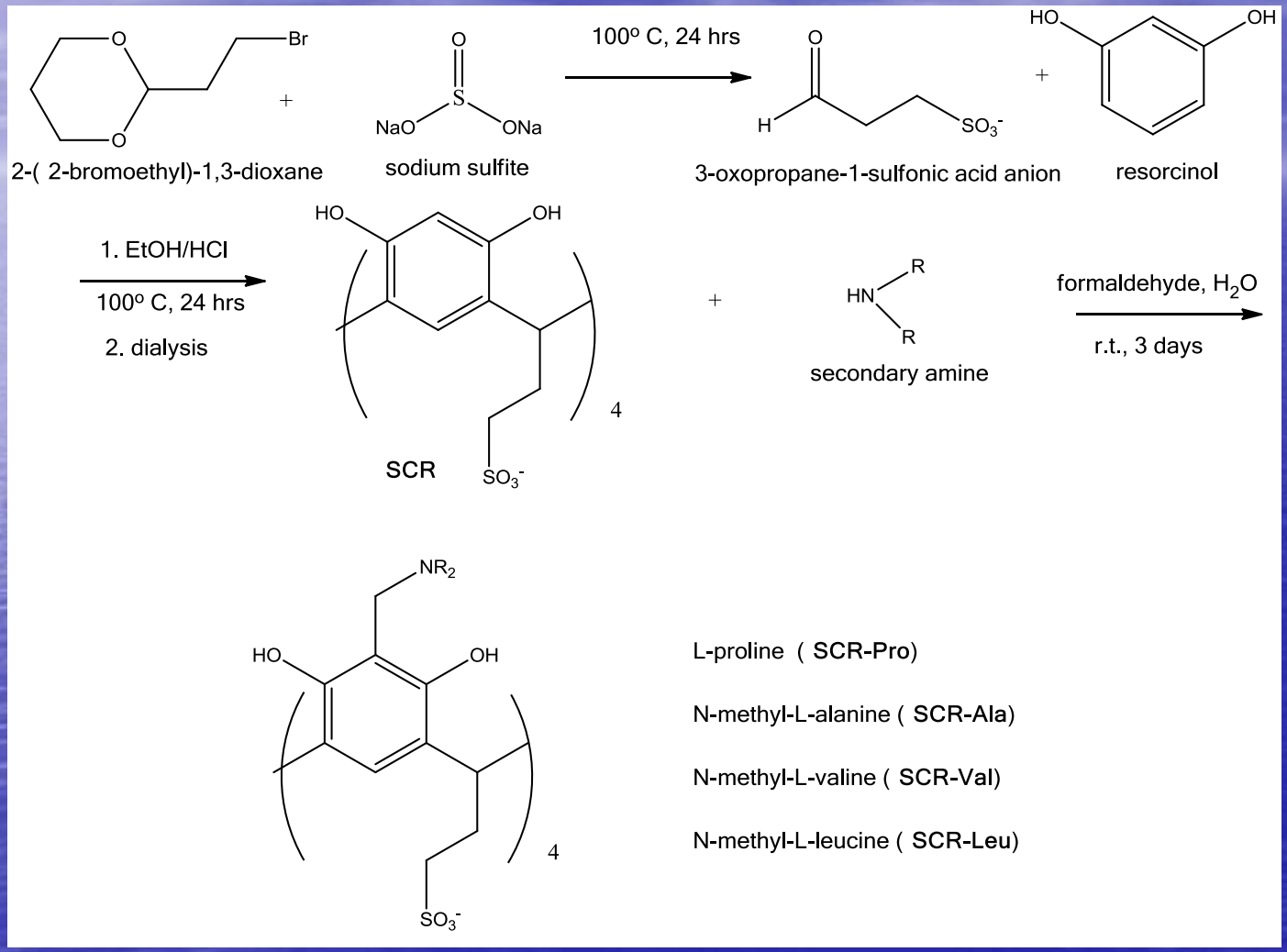






^{1}H NMR (400 MHz, D_2O) (a) 10 mM tyrosine (L>D), with (b) 10 mM native α-CD, (c) 20 mM native α-CD, (d) 10 mM α-CD GTAC (DS = 1.5), and (e) 20 mM α-CD GTAC (DS = 1.5).

