

Partitioning, Aqueous Solubility, and Dipole Moment Data for *cis*- and *trans*-(4-Methylcyclohexyl)methanol, Principal Contaminants of the West Virginia Chemical Spill

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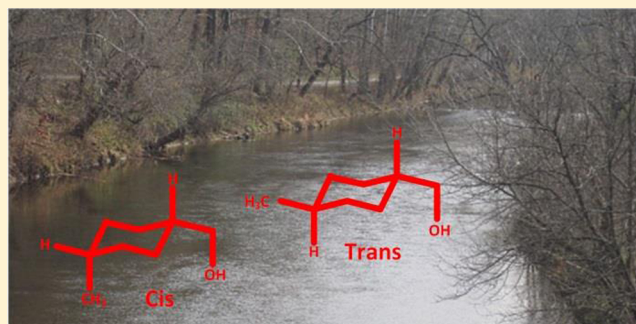
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S Supporting Information

ABSTRACT: In 2014, the U.S. National Response Center recorded more than 30000 incidents of oil spills, chemical releases, or maritime security issues, including crude (4-methylcyclohexyl)methanol (MCHM) that contaminated river and drinking water in West Virginia. This research yielded physicochemical partitioning data for the two major compounds released in West Virginia, *cis*- and *trans*-(4-methylcyclohexyl)methanol. Octanol–water partition coefficients (K_{OW}) were 225 for *cis*-4-MCHM and 291 for *trans*-4-MCHM. The aqueous solubility for total 4-MCHM was 2250 mg/L at 23 °C; solubilities of individual isomers were dependent on their mole fractions. The *cis* isomer was more soluble and less well sorbed to activated carbon than the *trans* isomer, consistent with its lower K_{OW} . The partition behavior is supported by a larger computed solvated dipole moment for the *cis* form than for the *trans* form at the MP2 aug-cc-pwCVDZ SMD level of theory. Different partition properties would result in the differential fate and transport of *cis*- and *trans*-4-MCHM in aqueous environments.



INTRODUCTION

In 2011, almost 10000 tons of 287 different chemicals spilled into U.S. waters from 1374 different facilities.¹ In 2014 alone, the U.S. National Response Center recorded more than 30000 incidents of oil spills, chemical releases, or maritime security issues, up slightly from the more than 29000 incidents recorded for 2013.² For spills involving technical grade chemicals or mixtures like petroleum, the chemical complexity can make impact assessment difficult. To assess contaminant fate and transport, accurate environmental partitioning coefficients are essential. The lack of partitioning data hinders the protection of human and environmental health, such as when 10000 gallons of the industrial chemical crude (4-methylcyclohexyl)methanol (MCHM) leaked from storage tanks and spilled into West Virginia's Elk River in 2014. Crude MCHM subsequently contaminated the Elk, Kanawha, and Ohio Rivers, plus the drinking water for more than 300000 people in Charleston, WV, and nine surrounding counties.^{3–7} “Do not use” the drinking water notices were issued by the water utility and West Virginia government. Residents readily detected MCHM's persistent licorice odor.⁷ A lack of MCHM partitioning data

impeded predicting short- and long-term fate and transport in the environment, and throughout drinking water treatment plants and distribution systems. For MCHM, partitioning and solubility data were not present on the material safety data sheet (MSDS)⁸ or required for this chemical under the Toxic Substances Control Act.^{3,9} The lack of data on MSDS is not uncommon. For example, similar data gaps were noted for other industrial chemicals:⁹ 1-chloro-3-methylbenzene (3-chlorotoluene),¹⁰ trichloroacetaldehyde (chloral),¹¹ and the complex mixture coal tar creosote,¹² reported to contain 52 chemicals.¹²

Soon after the spill, monitoring data revealed two major components: *cis*- and *trans*-4-MCHM in an approximately 1:2 ratio in crude MCHM.^{5,7} The more abundant *trans*-4-MCHM was primarily responsible for the licorice odor. Its air odor threshold concentration was 0.060 ppb-v, which is approx-

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imately 2000 times lower than that of the *cis* isomer and illustrates the complexity of evaluating chemical mixtures.⁷ Approximate partition values for (4-methylcyclohexyl)-methanol can be estimated with the U.S. Environmental Protection Agency's (EPA) EPI Suite,¹³ but this software cannot distinguish geometric isomers. Crude mixtures of substituted cyclohexanes contain many geometric isomers arising from axial/equatorial substitution patterns. The pesticide hexachlorocyclohexane (i.e., lindane) is a mixture of eight isomers; the isomer K_{OW} values vary by 2-fold and bioconcentration factors by 25-fold.¹⁴ Likewise, *cis*- and *trans*-dichloroethene have nearly a 2-fold difference in aqueous solubility and K_{OW} values¹⁵ and different biological degradation rates.¹⁶

