High Performance Liquid Chromatography of 2,2-*bis*(4-Hydroxycyclohexyl)propane

R. G. Gaughan[a]; J. F. Schabron[a]

[a] Phillips Research Center, Phillips Petroleum Company, Bartlesville, Oklahoma

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HIGH PERFORMANCE LIQUID CHROMATOGRAPHY OF

2,2-BIS(4-HYDROXYCYCLOHEXYL)PROPANE

R. G. Gaughan and J. F. Schabron

Phillips Petroleum Company

Phillips Research Center

Bartlesville, Oklahoma   74004

ABSTRACT

The three isomers of 2,2-bis(4-hydroxy-
cyclohexyl)propane, and its major impurities were
separated by high performance liquid chromatography.
Isolated components were identified by mass
spectrometry, nuclear magnetic resonance, and infrared
spectroscopy. Preparative liquid chromatography
effected the purification of 18g of pure 2,2-bis(4-
hydroxycyclohexyl)propane in 30 minutes.

INTRODUCTION

We wanted to develop methods to characterize
the impurities of commercial 2,2-bis(4-hydroxy-
cyclohexyl)propane(Figure 1, structure b). We also

13

needed 2,2-bis(4-hydroxy-cyclohexyl)propane in its
pure form(> 99.7%). Monofunctional impurities produced
in its synthesis were undesirable. Commercial 2,2-
bis(4-hydroxy cyclohexyl)propane formed by the
hydrogenation of bisphenol A (Figure 1, structure a)
possesses an average purity of about 90%. The
hydrogenolysis and elimination side products (Figure
1, structures c and d) that are suspected to be
formed, besides the expected 2,2-bis(4-hydroxycyclo-
hexyl)propane (also called hydrogenated bisphenol A or
(HBPA)) product, are shown in Figure 1.

In addition, to wanting pure HBPA, separation
of the axial, axial (Figure 2, structure e), axial,
equitorial (Figure 2, structure f) and equitorial,
equitorial (Figure 2, structure g) HBPA isomers was
desired. Standard methods of purifying HBPA such
as recrystallization and distillation[1] were inade-
quate. Because we also wanted to isolate the pure

(a)

(b)   (c)   (d)
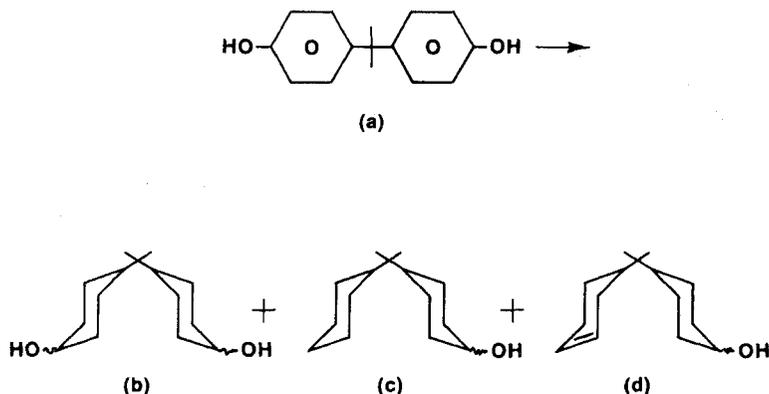
Figure 1

Products Formed From The Hydrogenation of

Bisphenol A.

(e)   (f)   (g)
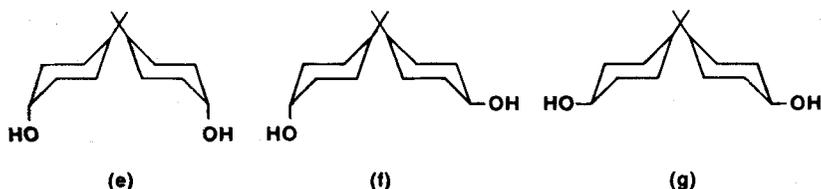
Figure 2

The Three Isomers of 2,2-bis(4-hydroxy-
cyclohexyl)propane.

isomers of HBPA, a liquid chromatographic separation
was in order.

The present work describes the separation of
HBPA isomers and several impurities by liquid chrom-
atographic techniques, followed by characterization of
the material obtained.

MATERIALS AND METHODS

Instrumentation

Infrared (IR) spectra were obtained on a
Perkin-Elmer 137 sodium chloride infrared spectro-
meter. Solid samples were run as potassium bromide
KBr pellets using mixtures of 1% by weight. All
absorptions were reported in wave numbers (cm^{-1}).

