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Epoxide Formation from Heterogeneous Oxidation of Benzo[a]pyrene with Gas-Phase Ozone and Indoor Air

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Abstract

The formation of two classes of epoxide products from the heterogeneous reaction of benzo[a]pyrene (BaP) with gas-phase ozone was demonstrated. BaP was coated on a Pyrex glass tube and oxidized with different concentrations of ozone. After oxidation, the epoxide products were derivatized by \(N\)-acetylcystein (NAC) and then analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The results show that in addition to mono-epoxides, diol-epoxides were also formed. BaP exposed to genuine indoor air also produces mono- and diol-epoxides, having similar chromatograms as those produced by oxidation of BaP by low concentrations of ozone. Although it is well recognized that diol-epoxides are formed from BaP oxidation in the human body and that they exhibit carcinogenicity via formation of adducts with DNA, this is the first demonstration that such classes of compounds can be formed by abiotic heterogeneous oxidation.

Introduction

Polycyclic aromatic hydrocarbons (PAHs) are a ubiquitous class of air pollutants that are generated as by-products from incomplete combustion, which include coal, fossil fuel and biomass burning, as well as industrial processes.\(^1,2\) Studies have also demonstrated the formation of PAHs in indoor environments from meat cooking, candle burning and tobacco smoking.\(^3,4\)
Due to their toxic effects on human health, PAHs and their biological/chemical
degradation products have received extensive attention. While several mechanisms for
metabolic activation of PAHs have been proposed, such as bay region diol-epoxide
formation, radical cations and redox-active quinone generation, the diol-epoxide
pathway is believed to play an essential role in the metabolism and toxicity of PAHs.
For example, for benzo[a]pyrene (BaP), it is well accepted that the carcinogenic effect
exerted by BaP on humans is through the metabolic formation of a bay-region diol-
epoxide, benzo[a]pyrene-7,8-diol-9,10-epoxide (BPDE). This is the ultimate
carcinogenic oxidation product of BaP, reacting with DNA to form adducts that lead to
miscoding and mutations. The diol-epoxides are also formed from metabolism of
other PAHs, e.g. phenanthrene, chrysene, methylchrysene, benzo[c]chrysene,
dibenzo[a,l]pyrene, 7,12-dimethylbenz[a]anthracene, and benzo[c]phenanthrene. Among them, the non-bay region diol-epoxides from
metabolites of dibenzo[a,l]pyrene, 7,12-dimethylbenz[a]anthracene and
benzo[c]phenanthrene are found to be more carcinogenic than BPDE. In addition,
the formation of mono-epoxides was also reported from biotic reactions of
naphthalene, phenanthrene, dibenz(a,h)anthracene, benz[a]anthracene and
BaP. Toxicological studies have shown that the mono-epoxides formed via biotic
degradation of BaP are mutagenic and cytotoxic.

Chemical degradation of PAHs in environmental systems such as the soil and
atmosphere leads to a series of oxygenated PAHs, such as ring-retaining phenols,
quinones and nitro-PAHs and ring-opening carbonyls and carboxylic acids. Moreover, photolytic degradation of PAHs and quinones under UV light has been
reported to generate reactive oxygen species (ROS) through energy or electron transfer
from photochemically-activated PAHs or quinones/semiquinone radicals to the ground
state of molecular oxygen or biochemical molecules in cells. Most recently, using
electron paramagnetic resonance spectrometry, it was reported that long-lived radicals
were formed (likely semiquinone radicals) from chemical reaction of several PAHs
(anthracene, pyrene, BaP and benzo[ghi]perylene) and quinones (1,4-naphthoquinone
and 9,10-anthraquinone) with gas-phase ozone, consistent with earlier work of
Shiraia et al. who proposed the formation of reactive intermediates with lifetimes on
the order of 100 seconds arising from ozonolysis of PAHs. Theoretical and
experimental studies have also proposed the generation of epoxides from chemical
degradation of PAHs. However, to date, there has been only one experimental study
that investigated mono-epoxide formation from heterogeneous oxidation of BaP with
ozone, where it was reported that the yield of BaP-4,5-epoxide (4,5-BPME, Figure 1a)
is 0.5%. Given the importance of PAHs and the toxic effects of the PAH-epoxides, the overall
goal of this work is to investigate the generation of epoxide products from ozone
heterogeneous oxidation of BaP in order to address the following questions: (i) To what
degree are epoxides formed, especially diol-epoxides? (ii) Are epoxides formed under
genuine environmental conditions, such as when PAHs are exposed to room air?
Experimental