Synthesis of Calix[4]resorcinarenes

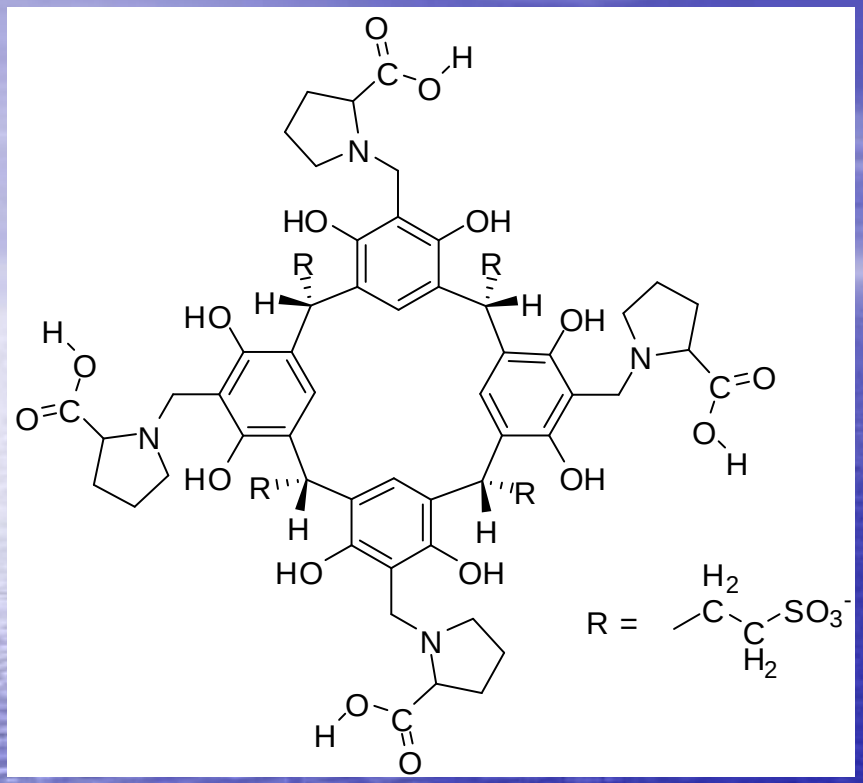


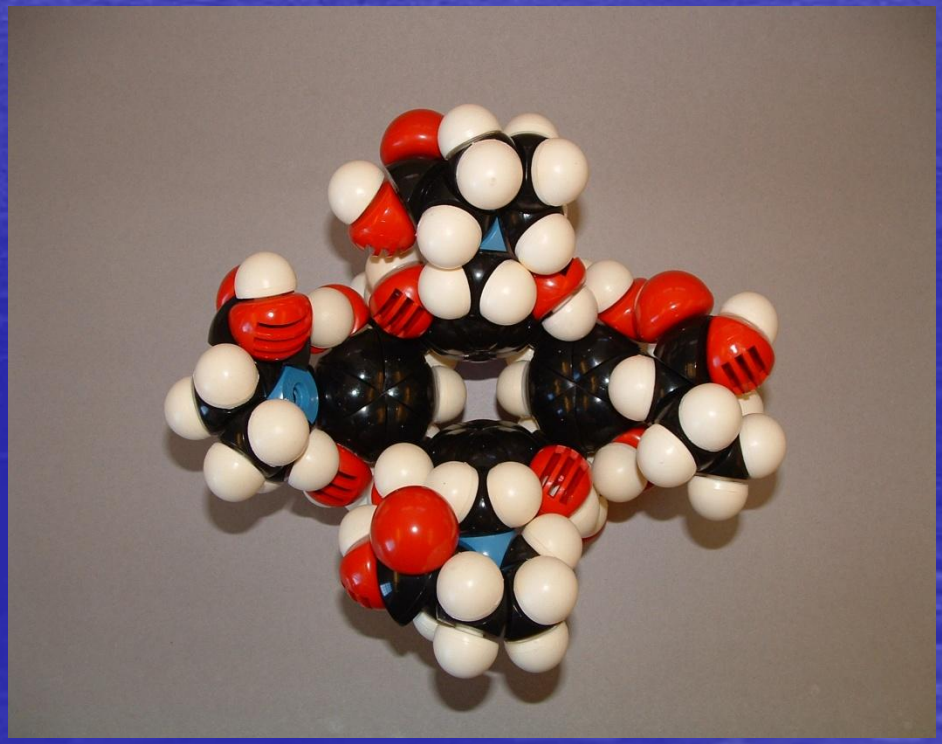
Yanagihara, R.; Tominaga, M.; Aoyama, Y. *J. Org. Chem.*, **1994**, *59*, 6865-6867.

Dignam, C. F.; Zopf, J. J.; Richards, C. J.; Wenzel, T. J., *Journal of Organic Chemistry*, **2005**, *70*, 8071-8078.

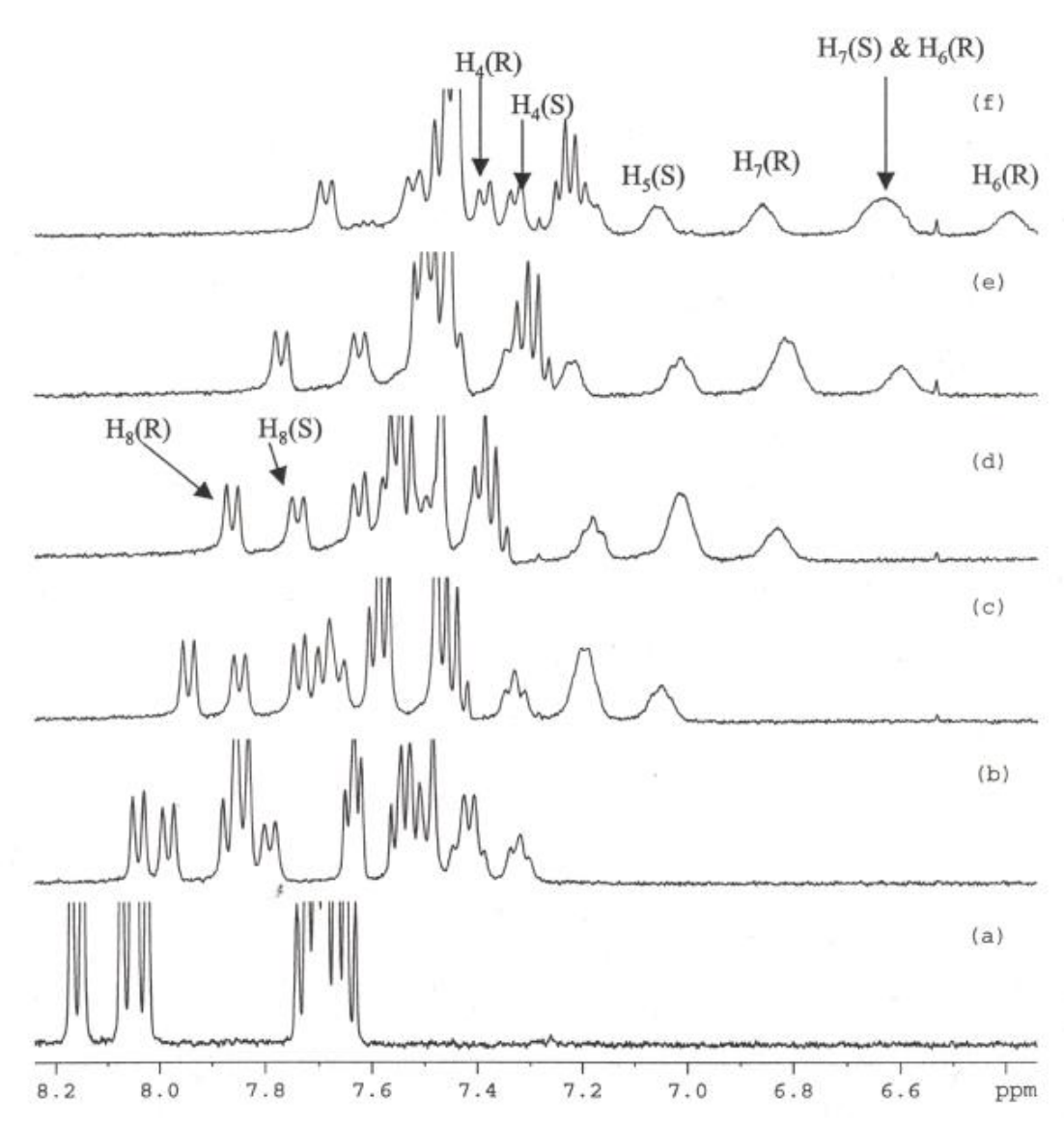
Dignam, C. F.; Richards, C. J.; Zopf, J. J.; Wacker, L. S.; Wenzel, T. J., *Organic Letters*, **2005**, *7*, 1773-1776.

