Regioselective Synthesis of a Branched Isomer of Nonylphenol, 4-(3′,6′-Dimethyl-3′-heptyl)phenol, and Determination of its Important Environmental Properties

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Abstract: A method for the synthesis of a pure nonylphenol isomer, 4-(3′,6′-dimethyl-3′-heptyl)phenol, by Friedel–Crafts reaction between anisole and 3-bromo-3,6-dimethylheptane that gives a 47.3 % overall yield is reported. The reactions were followed by GC-MS, and the chemical structures are in agreement with the NMR and IR spectra. The log K_{ow} value for this compound, its water solubility, vapor pressure, and Henry's Law constant were also determined. These physicochemical properties were required for prediction of the compound's behavior in aquatic ecosystems.

Keywords: environmental chemistry · Friedel–Crafts alkylation · nonylphenol isomer · synthesis design

Introduction

Nonylphenols (NPs) are an important class of isomeric compounds, available as a mixture of more than 20 isomeric compounds and used for the production of nonylphenol polyethoxylate surfactants.[1] The synthesis of single isomers of nonylphenol has not been reported. The commercial preparation of NPs is performed through Friedel–Crafts alkylation of phenol with technical nonene, a complex mixture consisting predominantly of nine-carbon olefins and referred to as propylene trimer.[1, 2] The alkylation reaction results in a very complex mixture of 90–93 % *para*-substituted nonylphenols (both straight- and branched-chain isomers) and minor quantities of *ortho* isomers. High resolution chromatography on a 100 m capillary column GC with 400 000 theoretical plates has shown that the branched isomers—such as 4-(3′,6′-dimethyl-3′-heptyl)phenol (**7**), 4-(3′,6′-dimethyl-4′-heptyl)phenol, 4-(4′,6′-dimethyl-4′-heptyl)phenol, 4-(2′-methyl-4′-octyl)phenol, 4-(2′-methyl-2′-octyl)phenol, and 4-(4′,6′-dimethyl-2′-heptyl)phenol—exist in the product mixture in higher concentrations than all the other components.[3] These isomers have also been detected by GC-MS and some of them separated by HPLC in environmental studies.[1, 4, 5] In the laboratory, microsynthesis attempts to obtain a single isomer of ring-labeled ^{14}C-NP by using ring-labeled ^{14}C-phenol and non-1-ene gave three major isomers: 4-(2′-nonyl)phenol, 4-(3′-nonyl)phenol, and 4-(4′-nonyl)phenol.[2, 4] The isomerization occurs due to the relative instability of the formal primary carbocation formed from nonene in the presence of the acid catalyst, which then alkylates the phenol preferentially at the *para* position.[9] The only other reported laboratory synthesis attempt involved preparation of a radiolabeled technical ^{14}C-NP mixture by means of an alkylation reaction between ^{14}C-phenol and technical nonene.[4]

The synthesis of pure isomers of NP is of interest because of the known estrogenicity and persistence of this compound in aquatic environments.[4–6] It has not, however, been established which of the isomers are responsible for these estrogenic effects, since none of the pure single isomers has been synthesized before to enable such studies. However, a lot of interest is focused mainly on the branched isomers, due to their high concentrations in the mixture and the belief that they may be more estrogenic than the straight-chain isomers. We have synthesized the branched isomer 4-(3′,6′-dimethyl-3′-heptyl)phenol (**7**), both as a normal standard and in its ^{14}C-ring-labeled form for use in toxicity and metabolism studies. The complex technical mixture of *p*-nonylphenol isomers has been well studied and its fundamental physicochemical properties, useful for prediction of its ecotoxicological behavior, have been reported.[5, 23–26] In order to predict the environmental behavior and toxicity of the single isomer that

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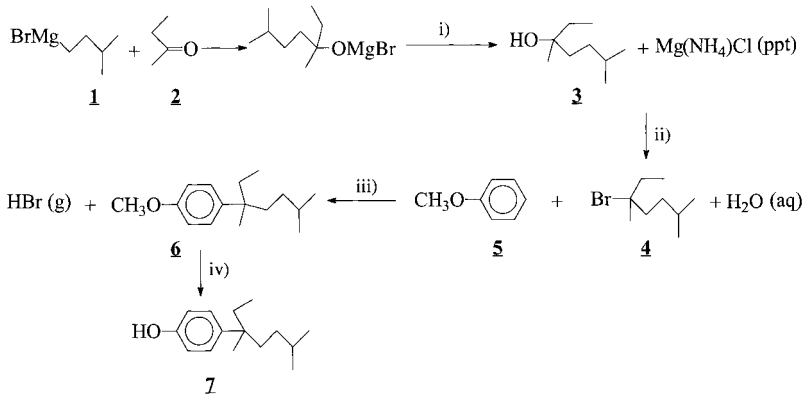
we had synthesized, we determined some of its major physicochemical properties, including its octanol–water partition coefficient ($\log K_{ow}$), water solubility (S_w), vapor pressure (VP), and its Henry's Law constant (H). These parameters were necessary in helping us design experiments to study the distribution, fate, and effects on molluscs (*Lymnaea stagnalis L.*) of this isomer in aquatic environments.