**Chemicals.** Benzo[a]pyrene, squalane, anhydrous tetrahydrofuran (THF), ammonium hydroxide solution and N-acetylcystein (NAC) were purchased from Sigma-Aldrich without further purification; benzo[a]pyrene-7,8-dihydrodiol-9,10-epoxide (BPDE) and benzo[a]-pyrene-9,10-dihydrodiol-7,8-epoxide (rev-BPDE), a structural isomer of BPDE (Figure 1b), were purchased from the MRI Global Chemical Carcinogen Reference Standard Repository (Kansas City, MO); methanol (MeOH), acetonitrile (ACN), dichloromethane (DCM) were from EMD Chemicals; and formic acid was from Fisher Scientific. The NAC was pH adjusted to 10 with 50% NaOH/H2O solution for the derivatization of the epoxides.

**BaP Oxidation with O3.** To study the reactivity of BaP, samples were mixed in a liquid hydrocarbon, squalane, that is unreactive to ozone. Squalane was chosen because it is known to solubilize BaP and so enhance the reaction efficiency.41 As well, PAHs are co-emitted from combustion sources with low volatility alkanes, and they co-condense on particle and indoor surfaces.47,48

20 mg of BaP and 200 mg of squalane were dissolved in 10 mL of DCM. 50 µL of the BaP/squalane solution was diluted into 50 mL DCM for quantification of BaP before oxidation using direct analysis in real time-mass spectrometry (DART-MS). The remaining BaP/squalane/DCM solution was then added into a 20 cm long cylindrical Pyrex glass tube (2.5 cm ID) with both ends open. A BaP/squalane film was coated on the tube by rotating the tube with a small flow of nitrogen passing through to evaporate the DCM.

The experimental setup for ozone reaction is illustrated in Figure 2. In brief, the glass tube with the BaP/squalane coating was placed in a flow tube through which a flow of air mixed with O3 passed. The O3 was generated by passing 1.8 L/min synthetic air through an O3 generator. The generator is composed of a Pen-Ray lamp with a metal cover and a quartz cell. The O3 concentration was regulated by adjusting the metal cover and was measured by a UV photometric O3 monitor (Thermo Model 49i). In order to investigate the effect of ozone concentration on product formation, the BaP was oxidized under two different conditions: one with high O3 (>2.5×10^{13} molecules/cm^3) oxidation for 2 hr and the other with low O3 (1.2×10^{12} molecules/cm^3) oxidation for up to a week. A control experiment was conducted by passing air with no O3 through the coated glass tube.

**BaP Oxidation in Room Air.** 20 mg of BaP and 200 mg squalane were mixed in 10 mL DCM in a 50 mL glass beaker. The inner wall of the beaker was coated with BaP/squalane film by evaporation of the DCM under nitrogen. The beaker was placed into a fumehood in the laboratory for 14 days. The ozone concentration in the laboratory, monitored with the ozone analyzer, varied between (2.5-5)×10^{11} molecules/cm^3. The temperature (T) and relative humidity (RH) in the room were monitored with a hygrometer (Vaisala) as: T=21.2-24.3 °C and RH=6.6-10.2%. To account for the
depositional and/or reactive interference from the lab air, an identical glass beaker with
the same amount of squalane, but without BaP, was prepared and placed side-by-side
in the same fumehood with the BaP/squalane beaker.

**Direct Analysis in Real Time-Mass Spectrometry (DART-MS) Analysis of BaP.** In
order to confirm the reaction of BaP with ozone, the amount of BaP before and after
high ozone oxidation was quantified using DART-MS. A detailed description of the
DART-MS technique is given in our previous publication and the Supplementary
Information. In particular, on average about 60% of BaP was lost under high ozone
conditions.