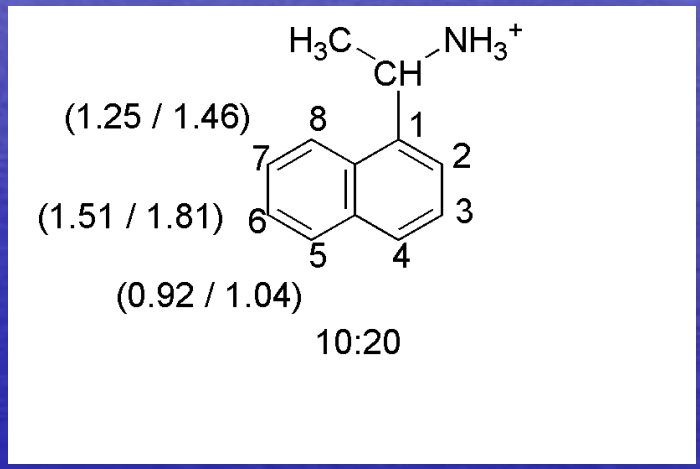
SCR-Pro





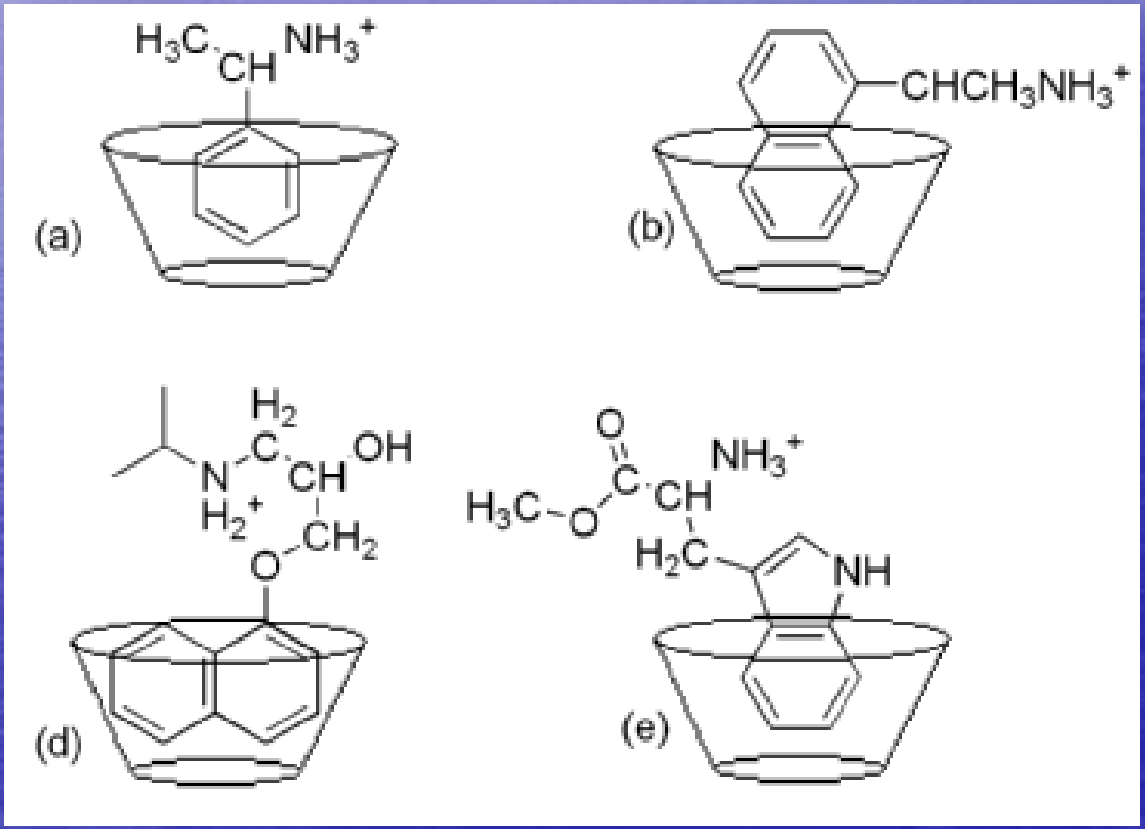
Water-soluble





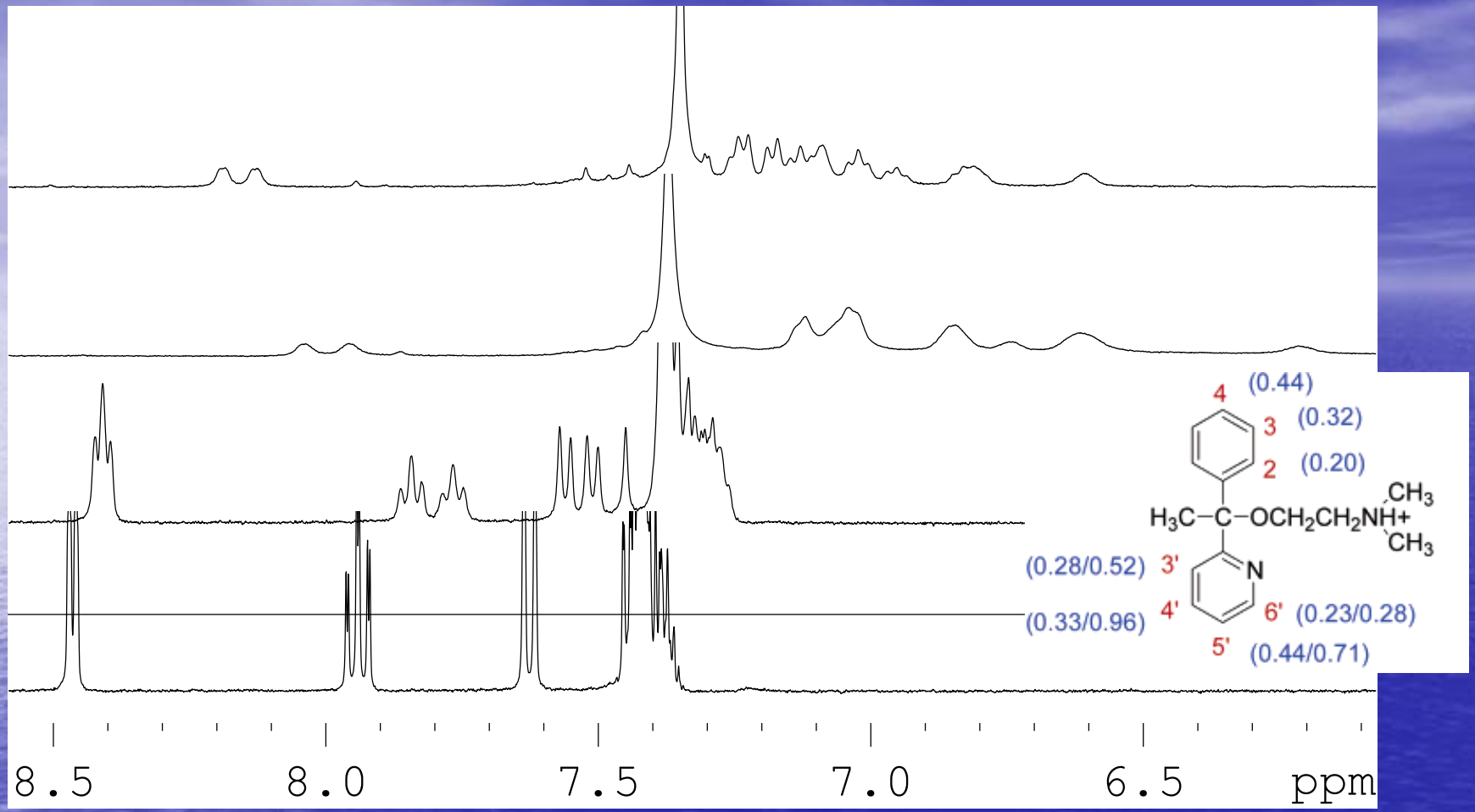
10 mM substrate with 2, 4, 6, 8, and 10 mM SCR-Pro

Geometries of Complexes



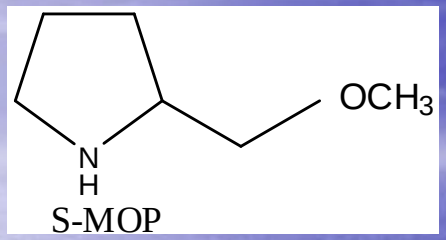
Association Constants

	(R)-enantiomer	(*S*)-enantiomer
1-Phenylethylamine HCl	68	97
1-(1-naphthyl)ethylamine HCl	361	595
Propranolol HCl	258	482
Tryptophan methyl ester HCl	59	113
Sodium tryptophan	67	40

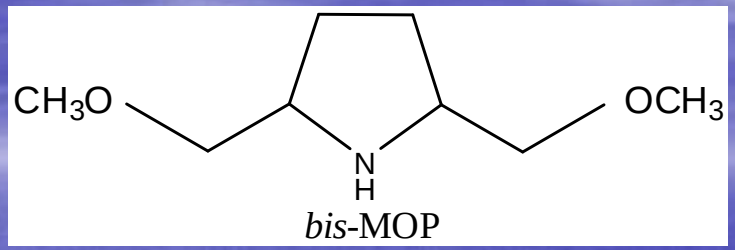


^{1}H NMR spectra (400 MHz, D_2O) of doxylamine (10 mM), (a) at 23° C, (b) with SCR-Pro (2 mM) at 23° C, (c) with SCR-Pro (40 mM) at 23° C and (d) with SCR-Pro (40 mM) at 50° C.