The water solubility of a compound determines its mobility between environmental compartments and influences its further distribution from the point of discharge to rivers and oceans. Water solubilities of organic pollutants also correlate well with their bioaccumulation potential through a single-variable linear-regression relationship, by which the often very high bioconcentration factors (BCFs) in aquatic organisms of organic chemicals with low water solubilities ($< 50\ \mu g L^{-1}$), such as the organochlorine pesticides and dioxins, may be predicted.[23] The bioaccumulation and retention potentials of organic chemicals are therefore important criteria for their ecotoxicological evaluation both in terrestrial and in aquatic organisms, especially in cases in which the acute toxicity of the chemical is low and the resultant physiological effects on the organisms are not noticeable until chronic effects are manifested in them.[24] The BCF also determines the distribution of chemicals in various target organs in the body of an organism, for example in the adipose tissue, muscle, liver, brain, and kidney, and is therefore relevant in studies of phenolic compounds, the toxicities of which have been reported to increase proportionately with their lipophilicities.[23, 24] Except for chemicals with very high molecular weights (MWs) and those that are readily metabolized by target organisms, the tendency of organic compounds to bioconcentrate has also been shown to be strongly related to their lipophilicities, expressed in the form of $\log K_{ow}$ values.[26] The $\log K_{ow}$ value of a compound therefore gives a good indication of its bioaccumulation potential and is important for the design of toxicity and metabolism studies in aquatic ecosystems. We used the Flask and Shake Flask methods for water solubility and $\log K_{ow}$ determinations, respectively, as explained in the experimental section below.

The vapor pressure (VP) of a chemical also influences its distribution in the environment. In conjunction with external factors such as wind and temperature, the vapor pressure of a compound dictates its volatility in a given environment. The vapor-pressure value can be used to calculate the Henry's Law constant (H) for the compound, as the ratio of its vapor pressure and its water solubility. The Henry's Law constant of a compound therefore determines its vapor exchange across air–water interfaces and so is a good indicator of its persistence in aquatic environments.[21, 22] Several physical methods have been used to measure the vapor pressures of organic compounds, including the gas-saturation method and the effusion method, both of which are recommended by the OECD.[21, 22] Capillary gas chromatography has also been used to determine the vapor pressures of moderately polar and nonpolar compounds, for which the GC-determined vapor pressures correlate well with liquid-phase vapor pressures at given temperatures.[24] In our determinations, we used the effusion method, as described in detail in the Experimental Section.

Results and Discussion

We have synthesized the branched nonylphenol isomer, 4-(3′,6′-dimethyl-3′-heptyl)phenol (**7**) and determined its important environmental properties, that is water solubility, $\log K_{ow}$, vapor pressure, and Henry's Law constant, which are required to be able to predict its distribution and fate in aquatic ecosystems.[15–18, 20–26] The synthesis was accomplished by means of a Friedel–Crafts reaction between anisole (**5**) and the tertiary alkyl bromide 3-bromo-3,6-dimethyl heptane, followed by cleavage of the methoxy bond with a Lewis acid, BBr_3 (Scheme 1). The tertiary alkyl bromide, not commercially available, was synthesized by Grignard reaction between butan-2-one (**2**) and 1-bromo-3-methylbutane, followed by hydrolysis with water to yield 3-hydroxy-3,6-dimethylheptane (**3**), which was then heated under reflux in 48% HBr to yield the required tertiary alkyl bromide **4**. In our reaction, the Grignard reagent **1** was prepared in situ by dropwise addition of an equimolar amount of 1-bromo-3-methylbutane to Mg in anhydrous diethyl ether while stirring.[7] Due to the high reactivity of this tertiary alkyl bromide, it was not necessary to initiate the reaction by addition of iodine as is normally done in Grignard reactions. The reactants were cooled to control the rate of the reaction and then heated under reflux at 40 °C for 30 minutes before addition of butan-2-one. There was only a minimal possibility of side reactions with this tertiary alkyl bromide at the β-position to give alkenes, and cleavage of the Mg–R bond to give alkanes was also minimal. Hydrolysis was achieved by the addition of crushed ice, which produced excess HBr and precipitated $Mg(OH)_2$, followed by addition of 10% aq.



Scheme 1. Reaction scheme for the regioselective synthesis of 4-(3′,6′-dimethyl-3′-heptyl)phenol (**7**). i) 10% NH_4Cl; ii) HBr (48%), 1 h, reflux; iii) $AlCl_3$, hydrolysis; iv) BBr_3/CH_2Cl_2, 1.5 h, 0 °C.

NH_4Cl until all the precipitate redissolved. The reaction proceeded easily to yield 71.3% of 3,6-dimethylheptan-3-ol (**3**) after fractionation by distillation under vacuum (78–82 °C at 25 mmHg). The identity of this alcohol was also confirmed by GC-MS and NMR.

