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An Example of Lipophiloselectivity: The Preferred Oxidation, in Water, of Hydrophobic 2-Alkanols Catalyzed by a Cross-Linked Polyethyleneimine−Polyoxometalate Catalyst Assembly

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Abstract: A cross-linked polyethyleneimine polymer containing the $[ZnWZn_2(H_2O)_2(ZnW_9O_{34})_2]^{12-}$ polyoxometalate was prepared from branched polyethyleneimine (M_w = 600), the polyoxometalate, and a *n*-octylamine-epichlorohydrin cross-linking reagent. This catalytic assembly was active for the selective oxidation of 2-alkanols to 2-alkanones with aqueous H_2O_2 with reactions presumably occurring at a hydrophobic domain. Most importantly, the catalyst showed distinctive lipophiloselectivity, that is selectivity as a function of the lipophilic nature of a reaction substrate. The lipophiloselectivity was proportional to the relative partition coefficient (1-octanol/water) of the substrates.

Introduction

A key topic of interest in organic chemistry is the development of catalytic methods based on metal−organic compounds for engendering selectivity and specificity in reactions. Thus, stereo- and enantioselectivity are typically attained by ligand design of the environment around a reactive metal center; chemoselectivity is commonly obtained through the use of functional-group-specific catalysts, and regioselectivity is often realized by controlling the access of a substrate to an active reaction site. Much recent research in catalysis is also related to manipulation and optimization of reaction media, generally to achieve synthetic procedures with a low environmental load.[1] Thus, in addition to the use of classical organic solvents, efforts are being made to apply aqueous,[2] fluorous,[3] ionic liquid,[4] and supercritical fluid[5] reaction solvents.

From the point of view of substrate selectivity as a function of the lipophilic nature of a reaction substrate, herein termed lipophiloselectivity, the selective partition of a series of substrates between a reactive or catalytic phase and a nonreactive phase could easily be imagined to yield lipophiloselective reactions. Thus, conceptually and perhaps trivially, the use of organic, aqueous, fluorous, ionic liquid, and supercritical fluid *biphasic* reaction media can lead to a lipophiloselective reaction via the expected substrate solubility in the reactive phase. The question, however, that arises is *can one obtain a lipophiloselective reaction where the solubility properties of a series of substrates are either very similar or the lipophiloselectivity is opposite to the expected solubility in the reactive phase*? In this paper, we present perhaps the first such example of lipophiloselectivity. Therefore, using a polyethyleneimine-based hydrogel containing a polyoxometalate catalyst, we show that the oxidation of a series of secondary alcohols ranging from 2-pentanol to 2-hexadecanol to the corresponding ketones with hydrogen peroxide occurs with clear preference for the more lipophilic substrate even though the higher molecular weight homologues are insoluble in the aqueous phase that contains the catalyst.

Results and Discussion

Polyoxometalates are efficient catalysts for the oxidation of secondary alcohols to ketones using aqueous hydrogen peroxide as oxygen donor.[6] It has been shown that this reaction can also be carried out in aqueous reaction media[7] and that for water insoluble, hydrophobic substrates reactivity in aqueous biphasic media can be reached using alkylated polyethyleneimine/polyoxometalate synzymes. The hydrophobic domains in the water-soluble alkylated polyethyleneimine allowed solubilization of hydrophobic substrates and catalytic oxidation.[8] Hydrogels based on polyethyleneimine cross-linked with epichlorohydrin-ammonia mixtures are also known,[9] so in an extension of the