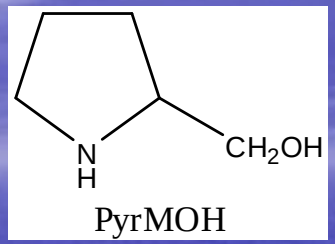
Other Calix[4]resorcinarene Derivatives



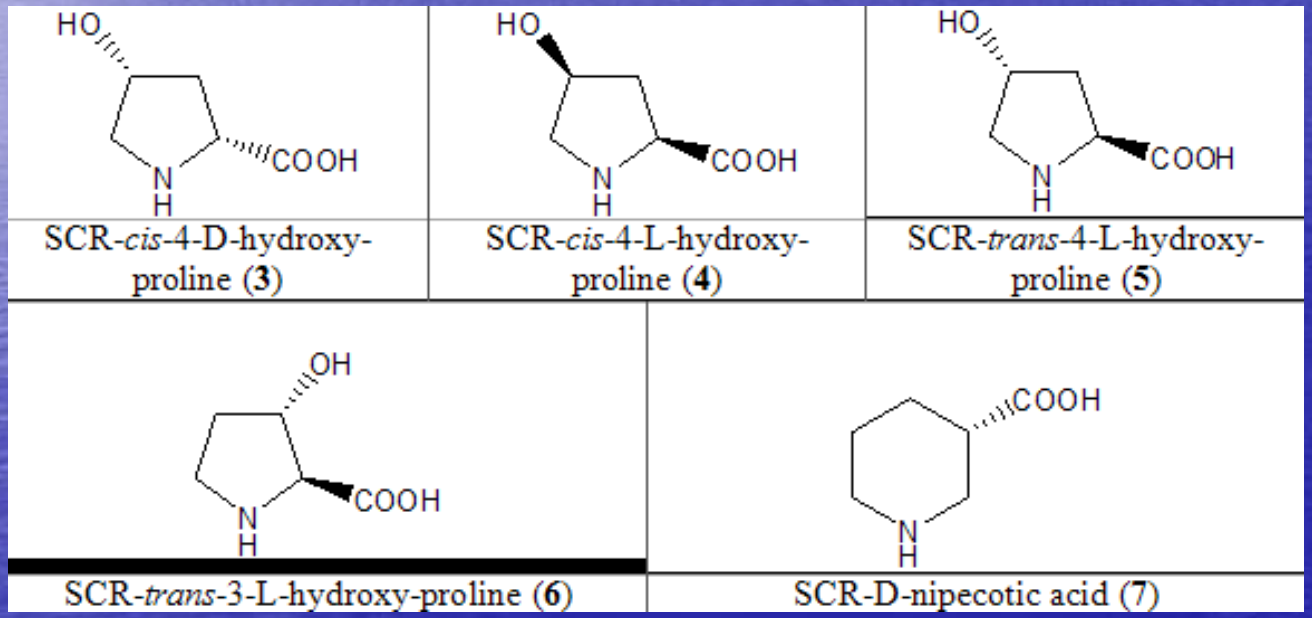
S-MOP



bis-MOP



PyrMOH

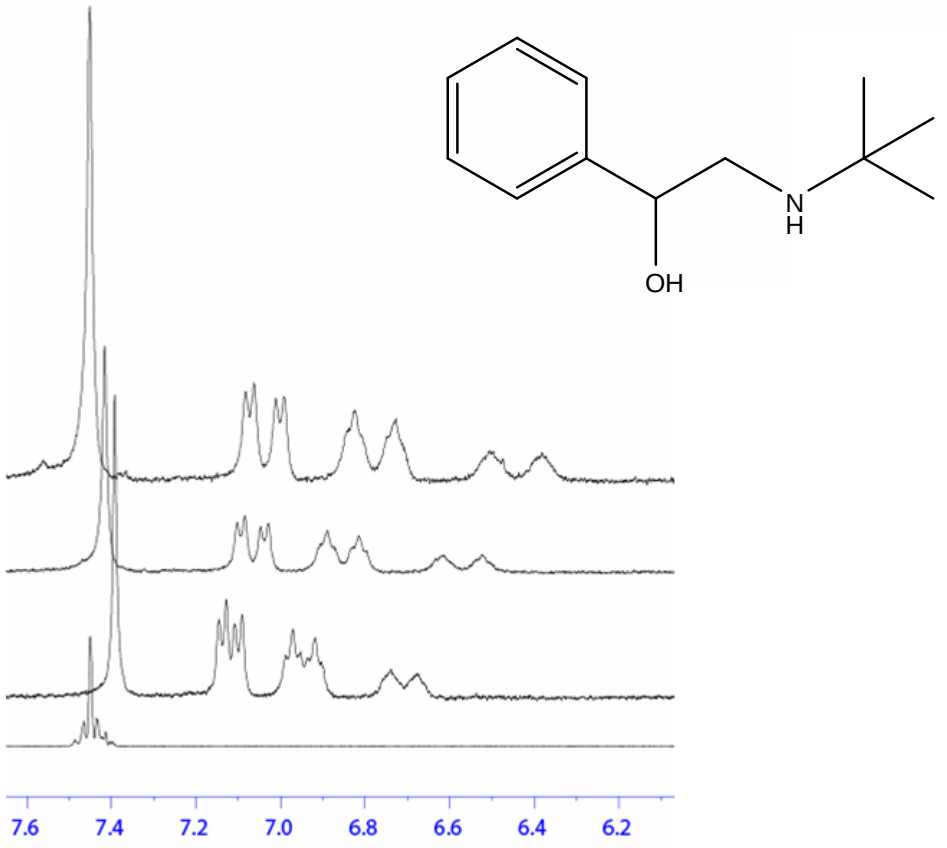


C.M. O'Farrell, J.M. Chudomel, J.M. Collins, D.F. Dignam, T.J. Wenzel, *Journal of Organic Chemistry*, **2008**, *73*, 2843-2851.

C.M. O'Farrell, T.J. Wenzel, *Tetrahedron Asymmetry*, **2008**, *19*, 1790-1796.