Mass spectra were obtained using a CEC 21-110
Mass Spectrometer equipped with a computerized data
system. FIMS was used to get simpler spectra with
fewer peaks, as too much fragmentation resulted using
EIMS.

Nuclear magnetic resonance (NMR) proton
spectra were obtained on a Varian EM 390 spectrometer,

operating at 90 MHz in the CW mode. Carbon 13 spectra
were obtained on a Varian CFT 20 at 20 MHz in the FT
mode. Chemical shifts are reported in parts per
million (ppm down field from tetramethylsilane
(Mallinkrodt). The spectra were obtained in CDCl$_3$
(Norell Chemical Co., Inc.) containing 1% by volume
of the internal standard tetramethylsilane .

        The analytical liquid chromatograph used in
this study was a Waters Model 204 liquid chromatograph
with a Model 6000-A pump, Model 401 refractive index
detector, and Model 450 variable wavelength detector
set at 254 nm and a dual channel 10 mv strip chart
recorder. The column used was a 3.9 mm id x 30 cm μ-
Porasil column packed with 10μm porous silica obtained
from Waters Associates, Milford, Mass.

        The preparative liquid chromatograph was a
Waters Prep 500-A equipped with solvent delivery
system, refractive index detector and strip chart
recorder. The two cartridge μ-Porasil columns
employed measured 5.7 x 30 cm and were packed with 325
g of 50-100 μ porous silica. These columns were
obtained from Waters Associates, Milford,
Massachusetts.

Thin Layer Chromatography

        Thin layer chromatography (TLC) was effected
using either 25 x 75 mm Baker Flex 1 B-F precoated
silica gel sheets (J. T. Baker Company) or 25 x 75 mm
precoated 60 F-254 silica gel plates (E. Merck
Laboratories) in vapor saturated jars (6 x 12 cm).
Visualization of the developed spots, using the Baker
Flex plates, was accomplished by iodine staining.

Developed spots on the EM plates were   visualized
with 254 nm light followed by staining with a 10%
solution of phosphomolybdic acid in 100% ethanol,
followed by heating.

Reagents

       All solvents used were reagent grade.
Chloroform used in the high performance liquid
chromatography work was filtered through a Millipore
Type F-H 0.5 mm filter prior to use. HBPA, used for
preparative separations, was obtained from
commercially available sources..

RESULTS AND DISCUSSION

Thin Layer Chromatography

       TLC was investigated for detecting impurities
present in commercial HBPA and as a method of
selecting an eluting solvent for preparative HPLC.
Several solvent systems were evaluated using silica
chromatographic plates for their ability to separate
the impurities from HBPA. The solvent systems of 3%
or 4% (v/v) methanol in chloroform were ideal for
impurity detection by TLC. Monofunctional impurities,
later identified as 2-cyclohexyl-2-(4[a]-hydroxy-
cyclohexyl)propane (Figure 3, structure h) and
2-cyclohexyl-2-(4[e]-hydroxycyclohexyl)propane (Figure
3, structure i), were separated as well as the three
isomers of HBPA.
       When TLC was used to aid in the selection of a
mobile phase for preparative HPLC, an important

(h)   (i)
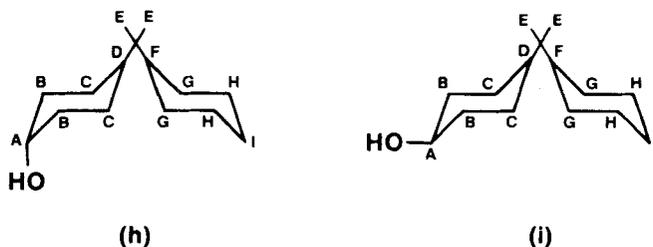
Figure 3

The two major impurities found in
2,2-bis(4-hydroxycylohexyl)propane
(the letters correspond to ^{13}C nmr resonances
listed in Table III).

criteria required the solvent system to elute the
three isomers of HBPA to retardation factor (R_f)
values between 0.15 and 0.35. This R_f range has been
shown to be optimal in terms of sample loading,
resolution, residence time and solvent usage[2]. Also,
the solvent system chosen had to dissolve acceptable
amounts of HBPA so that 20g quantities of 90% pure
material could be purified per injection. Two percent
methanol in chloroform came closest to meeting the
above-mentioned criteria. Experimentally, however,
one percent methanol in chloroform turned out to be
the best for preparative HPLC. Table I lists the HBPA
R_f values for four solvent systems tried.