A number of methods have been reported for nucleophilic substitution of hydroxyl groups by bromine ions, including sulfonation or phosphorylation followed by substitution of the alkyl sulfate/phosphate by bromide.[8, 9] Sulfonation prevents the formation of rearrangement products, making the reaction suitable for primary, secondary, and tertiary alkyl halides, although tertiary sulfonates are extremely reactive. Sulfonation followed by bromination with PBr_3 has also been used with, for example, pentan-3-ol, although two products, 2- and 3-bromopentane, were obtained in this case.[8] Primary, secondary, and tertiary alcohols can also be halogenated by treatment with the appropriate NaX, KX, or NH_4X in polyhydrogen-pyridine solution.[9] The method we used was based on a simple reported halogenation reaction with HX.[7, 8] With this method, HBr and HI react easily for all primary, secondary, and tertiary alcohols, the reactions being performed by refluxing the alcohol in the hydrogen halide solution for 6 hours. In this case, however, side reactions such as isomerization and formation of alkenes are also to be expected. We were able to carry out this substitution by refluxing the tertiary alcohol **3** in 48% HBr for one hour before chilling the reaction by the addition of ice-cold water, to give an 80.6% yield of crude product. Fractionation of the crude product was done by distillation under vacuum (83–91 °C, 23 mmHg) to yield the pure alkyl bromide product (47.9%), confirmed by GC-MS and NMR.

A Friedel–Crafts reaction between anisole (**5**) and the tertiary alkyl bromide **4** was achieved by $AlCl_3$-catalyzed alkylation as reported.[7] This reaction was performed on a micro scale in order to establish a procedure for synthesis of the ^{14}C-ring-radiolabeled 4-(3′,6′-dimethyl-3′-heptyl)phenol isomer required for toxicity and metabolism studies. In Friedel–Crafts reactions, the polarization of the R–X bond increases from primary to secondary to tertiary alkyl bromide, and electrophilic activity therefore also increases in the same order. The alcohol requires at least equimolar quantities of Lewis acid and a water-free environment. Excess anisole was used in our reaction to get a monoalkylated product and avoid further alkylation on the benzene ring. Electrophilic substitution reactions at other positions in the benzene ring were avoided by working at low temperatures; this ensured predominant substitution at the *para* position. Our product isomer was later compared with a similar standard isomer obtained by a modified macroscale synthesis based on the procedures followed in this microsynthesis.[27] The identity of the liquid product, 1-(3′,6′-dimethyl-3′-heptyl)-4-methoxybenzene, was confirmed by GC-MS (MW 234) and NMR, and had a refractive index of 1.4909 (21.15 °C); the compound was also characterized by IR. There were traces (approximately 1%) of the *ortho* isomer apparent in the NMR spectra. The methoxy bond in the resultant ether was then cleaved to give the required branched *p*-nonylphenol isomer. This cleavage was also done on a micro scale, as explained in the procedure given in the Experimental Section.

Several procedures for the cleavage of aryl alkyl ethers that avoid simultaneous cleavage of the phenyl alkyl bonds have been reported. They include the use of organosilicon compounds such as iodomethyl silane, Lewis acids such as $AlCl_3$ and $AlBr_3$, hydrogen halides, dilute hydrochloric acid, dimethyl boron bromide, and boron tribromide (BBr_3).[10–14] The reaction conditions with these reagents also prevent any possibility of attack on the hydroxyl group. Boron tribromide, for example, has been used effectively for de-ethylation of aryl alkyl ethers and can cleave linear alkyls of chain lengths of up to C_{10}, to yield mixtures of products including phenols.[10] In our microsynthesis, after attempts with BI_3 (stirring for 15 minutes in CH_2Cl_2 at 0 °C, GC-MS analysis of reaction mixture) had failed to give a reaction, we changed to BBr_3, which we found to be more reactive and a lot cheaper. The micro reaction was performed by addition of a measured volume of BBr_3 to the reactants in CH_2Cl_2 and stirring at 0 °C for 1.5 hours, followed by hydrolysis with water for 1 hour at the same temperature. We found that both S_N1 and S_N2 reactions were competing in such a way that re-formation of large amounts of the alkyl bromide was favored if the reaction was allowed to run for longer than 1.5 hours. A good yield (81%) of crude liquid product was obtained after separation of the organic phase from the aqueous phase and drying the product in a rotary evaporator under a vacuum. Unreacted compounds and other impurities were removed by TLC separation (TLC plates: silica gel $60F_{254}$ (20 × 20 cm), solvent: 5% diethyl ether in *n*-hexane, UV 254; *R*f for **6**: 0.54, *R*f for **7**: 0.14). The clean product **7** was then analyzed by GC-MS (MW 220), IR, and NMR. It had a refractive index of 1.5068 (21.15 °C). By HPLC, it was more polar (*R*t: 3.1 min) than the technical mixture (*R*t: 5.4 min).

Table 1 shows some of the determined physicochemical properties of the branched isomer of *p*-nonylphenol, compared with those reported for the technical mixture.