The research objectives were (1) to confirm the *cis:trans* ratios in pure and crude 4-MCHM, (2) to measure octanol–water partition coefficients (K_{OW}), aqueous solubilities, and carbon sorption for *cis*- and *trans*-4-MCHM, (3) to calculate dipole moments and molar volumes of these isomers, and (4) to assess the consistency of experimental and computational data and then compare them to calculated values from EPI Suite.¹³

MATERIALS AND METHODS

Reagents. Pure (4-methylcyclohexyl)methanol (CAS Registry No. 34885-03-5, 98% pure) from TCI America comprised *cis*- and *trans*-(4-methylcyclohexyl)methanol with a 2.08:1 *cis:trans* ratio [see the nuclear magnetic resonance (NMR) results]. Crude MCHM was courtesy of Eastman Chemical (Kingsport, TN) and contained 86.5% *cis*- and *trans*-4-MCHM⁷ with a 1:1.75 *cis:trans* ratio (see NMR results). Other reagents and crude MCHM components are described in Text S1 of the Supporting Information.

NMR Spectroscopy. The *cis:trans* ratios in pure and crude MCHM were determined by NMR at 25 °C using a Bruker Avance-III 600 MHz spectrometer with a TBI probe with Z gradient. Samples of 30 μ L of pure 4-MCHM, crude MCHM, or individual high-performance liquid chromatography (HPLC) fractions representing *cis*- and *trans*-4-MCHM isomers (see below) were mixed with 690 μ L of $CDCl_3$ containing 0.05% tetramethylsilane (details are provided in Text S1 of the Supporting Information).

Dipole Moment and Molar Volume Computations. Stochastic conformational searches of *cis*- and *trans*-4-MCHM were performed using the MOE software package.¹⁷ From these guess structures, geometry optimizations and vibrational analyses were conducted using post-Hartree–Fock *ab initio* methods. All dipole moments were computed using Gaussian09¹⁸ at the MP2 (full core) aug-cc-pwCVDZ level of theory in the gas phase and with the SMD implicit solvation model with water parameters.¹⁹ Relative contributions to dipole moments of the *cis*- and *trans*-4-MCHM were determined using Boltzmann averaging (at 298.15 K) of all conformers based on free energy differences. Molar volumes were computed using the geometria polihedro (GePol) algorithm in Gaussian03 (see Text S1 of the Supporting Information).^{20,21}

K_{OW} Partitioning and HPLC Method. As described in Text S1 of the Supporting Information, reversed phase HPLC was used to separate the isomers and determine K_{OW} values. To prepare individual isomers for NMR, *cis* and *trans* isomers in 27000 mg/L pure 4-MCHM in methanol were separated with 60% methanol and 40% water. Prior to NMR, methanol was

removed from the two collected fractions under a nitrogen stream, and water was lyophilized. K_{OW} was determined using the OECD HPLC method,²² reference K_{OW} values,²³ and five replicates for each isomer, as described in Text S1 of the Supporting Information.

Aqueous Solubility. The slow stir method²⁴ determined water solubilities at 23 and 4 °C for quadruplicate samples of five different mole fraction ratios of *cis*- to *trans*-4-MCHM: (1) pure 4-MCHM at 0.67:0.33, (2) crude MCHM at 0.35:0.61, and three mixtures of pure and crude [(3) mix 1 at 0.43:0.54, (4) mix 2 at 0.57:0.41, and (5) mix 3 at 0.50:0.47]. Replicates were contained in silanized²⁵ 40 mL vials with 40 mL of reagent water and 1 g of 4-MCHM mixture. Experimental data at two temperatures allowed calculation of the excess enthalpy of solvation. Mole fraction calculations, solubility, GC-FID, and thermodynamic solvation property calculation methods are described in Text S1 of the Supporting Information.

Carbon Sorption. Adsorption experiments at 23 °C used crude MCHM and reagent water to prepare a solution containing 117 mg/L *cis*-4-MCHM and 233 mg/L *trans*-4-MCHM in contact with a commercially available virgin granular activated carbon typically used to treat drinking water. A 100 mL volume of the crude MCHM solution was added to amber glass jars containing 0.01–1 g of carbon. The jars were gently shaken on a shaker table for 2 days, after which aqueous *cis*- and *trans*-4-MCHM were determined by GC-FID (see Text S1 of the Supporting Information). Data were fit to a Freundlich isotherm.²⁶

Statistical Analyses. R version 3.1.2²⁷ determined trend lines and significance at $\alpha = 0.05$. Unless stated otherwise, reported values are means $\pm$ the standard error.