Identification of HBPA Isomers and Impurities

        For the HPLC work with HBPA, the mobile phase
was chloroform at 4mL/min. The amount of sample
injected was 438-772 mg. Four commercial HBPA samples
from different sources were evaluated. Two of the

Table I

HBPA R_f VALUES

Solvent System MeOH in CHCl$_3$ (Volume %)	HBPA Isomer		
	axial,axial	axial,equit.	equit,equit.
4%	0.43	0.29	0.20
3%	0.38	0.26	0.18
2%	0.27	0.17	0.12
1%	0.16	0.09	0.06

samples were completely chloroform soluble. There was
a significant amount of chloroform insoluble material
in the other two samples. This insoluble material was
identified later as the equitorial,equitorial isomer
of HBPA (Figure 2, structure g). Chromatograms of the
chloroform soluble portions of the four samples are
shown in Figures 4-7. These chromatograms show signi-
ficant differences in impurities for the four samples.

     For identification work, about 20 mg portions
of each of the chloroform soluble material from the
HBPA samples were injected onto the HPLC system and
fractions corresponding to the peaks of interest were
collected. These peaks are those labeled A-M in
Figures 4-6. Material for unlabeled peaks was not
collected. It was assumed that the peaks represented
the major impurities and components present in the
four samples, even though they were not collected for
all four. The fractions were evaluated by mass spec-
trometry. The results of the identification work are
summarized in Table II. In many cases, insufficient
amounts of impurities were isolated for complete
identification. The major impurities were character-
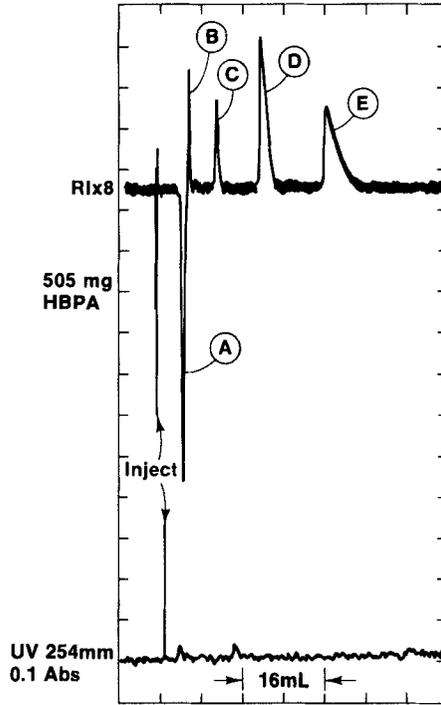
Figures 4-7

HPLC chromatogram of four differentcommercial HBPA
samples, conditions as in text.

ized in more detail following preparative liquid
chromatography. This is described in the following
section.

Preparative LC Separation

        The 1% methanol in chloroform solvent was
pumped at a rate of 200 mL per minute. Sample
preparation involved making a saturated solution of
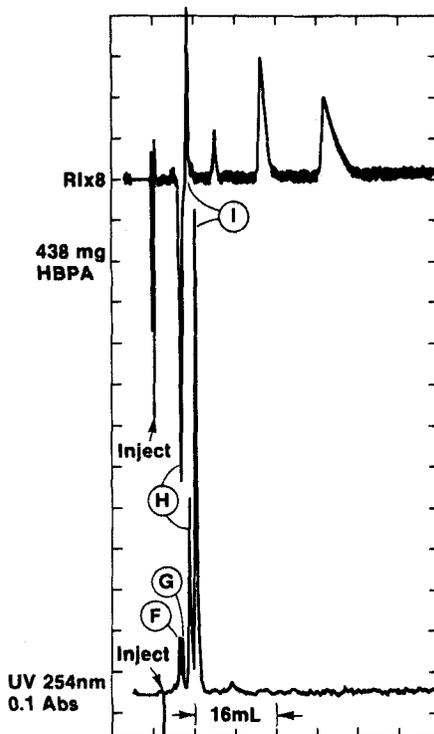
Figure 5

HBPA in the above-mentioned solvent which contained
20g of crude (90% pure) HBPA per 100 mL of solution.
One hundred milliliter aliquots were injected by
pumping the solution directly on the column. The
first separation simply involved the removal of
impurities from the three isomers of HBPA (Figure 8),
affording 18g of pure (>99.7%) HBPA.   Next, the
isomers of HBPA were separated using the same solvent
system, by collecting the appropriate fractions.
Finally, the impurities were isolated in a separate
operation using chloroform as the eluting solvent.
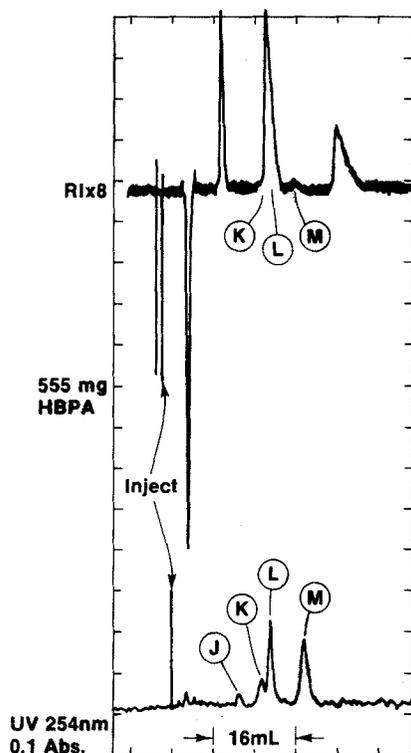
Figure 6