The structure–property relationships that apply to hydrophobic organic compounds such as chlorobenzenes and alkylbenzenes have been found to apply to alkylphenols as well, but the relationships are more scattered for alkylphenols because of their relatively higher polarity. The correlations developed for nonpolar organic chemicals cannot therefore be applied directly to alkylphenols. The physicochemical properties of the synthesized isomer were found to be different from those of the technical mixture. From high-resolution gas chromatography and GC-MS data of the resolved isomers in the technical isomeric nonylphenol, the proportion of this isomer in the mixture can be estimated as less than 10%, and so its physicochemical properties would not be expected to be very similar to those of the technical compound mixture.[1, 3] The $\log K_{ow}$ value in particular was lower, although this low value was consistent with the high water solubility of the compound (ten times that of the technical compound). Its $\log K_{ow}$ value is closer to that of the branched compound 5-*tert*-butyl-2-methylphenol (water solubility: 410 at 25 °C, $\log K_{ow}$: 2.62 at 25 °C), which has a similar structure. The tertiary structure of the isomer molecule is almost symmetrical, and so the molar volume of the molecule would be expected to be slightly smaller than those of less branched and straight-chain isomers of *p*-nonylphenol mole-

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Table 1. The determined physicochemical properties of the isomer 4-(3′,6′-dimethyl-3′-heptyl)phenol, compared with those of other similar compounds, obtained from the literature.[a]

Compound	S_w [mg L^{-1}]	VP [Pa]	H [Pa m^3 mol^{-1}]	log K_{ow}
4-(3′,6′-dimethyl-3′-heptyl)phenol	53.69 (pH 5)[c]	1.93×10^{-2} [c]	7.91×10^{-2} [c]	1.89[c]
		3.57×10^{-2} [d]		3.4[b][18]
nonylphenol	5.43[e][18]	2.07×10^{-2} [c]	8.39×10^{-1} [c]	4.48[e][17]
(technical mixture)	6.35[d][18]	3.77×10^{-2} [d]	13.1×10^{-1} [d]	
pentachlorophenol	14[d] (pH 5.1)	2.27×10^{-2} [d]	1.27×10^{-2} [d]	5.05[d] (pH 5.1)
phenol	88360 (pH 5.1)[d]	42.93[f]	5.0×10^{-2} [d]	1.5[d]
4-octylphenol	12.6[e]	–	–	4.12[e]
2-methyl-5-*tert*-butylphenol	410[d]	3.69[d]	1.35[d]	2.62[b, d]
2,3,5-trimethylphenol	762[d]	2.43[d]	0.43[d]	2.86[d]

[a] Data from the literature were obtained from Wan-Ying Shiu et al.[25] unless indicated otherwise. [b] calcd. [c] 20 °C. [d] 25 °C. [e] 20.5 °C. [f] 24.85 °C. Note: Experimentally determined log K_{ow} value was lower than that obtained by calculation (3.4) with the formula log $K_{ow} = -0.747 + 0.73$.[25]

cules. The smaller molar volume would consequently be expected to affect the water solubility and vapor pressure of the single branched isomer. The tertiary structure of the single branched isomer also enhances the polarity of the phenolic bond and makes it easier for the molecule to form hydrogen bonds with water molecules; this would also enhance its water solubility relative to that of a straight-chain isomer. The vapor pressure of the synthesized single branched isomer was, however, found to be similar to that of one of the components of the technical *p*-nonylphenol mixture resolved by capillary GC as reported by Bidleman and Renberg, who found vapor pressures ranging between 5.7×10^{-2} and 17.4×10^{-2} Pa for the various resolved isomers at 25 °C.[24] From its log K_{ow} value, the synthesized branched isomer would be expected to have a slightly lower bioaccumulation potential than technical *p*-nonylphenol in aquatic organisms, given the same species of organisms and exposure concentrations.

From these results, we can conclude that, like other phenolic compounds, this branched isomer would mainly tend to be associated with sediments and soils, and its persistence in the environment would be mainly governed by its degradation in those media. Its volatilization loss from water and soil would be relatively less than that for technical *p*-nonylphenol, because of its lower air–water ratio partition coefficient of 3.25×10^{-5} at 20 °C, which is comparable to those of pentachlorophenol and phenol. Because of its higher water solubility and lower vapor pressure, the isomer should be less persistent than the technical *p*-nonylphenol mixture in aqueous media. At normal aquatic conditions (pH 7–8), negligible dissociation of the *p*-nonylphenol isomer is to be expected, on the assumption that it has a p*K*a value close to the 10.8 reported for the technical *p*-nonylphenol mixture.[28] Under these conditions, if the compound were to be discharged through air, it would rapidly be removed and be deposited in water and soil. Little vapor loss would occur when discharged into water, but appreciable amounts would be deposited onto sediment. The air–water partition coefficient for the branched isomer was found to be ten times lower than that for the technical mixture (3.44×10^{-4} Pa m^3 mol^{-1} K^{-1} at 20 °C); this indicates that the isomer would be less rapidly volatilized from water and therefore more persistent in aqueous environments than the technical *p*-nonylphenol mixture.