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(1) Adams, D. J.; Dyson, P. J.; Taverner, S. J. *Chemistry in Alternative Reaction Media*; Wiley: Weinheim, Germany, 2003.
(2) (a) Cornils B. *J. Mol. Catal. A. Chem.* **1999**, 143, 1−10. (b) Cornils B. *Org. Proc. Res. Dev.* **1998**, *2*, 121−127.
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(5) For general discussion of oxidation in $scCO_2$, see Theyssen, N.; Hou, Z.; Leitner, W. *Chem.*−*Eur. J.* **2006**, *12*, 3401−3409, and references therein.
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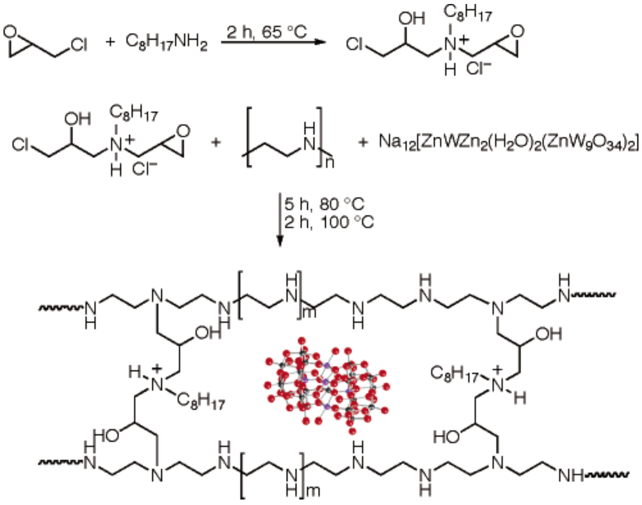
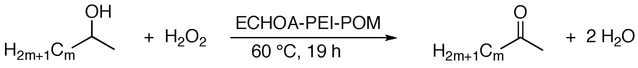
Scheme 1. Synthesis of Cross-Linked Polyethyleneimine Containing $[ZnWZn_2(H_2O)_2(ZnW_9O_{34})_2]^{12-}$[a]



[a] For clarity: simplified 2D representation and polyethyleneimine is shown as a linear polymer although it is branched.

Scheme 2. Oxidation of $C_mH_{2m+1}CH(OH)CH_3$.



alkylated polyethyleneimine/polyoxometalate synzyme concept, a more rigid polyethyleneimine-based hydrogel containing the $[ZnWZn_2(H_2O)_2(ZnW_9O_{34})_2]^{12-}$ polyoxometalate[10] was synthesized in two steps, Scheme 1.

First, 2 equiv of epichlorohydrin were reacted with 1 equiv of octylamine at 65 °C for 2 h to yield, as evidenced by ^1H NMR, a quaternary ammonium salt, epichlorohydri*n*-octylamine (ECHOA). The mixture was then reacted further in situ with an aqueous solution of branched polyethyleneimine, PEI, ($M_n \approx 600$; $M_w \approx 800$) in the presence of $Na_{12}[ZnWZn_2(H_2O)_2(ZnW_9O_{34})_2]$ (POM). The three-dimensional cross-linked polymer (ECHOA−PEI−POM) obtained (for clarity, Scheme 1 is a simplified two-dimensional representation with PEI shown as a linear polymer) was purified by dialysis to remove HCl/NaCl and was then lyophilized to a dry powder. Upon addition of the polymer to water at 90 °C, it swells and is dispersed to transparency; thus, it is apt to call the polymer a hydrogel. By elemental analysis, the hydrogel contains ~0.35 mmol POM per 100 g. (~1.75 wt %).

To gauge the catalytic activity of the ECHOA−PEI−POM catalyst, secondary alcohols, $C_mH_{2m+1}CH(OH)CH_3$ ($m = 3-14$), were selectively (>99%) oxidized to the corresponding ketones in water using aqueous hydrogen peroxide as the oxidant, Scheme 2. The reactions were biphasic, consisting roughly of a catalyst aqueous phase with H_2O_2 and an alcohol/ketone organic phase and carried out using a H_2O_2:alcohol:POM ratio of 14160:5660:1 with a POM concentration of 0.156 mM in water. The results showed that the degree of reaction defined as TON (turnover number = mol substrate reacted per mol catalyst) was proportional to the lipophilicity of the substrate. For example, the kinetic profile of a competitive reaction between 2-tetradecanol and 2-hexanol showed that the former was far more reactive, Figure 1. Thus, 2-tetradecanol is immediately (first 2 h) more reactive than 2-hexanol even though the later is intrinsically more soluble in the aqueous catalyst phase.[11] We have no clear understanding of the initial "jump" in the 2-tetradecanol reactivity, however, it is important to note that the rate of oxidation 2-tetradecanol is consistently higher than that of 2-hexanol throughout the course of the reaction.