**BaP Epoxide Derivatization.** In biochemistry, NAC has long been used to derivatize
epoxides generated from metabolism of PAHs. In this work, the NAC
derivatization of BaP-epoxide is adapted from Upadhyaya et al. Two commercially
available BaP diol-epoxide isomers (i.e. BPDE and rev-BPDE, Figure 1b) were used to
evaluate the derivatization reaction and establish the LC-MS/MS method. The
derivatization reaction of BaP-epoxides with NAC is illustrated in Figure 1 using BaP-
4,5-epoxide (i.e. 4,5-BPME, Figure 1a) and BPDE (Figure 1b) as examples.

After ozone oxidation, BaP and its oxidation products were extracted with 20 mL THF.
The THF extract was first concentrated to 5 mL under a gentle stream of nitrogen; then
2 mL of NAC aqueous solution (3.0 M, pH 10) were added and stirred at room
temperature (295±3K) for 16 hours. The resulting solution was then left for 30 min for
phase separation. The organic phase (top layer) was transferred to a conical tube and
concentrated under nitrogen and reconstituted with 1 mL MeOH. The MeOH extract
was vortexed for 1 min and then centrifuged at 6000 rpm for 5 min. For the high O3
experiments, the MeOH extract was directly analyzed via LC-MS/MS. For the low
ozone experiments, the 1 mL MeOH extract was further concentrated to 50 µL prior to
LC-MS/MS analysis. Sample blanks were prepared in the same manner. As neither
BPDE nor rev-BPDE were observed in the BaP oxidation products (see next section),
recovery analysis for NAC derivitization efficiency was not performed.

**LC-MS/MS Analysis.** An Acquity ultra performance liquid chromatograph (UPLC)
and a Xevo TQ-S MS/MS (Waters Corporation) were used to separate and analyze
NAC-derivatized BaP-epoxides in the samples. An atmospheric pressure electrospray
interface operating in negative ionization mode was used, and detailed LC-MS/MS
parameters are provided in the Supplementary Information. Chromatographic
separation was initially performed on a reverse phase C18 column (Kinetex 2.6 µm
C18 100Å, 2.1 × 50 mm, Phenomenex, Torrance, CA) with the column temperature at
40 °C; 0.1% ammonium hydroxide in Milli Q water and MeOH were the mobile phases.

Due to the co-elution of NAC-BPDE and NAC-rev-BPDE with the C18 column,
chromatographic separation was then achieved using an Acquity CSH fluoro phenyl
column (CSH-FP, 1.7 µm, 130Å, 2.1 × 50 mm, Waters, Milford, MA); the mobile
phases were 0.1% formic acid in MilliQ water and acetonitrile. The discussion of the
chromatographic separation is given in the Results and Discussion section. Neutral loss scan mode was used to identify any epoxides formed during the experiment, whereas multiple reaction monitoring (MRM) mode was used to identify specific epoxides (e.g., mono- or diol-epoxides) formed during the BaP oxidation.

**Result and Discussion**

1. **HPLC Method Development.** Multiple reaction monitoring (mass transition $m/z$ 464 $\text{[M-H]} \rightarrow m/z$ 317 $\text{[M-H-CH}_2\text{CH(CO}_2\text{H)]}$) parameters were optimized for NAC derivatization of two commercially available BaP diol-epoxide isomers, i.e. BPDE and rev-BPDE. The separations of NAC-BPDE and NAC-rev-BPDE were initially done on a reverse phase C18 column. In two separate LC runs for NAC-BPDE and NAC-rev-BPDE, two peaks were observed which resulted from the isomer adducts formed during the derivatization reactions (Figure 1). However, using this column, NAC-BPDE and NAC-rev-BPDE were not separated. An example of the LC chromatograms for NAC-BPDE and NAC-rev-BPDE is given in Figure 3a where it is seen that these species eluted around the same time (e.g., retention time: 2.90 and 2.95 min vs 2.91 and 2.96 min, respectively).

In order to separate NAC-BPDE and NAC-rev-BPDE, better chromatographic separation was evaluated using various stationary phases. The use of an Acquity CSH fluoro phenyl column demonstrated acceptable separation between NAC-BPDE and NAC-rev-BPDE (Figure 3b). Two isomeric peaks were again observed for both NAC-BPDE and NAC-rev-BPDE (Figure 3b). Although the isomer peaks of NAC-BPDE and NAC-rev-BPDE still overlapped with each other, the two derivatized compounds were identified (retention time: 5.71 and 5.82 min for BPDE and 5.63 and 5.70 min for rev-BPDE). All the remaining LC-MS analyses were performed using the CSH fluoro phenyl column.