Estimated Parameters from the U.S. EPA EPI Suite. For 4-MCHM, the log K_{OW} and aqueous solubility were estimated with KOWWIN (version 1.68) and WSKOW (version 1.42), respectively, within EPI Suite.¹³ Inputs were based on CAS Registry No. 034885-03-5; cyclohexanemethanol, 4-methyl- and Simplified Molecular Information and Line Entry System (SMILES) notation (OCC(CCC(C1)C)C1).

RESULTS AND DISCUSSION

NMR Spectroscopy. As demonstrated in Table S1 and Figure S1 of the Supporting Information, ¹H NMR of pure 4-MCHM and crude MCHM shows two upfield doublets at δ 0.92 and 0.89 ($J \sim 7$ and 6.6 Hz) and two downfield doublets at δ 3.55 and 3.45 ($J \sim 6.6$ and 5.3 Hz), assigned to CH_3 protons and CH_2 protons of CH_2 -OH, respectively, indicating the presence of two isomers. Signals in the 1.2–2.16 ppm region could be attributed to cyclohexane ring protons. For cyclohexanes substituted with methyl groups like 4-MCHM, downfield signals are assigned to the *cis* isomer and upfield signals to the *trans* isomer.²⁸ The doublets had a 2.08:1 *cis:trans* ratio for pure 4-MCHM and a 1:1.75 *cis:trans* ratio for crude MCHM, which are similar to published values.⁵

The proton-decoupled ¹³C NMR for pure and crude MCHM showed 12 singlets spread over the range of 18–70 ppm (six singlets at δ 66.31, 38.09, 30.62, 29.87, 25.16, and 19.99 for the *cis* isomer and six singlets at 68.70, 40.15, 34.62, 32.8, 29.47, and 22.61 for the *trans* isomer), confirming the presence of *cis* and *trans* isomers. The ¹³C chemical shift values closely agree with the reported values.²⁸

¹H NMR chemical shift values confirmed that the first eluting HPLC peak was *cis*-4-MCHM and the second *trans*-4-MCHM (Table S1 of the Supporting Information). Purified *cis* and *trans*

HPLC fractions were used to verify that the first eluting GC peak was *trans*-4-MCHM and the second *cis*-4-MCHM. Their respective elution times (and temperatures) were 6.20 min (224.0 °C) for the *trans* isomer and 6.67 min (233.4 °C) for the *cis* isomer.

Partitioning and Solubility. Figure 1 presents the plot of $\log K_{OW}$ and $\log k$ [chromatographic capacity factor (see Text

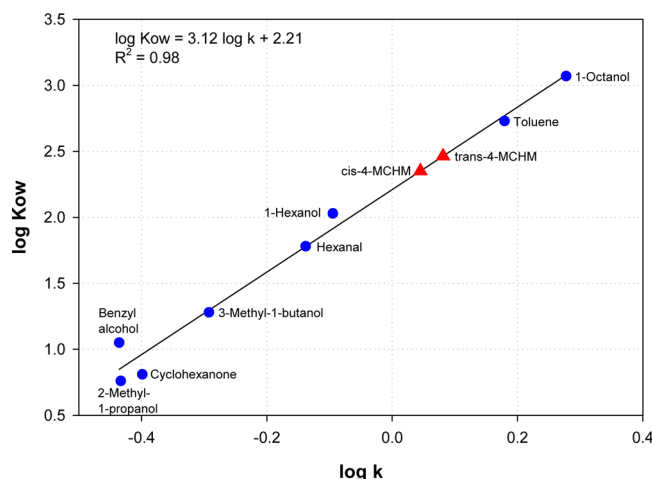


Figure 1. K_{OW} values of *cis*- and *trans*-4-MCHM (red triangles) were determined relative to eight compounds (blue circles) with known K_{OW} coefficients and determined capacity factors (k).

S1 of the Supporting Information)] to determine K_{OW} values for *cis*- and *trans*-4-MCHM relative to eight reference compounds.²³ As shown in Table 1, for *cis*-4-MCHM, $K_{OW} = 225 \pm 1$ ($\log K_{OW} = 2.35 \pm 0.005$), while for later eluting *trans*-4-MCHM, $K_{OW} = 291 \pm 1$ ($\log K_{OW} = 2.46 \pm 0.0002$) and was 30% higher than for the *cis* isomer. This difference was statistically significant ($p < 0.001$).