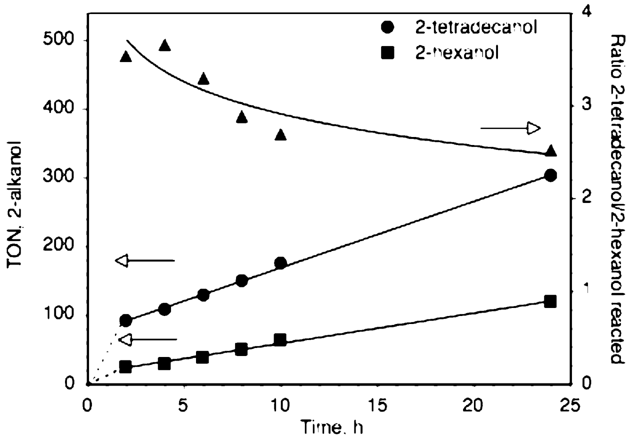


Figure 1. Reaction profile of the competitive oxidation of 2-hexanol and 2-tetradecanol using the hydrogel catalyst. Reactions conditions: 0.156 mM POM (15 mg ECHOA−PEI−POM) in 0.35 mL water with a H_2O_2/2-hexanol/2-tetradecanol/POM ratio 14160:2830:2830:1, 60 °C, 24 h. Results, analyzed by GC after extraction (3 × 1 mL) of the substrates/products into ethyl acetate, are an average of three measurements.

To confirm the uniqueness of the cross-linked polyethyleneimine−polyoxometalate catalyst assembly, a series of control experiments were performed. (i) A homogeneous reaction in acetonitrile using the tetrabutylammonium salt of the polyoxometalate (0.3 mmol 2-hexanol, 0.3 mmol 2-tetradecanol, 1.9 μmol $[(C_4H_9)_4N]_{12}[ZnWZn_2(H_2O)_2(ZnW_9O_{34})_2]$, 0.75 mmol 60% H_2O_2, 0.6 mL MeCN, 19 h, 60 °C) showed that 2-hexanol (45 turnovers) and 2-tetradecanol (42 turnovers) have essentially the same reactivity in a selective reaction to the corresponding ketone. This experiment also showed that the substrates in the hydrogel reaction system are more reactive than in the "regular" homogeneous system, possibly due to a higher local concentration of the substrates around the catalyst in the hydrogel system. (ii) An aqueous biphasic reaction using the previously described water-soluble alkylated polyethyleneimine/ polyoxometalate[8] (6.1 mg alkylated PEI, 1 μmol $Na_{12}[ZnWZn_2(H_2O)_2(ZnW_9O_{34})_2]$, 0.3 mmol 2-hexanol, 0.3 mmol 2-tetradecanol, 1.2 mmol 60% H_2O_2, 19 h, 60 °C) showed a preference for the reaction of 2-hexanol (87 TON) versus 2-tetradecanol (57 TON). (iii) A hydrogel prepared without the addition of the polyoxometalate showed no catalytic activity and the addition of $Na_{12}[ZnWZn_2(H_2O)_2(ZnW_9O_{34})_2]$ catalyst *after* formation of the hydrogel showed almost an exclusive reaction of 2-hexanol over 2-tetradecanol. Thus, ECHOA−PEI (15 mg) 1 μmol $Na_{12}[ZnWZn_2(H_2O)_2(ZnW_9O_{34})_2]$ mixed with both 2-hexanol and 2-tetradecanol (0.3 mmol each) in water (0.3 mL) containing 60%

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(10) The $Na_{12}[ZnWZn_2(H_2O)_2(ZnW_9O_{34})_2]$ polyoxometalate was originally synthesized by Tourné, C. M.; Tourné, G. F.; Zonnevijlle, F. *J. Chem. Soc., Dalton Trans.* **1991**, 143−151 and has been extensively used by us in recent years to catalyze oxidation with hydrogen peroxide *cf.* Witte, P. T.; Alsters, P. L.; Jary, W.; Müllner, R.; Pöchlauer, P.; Sloboda-Rozner, D.; Neumann, R. *Org. Proc. Res. Devel.* **2004**, *8*, 524−531 and references therein.

(11) The solubilities of 2-hexanol and 2-tetradecanol in water are 1.4 and ~0.00003 mass %, respectively.