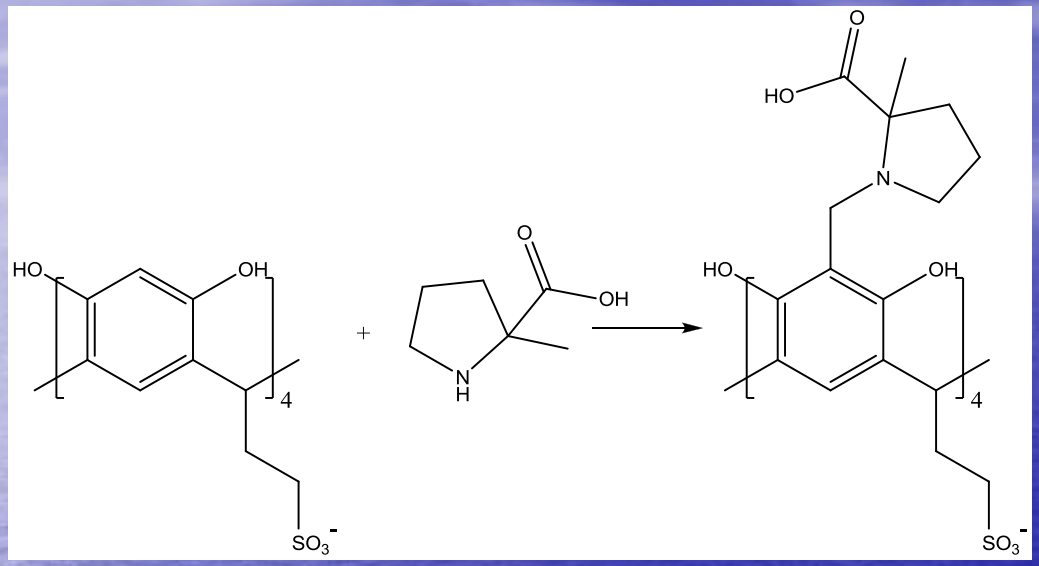
C.M. O'Farrell, K.A. Hagan, T.J. Wenzel, *Chirality*, **2009**, *21*, 911-921.

Hagan,K.A.; O'Farrell, C.M.; Wenzel, T.J., *European Journal of Organic Chemistry*, **2009**, 4825-4832.



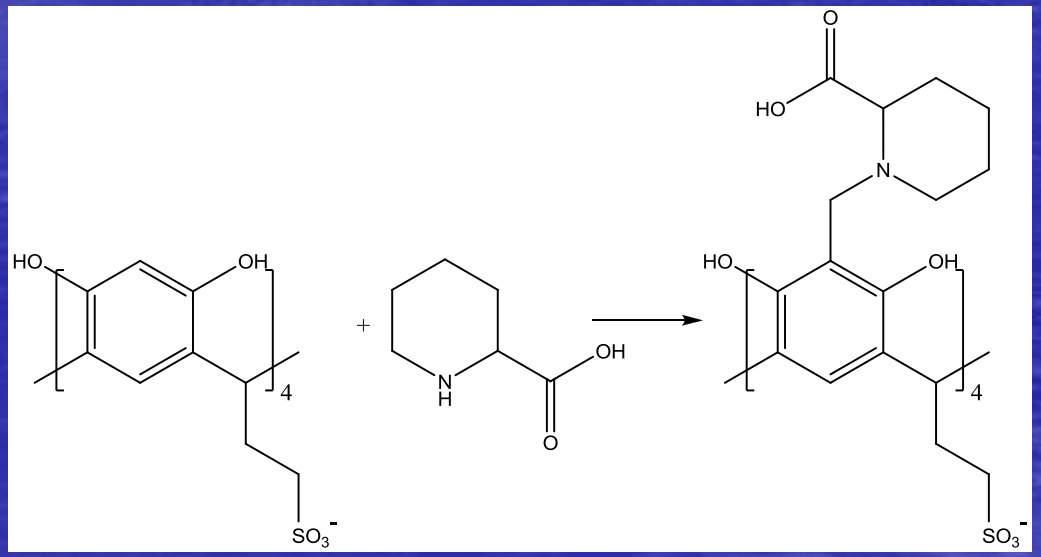
2-*tert*-butylamino-1-phenylethanol (10 mM) with 6, 8, and 10 mM of **SCR-t4L**

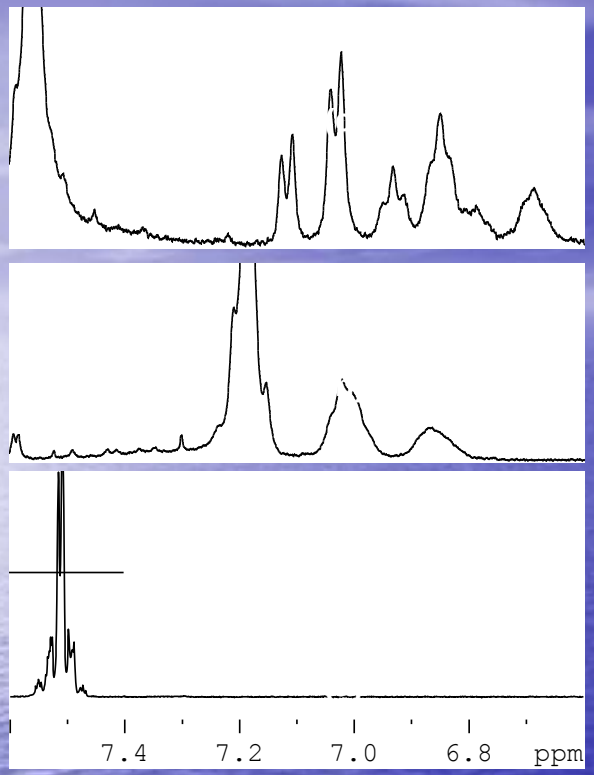
Our Latest Calix[4]resorcinarene Systems



α-methyl-L-proline (αMP)

L-pipecolinic acid (LPA)