The overall solubility of 4-MCHM at 23 °C is 2250 ± 50 mg/L and at 4 °C is 2430 ± 64 mg/L (Table 1). The slightly higher water solubility at 4 °C is statistically significant ($p = 0.026$). At environmental temperatures, the aqueous solubility of organic liquids varies slightly (factor of <2) and can increase

or decrease with temperature or even increase and then decrease within certain temperature ranges.²⁹ The calculated excess enthalpy and entropy of solvation (Table 1) reveal that the solvation thermodynamics for MCHM are consistent with molecules of similar size and polarity.²⁹ Interpretation of five mole fraction ratios tested demonstrates that *cis*-4-MCHM is more water-soluble than *trans*-4-MCHM (Figure 2 and Figure

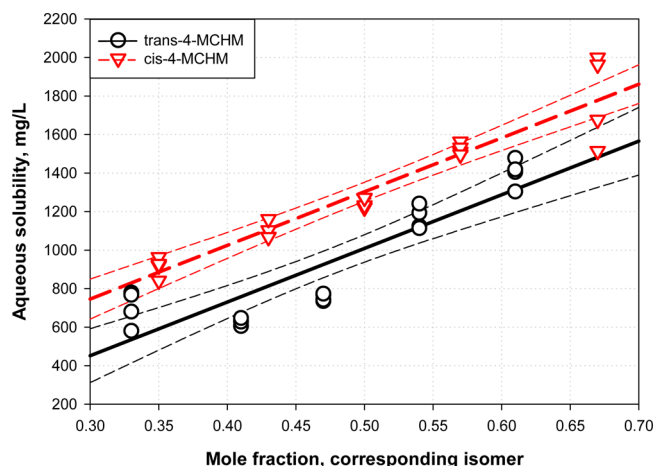


Figure 2. Aqueous solubilities of *cis*- and *trans*-4-MCHM at 23 °C are proportional to their individual mole fractions. Thick lines represent regressions. Light dashed lines correspond to 95% confidence intervals.

S2 of the Supporting Information). At 23 °C and a mole fraction of 0.5 (Table 1), the solubility of the *cis* isomer is 34% higher than that of the *trans* isomer. Like other solvent mixtures, *cis*- and *trans*-4-MCHM solubilities are proportional to their individual mole fractions in the organic phase.^{29–32} Although caution is advised for extrapolated data (Figure 2 and Figure S2 of the Supporting Information), extrapolating to a mole fraction of 1 for individual isomers yields solubilities of 2700 ± 108 and 2400 ± 180 mg/L for *cis*- and *trans*-4-MCHM at 23 °C, respectively.

Table 1. Physicochemical Parameters for (4-Methylcyclohexyl)methanol (means $\pm$ standard error for experimental measurements)

parameter	MSD sheet	EPI Suite 4-MCHM ^a	<i>cis</i> -4-MCHM	<i>trans</i> -4-MCHM	total 4-MCHM
K_{OW}	no data	355	$225 \pm 1^b \dagger$	$291 \pm 1^b \ddagger$	—
$\log K_{OW}$	—	2.55	$2.35 \pm 0.005^b \dagger$	$2.46 \pm 0.0002^b \ddagger$	—
aqueous solubility					
mg/L, at 23 °C	no data	2024	$1300 \pm 24^{b,c} \dagger$	$1010 \pm 34^{b,c} \ddagger$	2250 ± 50
mg/L, at 4 °C	no data	—	$1390 \pm 36^{b,c} \dagger$	$1120 \pm 32^{b,c} \ddagger$	2430 ± 64
ΔH_w^{ex} , kJ/mol ^d	—	—	—	—	-2.8 ± 1.7
ΔS_w^{ex} , J mol ⁻¹ K ^{-1e}	—	—	—	—	76.3 ± 5.7
carbon loading ^f , mg/g	no data	—	$12.8 \pm 1.1^b \dagger$	$26.5 \pm 1.2^b \ddagger$	—
dipole moment					
D, gas phase ^g	no data	—	1.530	1.586	—
D, implicit solvation ^h	no data	—	2.454	2.425	—
molar volume, cm ³ /mol	no data	—	138.9	138.9	—