Table 1. Lipophiloselectivity as a Function of the Alkylamine Incorporated in ECHxA−PEI−POM[a]

	absolute reactivity, TON		
amine	2-hexanol	2-tetradecanol	lipophiloselectivity
n-$C_4H_9NH_2$	95	93	0.98
n-$C_6H_{11}NH_2$	130	285	2.19
n-$C_8H_{17}NH_2$	135	350	2.59
n-$C_{16}H_{33}NH_2$	410	495	1.20

[a] Reaction conditions: 0.156 mM POM (15 mg ECHxA−PEI−POM) in 0.35 mL water with a H_2O_2/2-hexanol/2-tetradecanol/POM ratio 14160:2830:2830:1, 60 °C, 19 h. Results were analyzed by GC after extraction (3 × 1 mL) of the substrates/products into ethyl acetate.

aqueous H_2O_2 (0.75 mmol) at 60 °C for 19 h showed almost exclusive reaction of 2-hexanol (125 TON) versus 2-tetradecanol (3 TON). This result is compatible with an aqueous biphasic reaction system, polyoxometalate in water and a 2-alkanol organic phase, where the hydrogel has no impact on the catalysis and the selectivity is strictly determined by the relative solubility of 2-hexanol versus 2-tetradecanol in water. This would also suggest that in the new hydrogel-encapsulated polyoxometalate system described herein, the polyoxometalate remains entrapped in the hydrogel since the reaction profile (Figure 1) shows that 2-tetradecanol is more reactive than 2-hexanol along the entire reaction.

The chain length of the alkylamine used to prepare epichlorohydrin-amine salt (Scheme 1) that is later incorporated into the three-dimensional cross-linked polymer (ECHxA-PEI−POM) may have an effect on the lipophiloselectivty that can be attained. To ascertain this, a series of cross-linked polymers, ECHxA−PEI−POM, where xA is *n*-butylamine, *n*-hexylamine, *n*-octylamine, and *n*-hexadecylamine, were prepared and evaluated in the competitive oxidation of 2-hexanol versus 2-tetradecanol. The results, Table 1, in a series of oxidation reactions show that the incorporation of *n*-octylamine yielded the highest lipophiloselectivity (ratio 2-tetradecanol/2-hexanol reacted); a catalyst with *n*-butylamine showed no lipophiloselectivity. Similarly, incorporation of *n*-hexadecylamine into the polymer catalyst showed little lipophiloselectivity although overall reactivity was somewhat higher.

To get a better measure of the lipophiloselectivity, competitive reactions with equivalent amounts of two alcohols were carried out using the conditions described above using 2-tetradecanol as the reference substrate. From the results presented in Figure 2 one may clearly observe the lipophiloselectivity of the oxidation in a series of 2-alkanols. The results show that the lipophiloselectivity of 2-tetradecanol versus 2-pentanol to 2-heptanol is greater than 2-fold. The lipophiloselectivity of 2-tetradecanol versus 2-octanol to 2-undecanol levels off at about 1.5. Intuitively, it is also quite amazing that there was even lipophiloselectivity (ratio = 1.1) between 2-tetradecanol and 2-dodecanol in favor of 2-tetradecanol and between 2-tetradecanol and 2-hexadecanol (ratio = 0.81) in favor of 2-hexadecanol.

Because the oxidation reactions were carried out in a nominally aqueous media, it would seem logical that the hydrogel contains a hydrophobic domain(s) that is the reactive center. In this way, to obtain lipophiloselectivity, the substrates would need to selectively partition into the hydrophobic domain of the hydrogel catalyst. An accepted measure of the lipophilic versus hydrophilic nature of a compound is its partition