Pure material was obtained in each case by removing
the solvent at reduced pressure. The first separation
step allowed us to use HBPA as an isomer mixture. The
second step allowed us to isolate and identify the
three isomers of HBPA, while the last separation
allowed us to isolate and identify the major
impurities found in HBPA. The isomers of HBPA could
now be used individually or as a given mixture.

Isolation of the isomers of HBPA, via a
tedious multiple recrystallization sequence, was
reported by Terada in 1966[1]. Our spectrographic
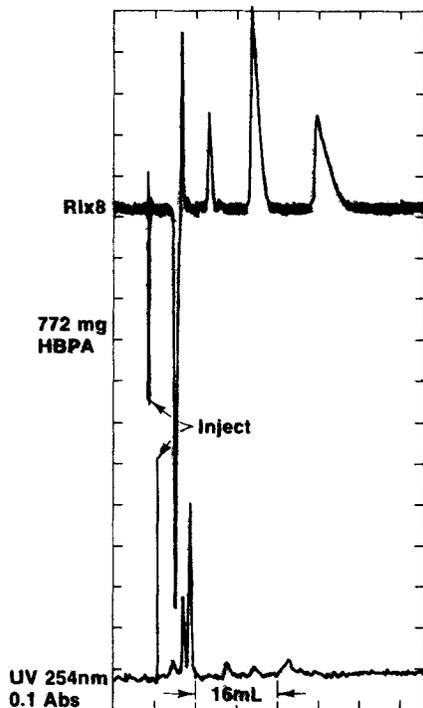
Figure 7

assignments of the three isomers were consistent with his and show up on the preparative HPLC chromatogram in Figure 8 as peak e (axial,axial); peak f, (axial,equitorial),and peak g (equitorial,equitorial). Figure 2 depicts these three isomers. The two impurities we found in commercial HBPA were different than those found in Terada's hydrogenated product. Therefore, we separated the two components of the impurity fraction and analyzed them by IR, ^{13}C NMR, ^{1}H NMR, and mass spectrometry. We identified the impurities as 2-cyclohexyl-2-(4[a]-hydroxycyclo-hexyl)propane (Figure 3,structure h) and 2-cyclohexyl-

Table II

MASS SPECTROMETRIC RESULTS FOR PEAKS

A THROUGH M IN FIGURES 4 - 7

Peak[a]	Mass Spectrometric Results

A   Complete identification not possible.
         Two fragments identified were

 m/e 125   m/e 123

B   Fragments identified were:

 m/e 125   m/e 123

 m/e 141   m/e 206

 m/e 204
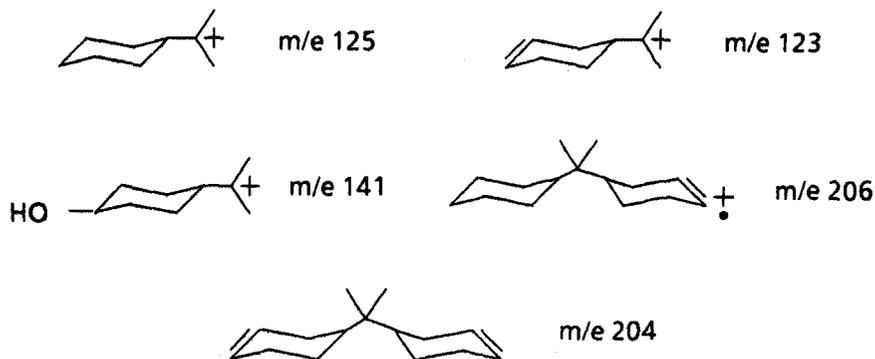
         None of the above are believed to
         represent molecular ions.

C, D, E   HBPA isomers.

F, G   Insufficient material for
               identification

[a] Peaks as in Figures 4-6.