^aEPI Suite does not distinguish isomers.¹³ ^bThe symbols $\dagger$ and $\ddagger$ indicate significant statistical difference between *cis*- and *trans*- isomers at $\alpha = 0.05$. ^cValues for individual *cis* and *trans* isomers presented at mole fraction = 0.5. ^d ΔH_w^{ex} is the excess enthalpy of the aqueous solvation calculated from the aqueous solubility.²⁹ ^e ΔS_w^{ex} is the excess entropy of the aqueous solvation calculated from the aqueous solubility.²⁹ ^fLoading on the activated carbon for an isomer equilibrium aqueous concentration of 1 mg/L. ^gMP2 aug-cc-pwCVDZ level of theory. ^hMP2 aug-cc-pwCVDZ level of theory with SMD.^{17,18}

trans-4-MCHM was better sorbed to activated carbon than *cis*-4-MCHM as shown in Table 1 and Figure S3 of the Supporting Information. Statistical analysis revealed that regression equation slopes for the isomers were not different, but the intercepts were different; the loading capacity at an aqueous concentration of 1 mg/L was 100% higher for the *trans* isomer (26.5 ± 1.2 mg/g) than for the *cis* isomer (12.8 ± 1.1 mg/g).

Computed Dipole Moments and Molar Volumes. The Boltzmann-averaged molar volumes of *cis*- and *trans*-4-MCHM were both $139.8 \text{ cm}^3/\text{mol}$, with no significant methodological dependence, which does not account for the differential solubility behavior of the *cis* and *trans* isomers.²⁹ As dipole moments are good predictors of molecular interactions with aqueous environments,^{29,33} differences in computed dipole moments were considered. A treatment of electron correlation and conformational averaging is crucial for obtaining qualitatively correct dipole moments and relative energies for *cis* and *trans* isomers. Figures S4 and S5 of the Supporting Information display nine *trans*-4-MCHM and seven *cis*-4-MCHM conformers, and Table S2 of the Supporting Information lists their computed relative free energies and dipole moments. Boltzmann-averaged MP2 aug-cc-pwCVDZ computations incorporating an implicit aqueous solvation model show *trans* and *cis* dipole moment values of 2.425 and 2.454 D, respectively. This 0.029 D difference is sufficient to rationalize the observed trends in solubility and K_{OW} . An accurate level of theory incorporating implicit solvation and conformational averaging produced dipole moments consistent with the observed solubility trend. To further illustrate the complexity in working with conformationally complex molecules, the computed Boltzmann-averaged gas phase *trans/cis* dipole moments, which are not predictors of aqueous phase behaviors, were reversed, with values equal to 1.586 and 1.530 D for the *trans* and *cis* forms, respectively.

Consistency and Comparison to EPI Suite. Table 1 shows that EPI Suite provided estimates within a factor of 2 for measured K_{OW} values and solubility. A concern is that EPI Suite overestimates K_{OW} and underestimates solubility; therefore, multiplicative errors could result when both estimated parameters are utilized. The higher water solubility for *cis*-4-MCHM is consistent with its lower K_{OW} . The measured partition coefficients are consistent with (a) a larger dipole moment for *cis*-4-MCHM, (b) a higher boiling point as evidenced by the longer GC t_{R} for *cis*-4-MCHM, and (c) a decreased level of sorption of the *cis* isomer on activated carbon. Experimental and theoretical evidence strongly indicates that fate and transport of *cis*- and *trans*-4-MCHM isomers will differ in aquatic environments and may further change over time when variance in their mole fractions occur.

Environmental Implications. Industrial chemical spills commonly involve chemical mixtures. The complexity of a chemical spill can increase when geometric isomers are involved, such as spills containing cyclohexane derivatives. While the tendency may be to treat geometric isomers as one compound, reports in the environmental fate and transport literature indicate that geometric isomers can possess different physicochemical properties that affect the fate, transport, and toxicity. EPI Suite is currently unable to perform geometric isomer-specific calculations. In fact, to capture subtle isomeric differences when computing fundamental physicochemical properties, thermal ensembles of low-lying conformers of each cyclohexane isomer must be considered. This research

illustrates the value of integrating experimental and computational chemistry for determining and explaining physicochemical properties of *cis* and *trans* isomers. For 4-MCHM, the differential octanol–water partitioning (K_{OW} for *trans* 30% greater than for *cis*), aqueous solubility (*cis* value 34% greater than *trans* value), sorption onto activated carbon (*trans* value 100% greater than *cis* value), and odor thresholds (*trans* value 2000-fold more odorous than *cis* value),⁷ corroborate that their environmental behavior is isomer-specific. Understanding the implications of the 2014 crude MCHM spill and contamination events involving complex mixtures and geometric isomers will require an understanding of the properties of individual components for the assessment of environmental fate and transport.

■ ASSOCIATED CONTENT

§ Supporting Information

Additional text, tables, and figures related to the materials and methods, results and discussion, and computations (Text S1, Tables S1 and S2, and Figures S1–S5). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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