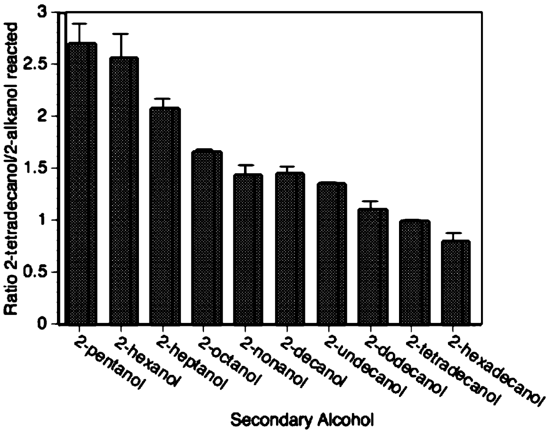

Figure 2. Lipophiloselective oxidation of 2-alkanols. Reactions conditions: 0.156 mM POM (15 mg ECHOA−PEI−POM) in 0.35 mL water with a H_2O_2/2-alkanol/2-tetradecanol/POM ratio 14160:2830:2830:1, 60 °C, 19 h. Results, analyzed by GC after extraction (3 × 1 mL) of the substrates/products into ethyl acetate, are an average of three measurements, and the error bars represent one standard deviation within each 2-alkanol and 2-tetradecanol pair.

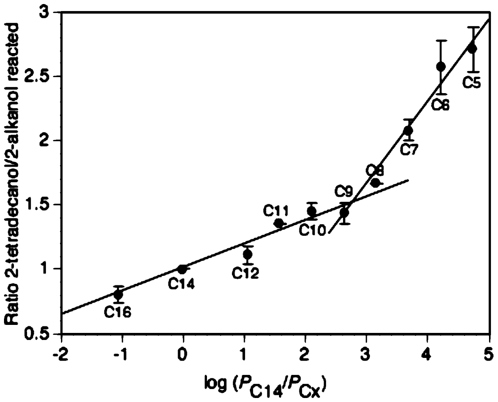

Figure 3. Lipophiloselectivity as a function of the relative partition coefficient.

coefficient as a solute, log *P*, between 1-octanol and water.[12] In this case, the relative partition coefficient, log P_{C14}/P_{Cx},[13] of the two competing substrates should be correlated with the lipophiloselectivity. Indeed, a structure−activity relationship plot of the lipophiloselectivities taken from Figure 2 as a function of log P_{C14}/P_{Cx} shows that there are nice correlations for competitive reactions, Figure 3.

In the range of 2-tetradecanol versus the more hydrophilic alcohols, the lipophiloselectivity is higher (slope = 0.78), whereas for the more lipophilic alcohols, the lipophiloselectivity is lower (slope = 0.27). It is not trivial to simply rationalize the break observed in the slope of the correlation plot. One explanation could be that the reference substrate used, 2-tetradecanol, being on the lipophilic end of the scale rather than in its center, leads to a distortion of the correlation. This may

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(13) Values for log *P* were taken from Yalkowsky, S. H.; Valvani, S. C. *J. Pharm. Sci.* **1980**, *69*, 912−922. A complete set of data is available for 1-alkanols whereas only a partial set of data is available for 2-alkanols. The 2-alkanols are consistently slightly more hydrophilic. However, because we are interested in the **relative** partition coefficient, log P_{C14}/P_{Cx}, these differences cancel out and the complete set of data for 1-alkanols can be used. The values for log *P* range from 1.25 (pentanol) to 7.2 (hexadecanol).

Table 2. Lipophiloselectivity as In a Competitive Oxidation as a Function of Varying Initial Mol and Mass Ratio of Substrates[a]

mol ratio 2-tetra-decanol/ 2-hexanol	mass ratio 2-tetra-decanol/ 2-hexanol	lipophiloselectivity
0.47	**1.0**	1.78
0.63	1.33	1.92
0.77	1.67	2.27
1.0	2.13	2.59

[a] Reaction conditions: 15 mg ECHOA−PEI−POM, 0.3 mmol (30 mg) 2-hexanol, 30−64.3 mg 2-tetradecanol, 0.75 mmol 60% H_2O_2, 0.35 mL H_2O, 60 °C, 19 h.

be related to the fact that the experimental ratio of 2-tetradecanol/2-alkanol reacted is based on initial equimolar amounts of substrates, whereas the relative partition coefficients are based on mass. Thus, equimolarity of the substrates is needed because we are comparing reactivity relative to mol % catalyst. On the other hand, use, for example, of equimolar amounts of 2-tetradecanol and 2-hexanol means using a substrate mass ratio of 214/102 that would unevenly affect the hydrophobicity of the system as a whole and may distort the linearity of the correlation between the molar based reactivity and the mass based partition function. Lipophiloselectivity in the competitive oxidation of 2-tetradecanol and 2-hexanol, as a function of the initial molar and mass ratio is presented in Table 2. Clearly, the use of an equal weight of substrates (entry 1) as opposed to use of initial equimolar amounts of substrate (entry 4) yielded a different and lower lipophiloselectivity although the reaction still significantly favored the more lipophilic 2-tetradecanol. Therefore, it seems reasonable to conclude that the nonlinearity or break in the correlation observed in Figure 3 is related to the fact that it is impossible to correlate reactivity and the partition function at equimolar and at an equal weight of substrates at the same time.