Conclusion

All the reaction steps and procedures were found to be reliable and reproducible. The microsynthesis of pure ^{14}C-ring-labeled 4-(3′,6′-dimethyl-3′-heptyl)phenol (NP) from ^{14}C-ring-labeled anisole was also achieved in good yield by following the established microsynthesis reaction procedures outlined in this paper. This microscale synthesis method is therefore considered to be a very important synthesis method both for native and for ^{14}C-radiolabeled forms of the isomer. The water solubility value (53.69 mg L^{-1} at 20 °C) and the log K_{ow} value (1.89) found for this isomer were, however, significantly different from those reported in the literature for the technical mixture (water solubility: 5.43 mg L^{-1} at 20.5 °C, log K_{ow}: 4.48).[17, 18] On the basis of the vapor pressure values, the Henry's Law constants, and the air–water partition coefficients, the branched isomer would be expected to be more persistent than the technical *p*-nonylphenol mixture in aqueous media, although it should tend to show relatively lower bioaccumulation in sediments and biota, if possible chemical degradation processes in aquatic environments are discounted.

Experimental Section

Anisole (density 0.995, 99% pure by GC), Mg turnings (98% pure), $AlCl_3$ (99% pure), and butan-2-one (density 0.805, 99% pure by spectrophotometric methods) were obtained from Aldrich, while 1-bromo-3-methylbutane (density 1.208, 95% pure by GC), anhydrous diethyl ether (99.5% pure by GC), 48% hydrobromic acid, and BBr_3 were obtained from Fluka.

GC-MS determination was performed on GC HP 5890 Series II and MS Finnigan SSQ 7000 machines; column: J&W DB-5 ms, 60 m, 0.25 mm i.d., film thickness 0.10 μm. Temperature program: 60 °C (1.5 min); 7.5 °C min^{-1} to 260 °C (12 min), injection temperature: 250 °C, 1 μL splitless injection: carrier gas: helium, pressure: 25 psi. MS conditions: full scan from mass 50 to 500, cycle time 0.7 sec, T = 150 °C. HPLC was performed on a Merck Hitachi System (L-6200A pump, L-4000 UV detector and D-2500 Chromato integrator), column: RP 18, 10 cm long, 5 mm i.d., solvent: 90% methanol in water, flow rate: 1.5 mL min^{-1}, isocratic conditions.

NMR spectra were measured with a Bruker DMX 500 NMR spectrometer, with a 5 mm inverse geometry probehead (90° (^{1}H) = 9.3 μs, 90° (^{13}C) = 9.8 μs) in $CDCl_3$ (δ = 7.25, 77.0) at 303 K. Phase-sensitive ^{1}H,^{13}C HSQC, HSQC-TOCSY (mixing time: 70 ms) and absolute value DQ-COSY NMR spectra were measured by using Bruker standard software. The assignment of proton resonances of compounds **6** and **7** was deduced from the HSQC-

NMR spectra, assisted by calculations of proton and carbon chemical shifts with the ACD/Labs (Pegnitz, Germany) HNMR and CNMR predictor program, version 4.5. IR was performed on a Perkin Elmer Model 552, from films.

Synthesis of 3,6-dimethylheptan-3-ol (3) from butan-2-one (2) and 1-bromo-3-methylbutane (1): Grignard reaction: Magnesium (12.2 g, 0.502 mol) was added to anhydrous diethyl ether (50 mL) in a reaction flask. 1-Bromo-3-methylbutane (60 mL, 0.48 mol) was then slowly added to the stirred mixture from a dropping funnel over one hour. The reaction was brought to completion by warming on a water bath at 40 °C for 30 minutes until all the Mg had disappeared. Butanone (36 mL, 0.4 mol, density 0.805 $g L^{-1}$) in anhydrous diethyl ether (65 mL) was then added to this reaction mixture, while still stirring and warming at 40 °C. After addition was complete, the reaction was allowed to continue for 2 hours. The reaction mixture was then cooled in an ice bath and hydrolyzed by the addition of crushed ice (50 g). Aqueous NH_4Cl (10%, 150 mL) was then added until the precipitate redissolved. The ether phase was then separated, the aqueous slurry phase was extracted twice with diethyl ether (100 mL), and the organic phases were combined. The ether phase was then washed with 10% $KHCO_3$ and dried overnight over Na_2SO_4, filtered, and evaporated in a rotary evaporator to yield 76.7% of the crude alcohol (55.6 g). This crude product was fractionated by distillation under vacuum (25 mmHg, 87–88 °C) to give pure product (49.6 g, 68.4%). The identity of the product was confirmed by NMR.

Synthesis of 3-bromo-3,6-dimethylheptane (4) from 3,6-dimethylheptan-3-ol (3): 48% HBr (40 mL, 1.5 mol) was added, with stirring, to 3,6-dimethylheptan-3-ol (47 g, 0.227 mol). The reaction mixture was heated under reflux for 1 hour and then chilled by the addition of ice-cold water. Separation of the two layers was performed rapidly. The alkyl bromide layer was washed twice with ice-cold water (30 mL), and then twice with ice-cold 40% methanol (30 mL). The separated organic phase was neutralized by shaking in a separating funnel with 10% $KHCO_3$ (30 mL) and then rinsed with ice-cold water (30 mL). The product was dried overnight over Na_2SO_4. After distillation, a number of by-products including alkenes were distilled off under vacuum at 83–104 °C (45 mmHg). The identity of the remaining colorless liquid product was confirmed by NMR.