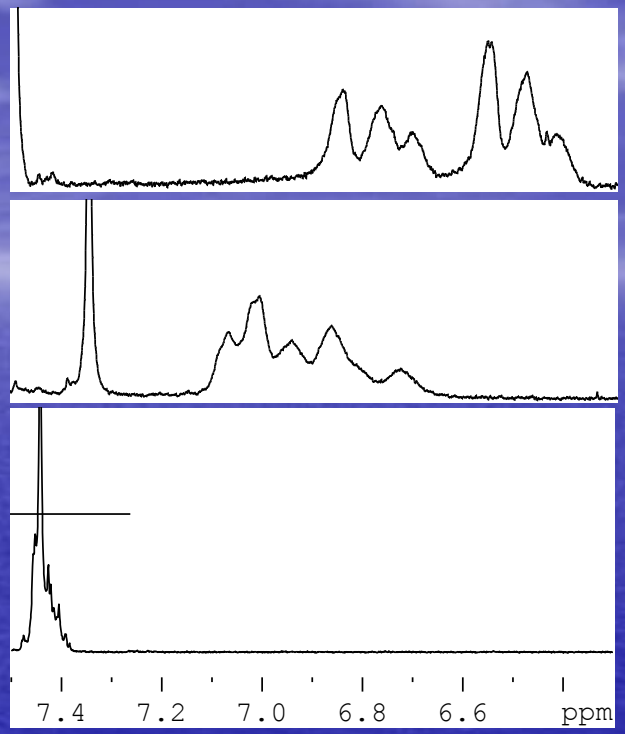


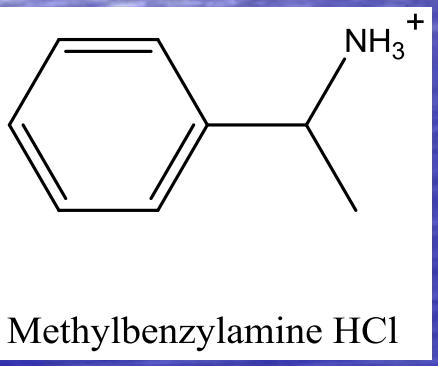


(c)

(b)

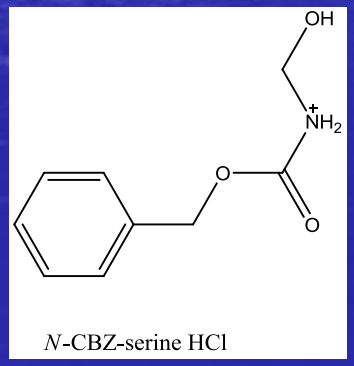
(a)





Methylbenzylamine HCl

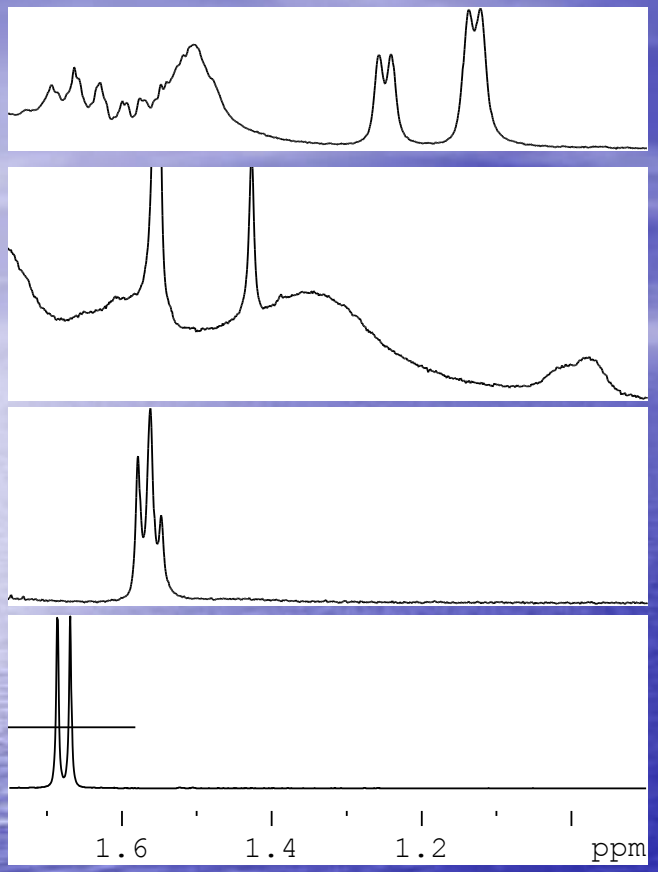
(a) 2/3-(*S*), 1/3-(*R*) (10 mM)
(b) t3L (30 mM)
(c) αMP (30 mM)