                                          (continued)

Table II (continued)

Peak[a]	Mass Spectrometric Results
H	The UV absorbing impurity is [structure] OH (isomer of I)
I	The UV-absorbing impurity is [structure] OH (isomer of H)
J	Complete identification not possible. Fragments seen included. [structure] m/e 123 HO [structure] m/e 141
K	Two major components – one is isomer of J; other showed the fragments. O [structure] m/e 97 O [structure] m/e 139 Neither component could be identified.
L	Isomers of compounds in J and K, none completely identified.
M	The UV-absorbing impurity is HO [structure] OH
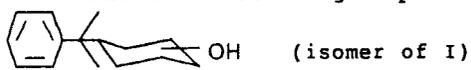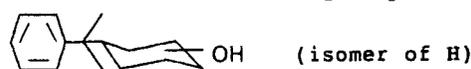
[a] Peaks as in Figures 4-6
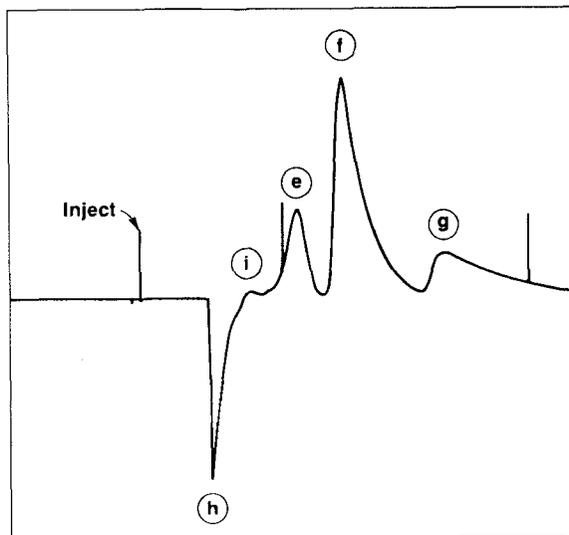
Figure 8

Prep LC chromatogram of HBPA, conditons as
in text. Peak identifications h, i: two
major impurities, (Figure 3);   e,f,g:
three HBPA isomers (Figure 2).

2-(4[e]-hydroxycyclohexyl)propane (Figure 3,structure
i).   Infrared spectroscopy showed that both impurities
were alcohols by their large OH stretching frequencies
at about 3350 cm-1.   Proton NMR eliminated the
possibility of any unsaturation in either impurity as
there was only one resonance in both spectra beyond
4.2ppm.   This broad peak at about 5.5 ppm was inte-
grated as a single proton in both spectra and was
identified as the alcohol proton.   The definitive
proof was found in ^{13}C nmr, which distinguished the
axial and equitorial isomers and high resolution mass
spectrometry, which showed that both impurities

possessed the same fragmentation pattern. The first impurity, h (Figure 3) , possessed the following spectra; (h) IR (film) 3350, 2940, 2890, 2865, 1449, 1378, 1270, 1100, 1019, 964, 800, and 698 cm^{-1}; ^{1}H nmr (CDCl$_3$) 5.32 (1.s [broad] alcohol)., 3.85 (1,m,hydroxymethine), 0.85 – 2.00 (20,m [broad] methylene and methine) and 0.60 ppm (6,s,gem dimethyls); ^{13}C nmr (CDCl$_3$) spectrum is listed in Table III;

field ionization mass spectra gave a base peak at m/e 125 [M-99] with characteristic peaks at 141 [M-83], 99[M-125] and m/e 83 [M-141].

CONCLUSION

Preparative LC allowed us to obtain quickly 18g quantities of pure HBPA from 20g of 90% pure HBPA.

TABLE III

CARBON 13 NMR OF AXIAL (h) AND
EQUITORIAL (i) 2-CYCLOHEXYL-2-(4-HYDROXYCYCOLHEXYL) PROPANE

Carbon/Atom (Figure 3)	Chemical Shift Axial Isomer (ppm)	Chemical Shift Equitorial Isomer (ppm)
A	66.1	71.4
B	33.6	36.3
C	20.6	25.8
D	43.7	42.9
E	20.5	20.6
F	43.9	44.3
G	27.4	27.4
H	27.2	27.2
I	27.0	27.0

It also gave us the ability to separate each isomer of HBPA so that we could use each isomer by itself or as a mixture and allowed us to isolate and identify the two major impurities found in commercial HBPA.

ACKNOWLEDGEMENTS

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1.   Terada, A.; Bull. Chem. Soc. Japan, 1966, 39, 2194.

2.   Rahn, P.C.; Woodman, M.; Beverung, W. Heckendorf, A., Waters Associates, "TLC to Prep", Waters Associates, Milford Massachusetts, 1979.