2. **Confirmation of the Detection of Epoxides.** To confirm the formation of the epoxides, a neutral loss scan of the cross-links derived from NAC-BPDE and NAC-rev-BPDE, i.e. loss of 147 amu, corresponding to a mass-to-charge transition of $\text{-CH}_2\text{CH(CO}_2\text{NHCOCH}_3+\text{H}_2\text{O}}$ was employed. Peaks in the chromatogram for the neutral loss scan of 147 amu (Figure 4, upper trace) appeared at the same retention times observed from the MRM transitions of diol-epoxides using the NAC-BPDE and NAC-rev-BPDE standards (Figure 4, lower trace).

To test the possibility that reactions between other PAH oxidation products and NAC might also result in the same neutral loss of 147 amu, three common PAH oxidation products were investigated. Benzene-1,4-diol, 5-hydroxy-1,4-naphthalenedione and anthraquinone (Figure SI-1) were derivatized with NAC, and were then subjected to the same neutral loss LC-MS/MS analysis. As expected, no peaks in the neutral loss scan of 147 amu were observed for any of these products (data not shown), validating that the use of neutral loss scan of 147 amu can identify NAC derivatives of epoxides.
3. Epoxide Formation from Heterogeneous Oxidation of BaP with O₃. The products for BaP oxidation with high O₃ (O₃>2.5×10¹³ molecules/cm³, for 2 hours) after NAC derivatization were analyzed by the LC-MS/MS using the same neutral loss scan. As can be seen in Figure 5a, a few epoxide products were observed (top panel). To further classify the epoxide products, the MRM mass transition (m/z 464 → m/z 317) for BaP diol-epoxide and the MRM mass transition (m/z 430 ([M-H]⁻ → m/z 283 ([M-H-\[\text{CH}_2\text{CH(CO}_2\text{)NHCOCH}_3\text{+H}_2\text{O}]⁻)) for mono-epoxide (Figure 1a) were also applied to the LC-MS/MS analyses.

There are a number of important observations in these experiments. For the high O₃ oxidation of BaP (Figure 5a), the retention times for most of the epoxides (top panel) match the mono- (6.41 and 6.56 min. in middle panel) and diol-epoxides (peaks in the bottom panel). However, the relative intensities for the epoxide peaks obtained by neutral loss scan mode (upper panel) and the diol-epoxides observed by MRM mode (lower panel) are different. The differences in relative intensity might be due to the formation of other epoxides (other than diol-epoxides) that eluted at the same time as the diol-epoxides. Evidence for the formation of other epoxides are the peaks at 4.87 and 6.83 min in the neutral loss scan, which were not observed in either the mono- or diol-epoxide chromatograms.

We also note that the same mono-epoxide formed at high ozone exposure (Figure 5a, middle panel) was also observed for low O₃ oxidation of BaP (Figure 5b, middle panel), but the relative intensities of the two peaks are different. It is possible that these two peaks are two different mono-epoxides that could not be resolved under current experimental conditions.

Another feature of note is the different chromatographic patterns between the diol-epoxides formed from BaP/O₃ reaction and the spiked NAC-rev-BPDE (Figure 5a, lower panel), suggesting that the diol-epoxides from ozonolysis of BaP are structural isomers of BPDE and rev-BPDE. This is not surprising because the diol and epoxide functional groups in BaP/O₃ reaction could be attached to different locations on the five-ring BaP structure. Due to the lack of standards, the identification of the specific structural isomers of the mono- and diol-epoxides from BaP/O₃ reaction is not possible.