Microsynthesis of 1-(3′,6′-dimethyl-3-heptyl)-4-methoxybenzene (6) by Friedel–Crafts alkylation with $AlCl_3$: Anisole (130 mg, 1.203 mmol) and $AlCl_3$ (3.18 mg, 0.0234 mmol) were added with stirring to 3-bromo-3,6-dimethylheptane (49.2 g, 0.0238 mmol) in *n*-hexane (30 mL). The mixture was heated under reflux below 20 °C overnight until no more HBr gas evolution was observed. Crushed ice was then added to the reaction mixture to hydrolyze the components, and the organic phase was separated, washed with distilled water (20 mL) and then with 10% NaOH (10 mL) solution, and then rinsed again with distilled water (20 mL) until neutral. The organic phase was then dried overnight over Na_2SO_4. The solvent was removed in a rotary evaporator to yield crude 1-(3′,6′-dimethyl-3′-heptyl)-4-methoxybenzene (**6**) (90.6 mg), together with traces of the *ortho* isomer (1% by NMR). The crude product was also analyzed by GC-MS (MW 234) and then used in its crude form for the second step of the microsynthesis as detailed below. TLC-purified compound **6** was characterized by IR and NMR. Refractive index = 1.4909 (21.15 °C); ^{1}H NMR: $\delta = 7.18$ (AA′XX′, $J = 9.0$ Hz, 2H; H2/6,), 6.83 (AA′XX′, $J = 8.9$ Hz, 2H; H3/5,), 3.79 (s, 3H; OCH3), 1.69 (m, H2′), 1.66 (m, H4′), 1.55 (m, H4′), 1.49 (m, H2′), 1.40 (hept, H6′), 1.23 (s, 3H; H3∀′), 1.01 (tq, $J = 11.3$, 6.6, 4.7 Hz 1H; H5′,), 0.85 (m, 1H; H5′), 0.83, 0.82 (d, $J = 6.7$ Hz, 6H; H6∀/H7′), 0.67 (t, $J = 7.5$ Hz, 3H; H1′); ^{13}C NMR: $\delta = 157.09$ (C1), 140.08 (C4), 127.41 (C3/5), 113.18 (C2/6), 55.10 (OCH3), 40.56 (C2′), 40.23 (C3′), 35.68 (C4′), 33.24 (C5′), 28.67 (C6′), 23.64 (C3∀), 22.64, 22.62 (C6′/C7′), 8.62 (C1′); IR: $\tilde{\nu} = 3037$, 2958, 2870, 2833, 1611, 1581, 1513, 1465, 1378, 1365, 1298, 1250, 1184, 1040, 826, 780, 757 cm^{-1}.

Cleavage of the methyl aryl ether 6 with BBr_3 to yield 4-(3′,6′-dimethyl-3′-heptyl)phenol (7): Cleavage of the methyl aryl ether with BI_3 failed to give any detectable amounts of the desired product, and so a change was made to BBr_3. The crude product **6** from the above microsynthesis step was completely dried in a rotary evaporator and then dissolved in CH_2Cl_2 (15 mL) in a two-necked reaction flask (with stirrer and reflux). This was cooled and stirred in an ice/water bath, and BBr_3 (5–6 drops, 184 μL, 1.936 mmol) was added to the reactants by pipette. The reactants were then stirred for 1.5 hours at 0 °C before addition of distilled water (10 mL). The hydrolysis was left to continue for one hour, after which the two phases were separated. The aqueous phase was washed with CH_2Cl_2 (20 mL), and the combined organic phase was dried overnight over Na_2SO_4, filtered, and then concentrated to yield 70.2 mg of crude product **7**. This crude product was confirmed by GC-MS and then purified by preparative TLC (TLC plate: silica gel, 20 cm × 20 cm; R_f: 0.14 (diethyl ether/*n*-hexane 10:190)). The pure compound was then analyzed by GC-MS and NMR and characterized. Refractive index = 1.5068 (21.15 °C); ^{1}H NMR: $\delta = 7.14$ (*AA′*XX′, $J = 8.8$ Hz, 2H; H2/6), 6.77 (AA′*XX′*, $J = 8.8$ Hz, 2H; H3/5); 1.70 (m, H2′), 1.67 (m, H4′), 1.56 (m, H4′), 1.49 (m, H2′), 1.43 (m, H6′), 1.23 (s, 3H; H3∀); 1.04 (tq, $J = 11.3$, 6.6, 4.6 Hz, 1H; H5′); 0.98 (m, 1H; H5′); 0.84, 0.82 (d, $J = 6.7$ Hz, 6H, H6∀/H7′); 0.69 (t, $J = 7.4$ Hz, 3H; H1′); ^{13}C NMR: $\delta = 152.88$ (C1), 140.34 (C4), 127.64 (C3/5) 114.66 (C2/6), 40.59 (C2′), 40.27 (C3′) 35.68 (C4′), 33.22 (C5′), 28.65 (C6′), 23.60 (C3∀), 22.63, 22,61 (C6∀, C7′), 8.60 (C1′); IR: $\tilde{\nu} = 3344$, 3031, 2959, 2927, 2870, 1612, 1596, 1513, 1466, 1380, 1236, 1181, 827 cm^{-1}.