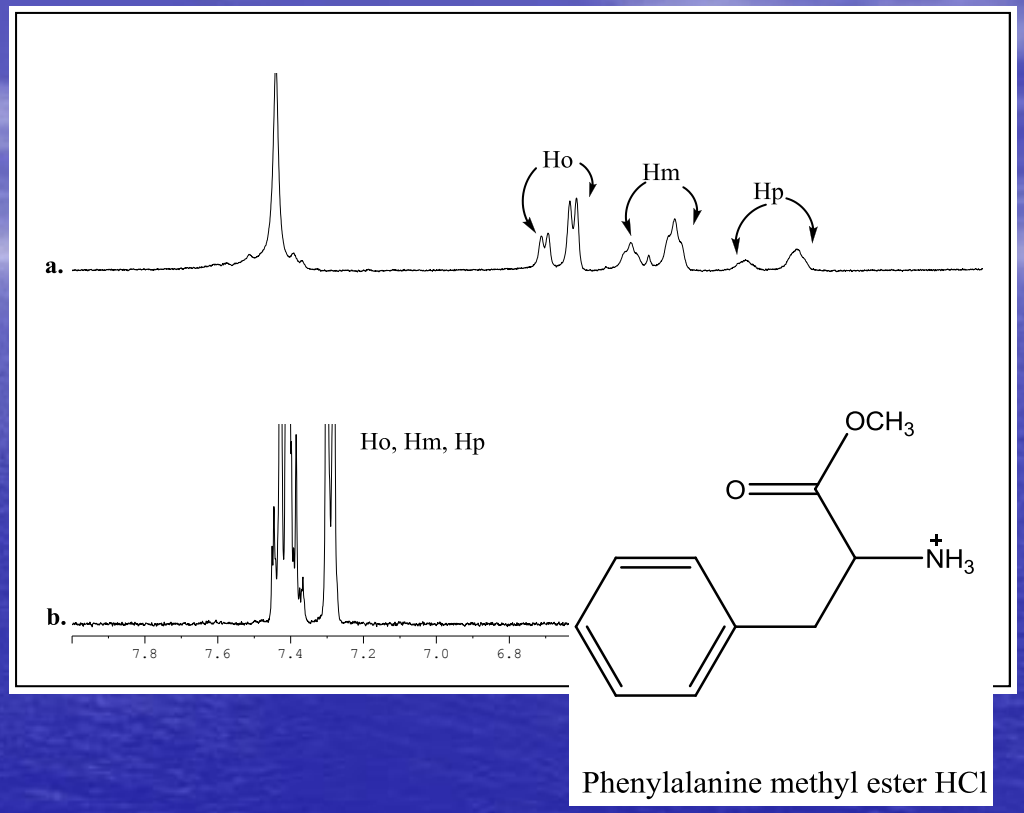
N-CBZ-serine HCl

(a) 2/3-L, 1/3-D (10 mM)
(b) c4L (10 mM)
(c) αMP (8 mM)

N.H. Pham, T.J. Wenzel, *Journal of Organic Chemistry*, submitted.



(a) *N*-benzyl-α-methylbenzylamine (10 mM) – CH_3
(b) 20 mM t3L
(c) 20 mM αMP
(d) 15 mM LPA



(a) 20 mM LPA
(b) 2/3-D, 1/3-L (10 mM)

Special Thanks To:

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- Research Corporation
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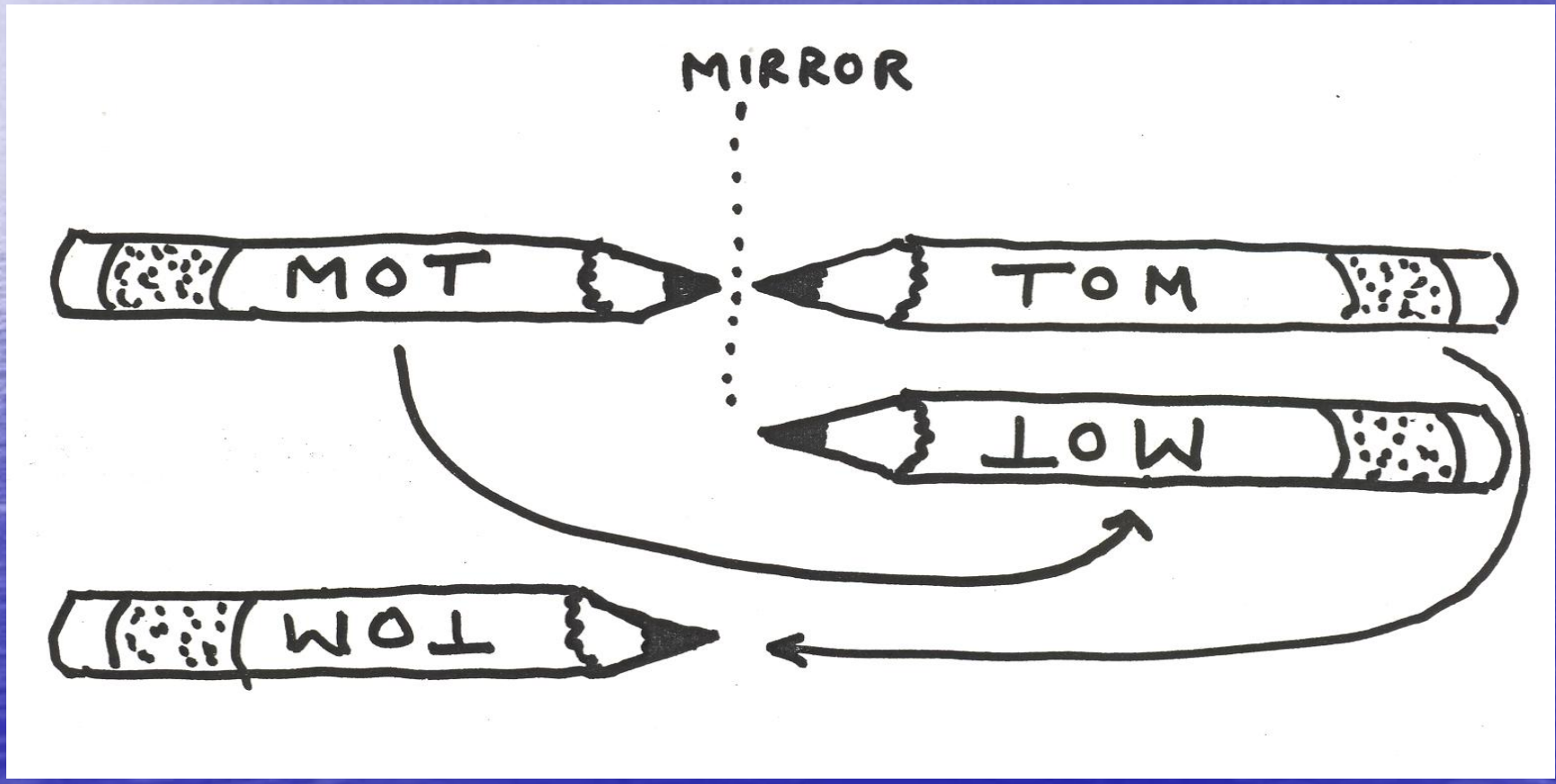
- Howard Hughes Medical Institute/Bates College
- Pfizer Pharmaceutical

THREE YEARS
OF ΔΔδs

Pens and pencils are chiral (right-handed) because of the writing



Be careful what you put on a pencil!