While the mono-epoxides from low ozone oxidation of BaP (Figure 5b, middle panel) show the same retention times with high ozone oxidation (Figure 5a, middle panel), the diol-epoxides from these two oxidation conditions are different. It can be seen from Figure 5a and 5b (bottom panels), more diol-epoxides are generated from high ozone reaction. In addition, the diol-epoxides from high ozone experiments are all eluted before the spiked rev-BPDE, whereas those from low ozone oxidation are eluted after the spiked rev-BPDE. The different diol-epoxide chromatographic patterns suggest that the diol-epoxides from high and low ozone oxidation are not the same, perhaps due to different reaction mechanisms that prevail at different ozone exposures.
To extend the environmental relevance of the observation of formation of diol-epoxides via abiotic mechanisms, a high O3 exposure was obtained by an experiment conducted with low O3 (1.2×10^{12} molecules/cm^3) over 7 days and the resulting chromatogram is presented in Figure 5c. It is clear that the mono- and diol-epoxides from 7 days of low O3 oxidation show similar chromatographic patterns to those from the 2 day oxidation (Figure 5b). The only difference between Figure 5b and 5c is that the latter shows more diol-epoxide formation, i.e. with the same amount of rev-BPDE spiked into the sample, the relative intensity of rev-BPDE in Figure 5c is lower than in Figure 5b.

4. Epoxide Formation from Exposure to Indoor Air. Epoxides were also observed when BaP was exposed to genuine room air for 2 weeks (Figure 5d), where the typical ozone concentrations (O3=2.5-5×10^{11} molecules/cm^3) were similar to those used in the Figure 5b and 5c experiments. The mono- and diol-epoxides formed via room air oxidation of BaP showed similar chromatographic patterns with those of low ozone oxidation in the flow tube (Figure 5c). The only difference between low ozone and room air oxidation of BaP is that the formation of the diol-epoxide at 7.03 min from ozonolysis of BaP (Figure 5c) was not observed in the room air oxidation experiment (Figure 5d).

Environmental Implications.

The overall conclusion arising from this work is that epoxides readily form from the heterogeneous ozone oxidation of a surface-adsorbed PAH, benzo[a]pyrene. This builds upon the classic work of Pitts et al. which showed that the mono-epoxide of BaP is formed under such conditions. More specifically, though, detailed LC-MS-MS analysis indicates that diol-epoxides also arise through this multiphase reaction. This is the first report of diol-epoxide formation from abiotic oxidation of BaP, while previous studies only focused on their formation from metabolic degradation of PAHs. Note that this work does not attempt to quantify the diol-epoxide products from BaP/O3 reaction due to the unavailability of the standards for the specific structural isomers.

The major environmental implication of this result is related to the highly toxic nature of BPDE, i.e. it is important to further investigate the toxicological effects of these BPDE isomeric products and the specific environmental pathways by which exposure could proceed need to be evaluated. Humans will be exposed to these products via a combination of dermal contact, inhalation or ingestion. As an example, previous studies on the PAH levels in indoor air and samples collected in indoor environments have reported that total PAH concentrations as high as 325 µg g^{-1} in household dust, with maximum BaP concentrations of 38.3 µg g^{-1}. Moreover, an exposure study revealed that dust ingestion contributes 42% of the non-dietary intake of PAHs in children. The evidence that epoxide formation can occur via indoor air oxidation of BaP indicates that these epoxides may be formed on dusts or other indoor surfaces where PAHs are deposited and exposed to ozone. The stability and health effects of these epoxides are important to assess the environmental significance of PAHs in such environments.
It should be noted that di-epoxides were not observed in the present work. However, we cannot rule out that they were formed in the ozonolysis of BaP but hydrolyzed in the derivatization process, giving rise to the observed diol-epoxides. Such chemistry would also occur in biotic environments. Therefore, even though the heterogeneous formation of di-epoxides followed by hydrolysis in the analytical work-up cannot be ruled out in this work, the environmental significance of the di-epoxide is that it will likely form the diol-epoxide in the human body.

Overall, this work indicates that further systematical investigations into epoxide formation from BaP and other PAHs and via other oxidants, such as the OH radical, is warranted.

Acknowledgements

This work was supported by the Alfred P. Sloan Foundation and by NSERC.