Determination of the $\log K_{ow}$ value of 7: The isomer standard 4-(3′,6′-dimethyl-3′-heptyl)phenol obtained from a modified macroscale synthesis procedure based on the above microsynthesis procedures was used for the determination of its important physicochemical parameters.[27] The determination of $\log K_{ow}$ was performed by the Shake Flask method, as described in the OECD methods of testing chemicals.[16] From the formula ($\log K_{ow} = -0.747 \times \log S_w + 0.73$, where S_w is the water solubility in mol L^{-1}), the $\log K_{ow}$ value of the single pure isomer of nonylphenol was estimated to lie in the range, from −2 to +4, recommended for the Shake Flask method.[15, 18, 19] The tests were performed at pH 5, conditions under which it was assumed that the isomer molecules would exist almost completely in nonionized form, based on the pK_a value of 10.8 stated for the *p*-nonylphenol technical mixture.[25] Analytical grade octan-1-ol and Millipore water (obtained from a Milli-Q Plus deionizer fitted with a RIOS system for removal of dissolved organic matter) were used. The Millipore water had an electrical conductivity of 18.2 M cm^{-1} and TOC < 30 $\mu g L^{-1}$ (ppb). Saturated stock solutions of octan-1-ol and water were made by shaking equal volumes of octan-1-ol and water in a 500 mL conical flask on a mechanical shaker for 24 hours and then allowing the solvent mixture to stand for six hours in a separating funnel to separate the two phases completely. 30 mL centrifuge tubes with Teflon caps were used for the tests, which were performed in duplicate with octan-1-ol/water ratios of 1:5, 1:2, 1:1, 2:1, and 2:1 with a total volume of 30 mL in each centrifuge tube. The nonylphenol isomer standard (0.0294 mg) containing ^{14}C-labeled nonylphenol (0.595 μg) was dissolved in octan-1-ol (60 mL) in a 250 mL conical flask, and aliquots of 5 mL, 10 mL, 15 mL, 20 mL, and 25 mL were taken into the centrifuge tubes. Appropriate volumes of water were then added to each centrifuge tube to make up the volume to 30 mL. The total radioactivity in the 60 mL stock solution was 578581 dpm (disintegrations per minute). The tubes were hand-shaken continuously for 30 minutes and then placed in a centrifuge (Heraus Biofuge 22R, 4000 rpm for 2 min.) to separate the octanol/water phases. Aliquots (1 mL) were taken in duplicate from both phases in each centrifuge tube, by Gilson standard pipette, into Ultima Gold scintillation cocktail (10 mL) for determination of the amount of radioactivity. The dpm values obtained from the scintillation counter were converted into μg values to determine the concentrations of the test compound in each tube, from which the ratios of concentrations of the compound in octan-1-ol and water were calculated. A $\log K_{ow}$ value of 1.89 ± 0.0056 was obtained.

Determination of the water solubility (S_w) of 7: From the equation $\log K_{ow} = -0.747 \log S + 0.73$, the water solubility was estimated to be at least 44.3 mg L^{-1}.[15, 18, 19] The experimental value was determined by taking, in duplicate, excess amounts of standard nonylphenol (29.1 mg) in CH_2Cl_2 (15 mL). Aliquots of this solution were then added to diatomaceous earth (600 mg) in glass centrifuge tubes with Teflon caps as follows: 5 mL (containing 9.70 mg of compound) in tube 1, 4.8 mL (9.31 mg of compound) in tube 2, and 5 mL (9.70 mg of compound) in tube 3. The solvent was then left to evaporate completely from each tube, leaving the nonylphenol absorbed onto the dry diatomaceous earth. Distilled water (25 mL, pH 5) was then added to each of the tubes, which were incubated at 30 °C under constant stirring for 96 hours. The tubes were then removed and left to equilibrate at 20 °C prior to centrifugation at 4000 rpm for 10 min. The water samples were then analyzed by HPLC, which gave an average water solubility value of 53.69 mg L^{-1} (0.244 mol m^{-3}) at 20 °C.