Conclusions

One may conclude that the magnitude of the slope of structure−activity relationship plots of the lipophiloselectivities such as the one presented in Figure 3 will determine the degree of the lipophiloselectivity. It will be interesting to see in the future which degrees of lipophiloselectivity can be attained in a variety of reaction systems using such hydrogels with incorporation of different catalysts. In general terms, it will also be of interest to further understand the reaction of hydrophobic substrates in aqueous media and what guiding principles may lead to selectivity. For example, the hydrogel catalyst described herein yielded a lipophiloselective reaction, yet a superficially similar non-crosslinked catalyst showed no lipophiloselectivity. Why is this so?

Experimental Section

Preparation of the Cross-Linked Polyethyleneimine−Polyoxometalate Catalyst Assembly. *N*-Octylamine (12.79 mmol, 2.1131 mL) was added dropwise (30 min) to epichlorohydrin (25.58 mmol, 2 mL), and the mixture was kept at 65 °C for 2 h. A typical ^{1}H NMR in $CDCl_3$ of this mixture showed that this reaction yielded ECHOA as shown in Scheme 1 with peaks at: 4.06 ppm, q, 1H, -$C\mathbf{H}OH$-; 3.86 ppm, m, 2H, $ClC\mathbf{H}_2$-; 3.45−3.57 ppm, m, 4H, -$^{+}NC\mathbf{H_2}CHOH$-, and -$^{+}NC\mathbf{H_2}CH(O)CH_2$-; 2.35−2.75 ppm, m, 5H, -$^{+}NC\mathbf{H_2}CH_2(CH_2)_5CH_3$-, and -$^{+}NCH_2C\mathbf{H}(O)C\mathbf{H}_2$-; 1.42 ppm, bs, 2H, -$^{+}NCH_2C\mathbf{H}_2(CH_2)_5CH_3$-; 1.24 ppm, bs, 10H, -$^{+}NCH_2CH_2(C\mathbf{H}_2)_5CH_3$-; 0.85 ppm, t, 3H, -$^{+}NCH_2CH_2(CH_2)_5C\mathbf{H}_3$-. Two singlets probably attributable to the OH and N^+H moieties were also observed at 3.67 and 3.73 ppm. Aqueous solutions of branched polyethyleneimene ($M_w = 600$) (1.6 mL, 4.88 M, 7.81 mmol amine moieties) and $Na_{12}[ZnWZn_2(H_2O)_2(ZnW_9O_{34})_2]$[14] (1.7 mL, 0.0678 M, 0.0115 mmol) were then added. The mixture was held at 80 °C for 5 h and then 100 °C for 2 h. After cooling, the mixture was dialyzed against water (4 × 2 L DDW) using dialysis membrane (MW cutoff-1000) and the compound was dried by lyophilization. Similar catalyst assemblies with *n*-butyl, *n*-hexyl and *n*-hexadecylamine were prepared in an identical manner.

Catalytic Reactions and Analysis. Typically, reactions were carried out by mixing a solution of ECHOA-PEI−POM (15 mg) in water (0.35 mL) with substrates (0.3 mmol) and 60% aqueous H_2O_2 (0.75 mmol, 0.0441 mL) in a closed magnetically stirred vial at 60 °C for 19 h. Specific conditions are given in each case in the footnotes of the figures and tables. At the end of the prescribed reaction time the substrates and products were extracted into ethyl acetate (3 × 1 mL, additional extraction yielded the same analyses) and analyzed by GC-FID using a 30 m, 5% phenylmethylsilicone column (RTX-5MS) with a 0.25 μm coating.

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Supporting Information Available: Full experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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