References


**Figure 1.** Structures of benzo[a]pyrene mono-epoxide (a), benzo[a]pyrene diol-epoxide and their N-acetylcysteine derivatization products (b).
Figure 2. Experimental set-up.
**Figure 3.** Chromatograms arising from the NAC derivatization of BPDE/rev-BPDE with C18 column (a) and CSH fluoro phenyl column (b)
Figure 4. HPLC analysis of NAC derivatization of BPDE (black trace) and rev-BPDE (red trace). The upper trace monitors the MS-MS neutral loss of 147 amu, whereas the lower trace is obtained from MRM mass transition (m/z 464 → m/z 317) for BaP diol-epoxide.
Figure 5. Chromatograms for the reaction of BaP with high O₃ (>2.5×10^{13} molecules/cm³) for 2 hours (a), low O₃ (1.2×10^{12} molecules/cm³) for 2 days (b), low O₃ (1.2×10^{12} molecules/cm³) for 7 days (c), and BaP oxidation in indoor air for 2 weeks (d). For each set of experiments, the neutral loss method is equivalent to that used in Figure 4, whereas MRM monitoring was used in the mono-epoxide and diol-epoxide runs (as described in the text). In all cases, the oxidation mixture was spiked with NAC-rev-BPDE.
TOC Art:

GAS

\[ \text{O}_3 \rightarrow \text{O}_3 \rightarrow \text{O}_3 \rightarrow \text{O}_3 \rightarrow \text{O}_3 \]

benzo[a]pyrene \rightarrow \text{benzo[a]pyrene diol epoxides}

SURFACE
Supplementary Information

Epoxide Formation from Heterogeneous Oxidation of Benzo[a]pyrene with Gas-phase Ozone and Indoor Air

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Pg S2 A detailed description of the DART-MS analysis of BaP.
Pg S3 Selected products from aromatic hydrocarbon oxidation.
Pg S4 Mass spectrometer parameters.
Pg S5 LC chromatographic separation parameters.
Direct Analysis in Real Time-Mass Spectrometry (DART-MS) Analysis of BaP. In order to confirm the reaction of BaP with ozone, the amount of BaP before and after high ozone oxidation was quantified using DART-MS. Upon completion of the oxidation experiment, the BaP on the glass tube was extracted with 20 mL of THF. 100 µL of the extracted solution was diluted into 50 mL DCM for DART-MS analysis. The remaining solution was then derivatized with NAC for the evaluation of epoxide generation. The details of the DART-MS technique employed in the present investigation is described in our earlier publication. Briefly, home-made Teflon capillary holders were used to mount 10 glass melting point capillaries with their bottom ends sealed. 1 µL of the BaP solution was deposited onto the sealed end of the capillary tube. After the solvent evaporated, the capillary holder was then placed on a motorized linear rail, located between the DART ion source (IonSense Inc., Saugus, MA) and a Vapur Interface (IonSense Inc.), that brought the sample to the MS. The moving speed of the rail was 0.3 mm/s. Helium (3.0 L/min at 500°C) was used in the DART source, and mass spectra were acquired using a JMS-T100LC time-of-flight mass spectrometer (JEOL USA Inc., Peabody, MA) with mass resolution of approximately 6000 at a mass-to-charge ratio (m/z) 600.
Figure SI-1. Selected products from aromatic hydrocarbon oxidation.

Benzene-1,4-diol       5-Hydroxy-1,4-naphthalenedione       Anthraquinone
**Mass spectrometer parameters**

**A) MS parameters**

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**B) MS/MS experiment**

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**C) Neutral loss scan experiment**

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<td>147</td>
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LC chromatographic separation parameters

i) Kinetex 2.6 µm C18 100 Å, 2.1 × 50 mm, Phenomenex
   Column temperature (°C): 40
   Mobile phase A: 0.1% ammonium hydroxide in Milli-Q H2O
   Mobile phase B: Methanol
   Injection volume (µL): 2

   LC gradient, total run time 8 min

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ii) CSH Fluoro Phenyl, 1.7 µm, 130 Å, 2.1 × 50 mm, Waters
   Column temperature (°C): 40
   Mobile phase A: 0.1% Formic acid in Milli-Q H2O
   Mobile phase B: Acetonitrile
   Injection volume (µL): 2

   LC gradient, total run time 9 min

<table>
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<tr>
<th>Time (min)</th>
<th>Flow rate (mL/min)</th>
<th>%A</th>
<th>%B</th>
<th>Curve</th>
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References