0947-6539/01/0722-4794 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 22

Determination of vapor pressures (VP) and Henry's Law constants (*H*) of compound 7 and of 4-nonylphenol technical mixture: Vapor pressures were determined by the effusion method.[20, 21] This method is also recommended by the OECD for the determination of VPs of substances of low volatility.[22]

The sample was stored in an evaporation stove, acting as an effusion cell under high vacuum conditions. The VP was calculated from the effusion rate of the substance. The effusion rate was determined from the condensation of molecules from the beam on a cooled plate of a highly sensitive microbalance in a fixed time interval. The VP was measured at six different temperatures between 23.00 and 48.50 °C, by using triplicate points for the condensation, as well as impulse methods. From the regression line, the VP of compound **7** was then calculated to be 1.93×10^{-2} Pa at 20 °C and 3.57×10^{-2} Pa at 25 °C. The Henry's Law constant for this compound was calculated from the relationship $H = \mathrm{VP}/S_w$ to be 7.91×10^{-2} Pa m^3 mol^{-1} at 20 °C. The VP of 4-nonylphenol (technical mixture) was also determined to be 2.07×10^{-2} Pa at 20 °C and 3.77×10^{-2} Pa at 25 °C; this gave *H* values of 83.87×10^{-2} and 130.61×10^{-2} Pa m^3 mol^{-1}, respectively. The air–water partition coefficient values given by H/RT were 3.25×10^{-5} Pa m^3 mol^{-1} K^{-1} (20 °C) for the isomer and 3.44×10^{-4} and 5.27×10^{-4} Pa m^3 mol^{-1} K^{-1} (20 °C and 25 °C, respectively) for the technical nonylphenol mixture.

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[1] B. D. Bhatt, J. V. Prasad, G. Kalpana, S. Ali, *J. Chrom. Sci.* **1992**, *30*, 203–210.
[2] R. Vittorio, S. Piergenido, *J. Chrom.* **1978**, *153*, 181–182.
[3] T. F. Wheeler, J. R. Heim, M. R. LaTorre, A. B. Janes, *J. Chrom. Sci.* **1997**, *35*, 19–30.
[4] A. C. Mehldal , K. Nithipatikom, J. J. Lech, *Xenobiotica* **1996**, *26*, 1167–1180.
[5] W. Giger, E. Stephanous, C. Schaffner, *Chemosphere* **1981**, *10*, 1253–1263.
[6] R. Ekelund, A. Bergman, A. Granmo, M. Berggren, *Env. Poll.* **1990**, *64*, 107–120.
[7] J. A. Barth, *Organikum*: *Organisch-Chemisches Grundpraktikum*, 20th ed., Johann Ambrosius Barth, Heidelberg **1996**, pp. 353–360.
[8] J. March, *Advanced Organic Chemistry*: *Reactions*, *Mechanisms and Structure*, 4th ed., Wiley, New York, **1992**, pp. 431–460.
[9] G. A. Olah, J. T. Welch, Y. D. Vankar, M. Nojima, I. Kerekes, J. A. Olah, *J. Org. Chem.* **1979**, *44*, 3872–3881.
[10] M. V. Bhatt, S. U. Mulkarni, *Synthesis* **1983**, 249–270.
[11] B. Jursic, *J. Chem. Research (S)* **1989**, 284–285.
[12] H. Niwa, T. Hida, K. Yamada, *Tetrahedron Lett.* **1981**, *22*, 4239–4240.
[13] Y. Guindon, C. Yoakim, H. E. Morton, *Tetrahedron Lett.* **1983**, *24*, 2969–2972.
[14] J. B. Press, *Synthetic Comm.* **1979**, *9*, 407–410.
[15] *Guidelines for the Testing of Chemicals*, *Vol. 1*, *105*, OECD, Paris, **1993**.
[16] *Guidelines for the Testing of Chemicals*, *Vol. 1*, *107*, OECD, Paris, **1993**.
[17] M. Ahel, W. Giger, *Chemosphere* **1993**, *26*, 1471–1478.
[18] M. Ahel, W. Giger, *Chemosphere* **1993**, *26*, 1461–1470.
[19] C. T. Chiou, D. W. Schmedding, M. Manes, *Environ. Sci. Technol.* **1982**, *16*, 4–10.
[20] M. A. V. R. Da Silva, M. J. S. Monte, *Thermochim. Acta* **1990**, *171*, 169–183.
[21] J. Niederfellner, D. Lenoir, G. Matuschek, F. Rehfeldt, H. Utschik, R. Brüggemann, *Quant. Struct.-Act. Relat.* **1997**, *16*, 38–48.
[22] *Guidelines for the Testing of Chemicals*, *Vol. 1*, *104*, OECD, Paris, **1993**.
[23] H. Geyer, A. G. Kraus, W. Klein, E. Richter, F. Korte, *Chemosphere* **1980**, *9*, 277–291.
[24] T. F. Bidleman, L. Renberg, *Chemosphere* **1985**, *14*, 1475–1481.
[25] W.-Y. Shiu, K.-C. Ma, D. Varhanickova, D. MacKay, *Chemosphere* **1994**, *29*, 1155–1224.
[26] B. G. Oliver, A. J. Niimi, *Environ. Sci. Technol.* **1985**, *19*, 842–849.
[27] J. O. Lalah, D. Lenoir, B. Henkelmann, G. Hertkorn, K. Günther, K-W. Schramm, A. Kettrup, unpublished results.
[28] O. Hutzinger, K.-W. Schramm, A. Fischer, K.-U. Goss, J. Klasmeier, Umweltchemikalien/Schadstoffwirkung Forschungsbericht 10602067, Umweltbundesamtes, Bayreuth Universität, **1991**, pp. 289.

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