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BOROHYDRIDE REDUCTION OF ALKYL PHENYL KETONES WITHIN A REVERSED-PHASE LIQUID CHROMATOGRAPHIC COLUMN

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The reductions of propiophenone and octanophenone to 1-phenylpropan-1-ol and 1-phenyloctan-1-ol, respectively, with sodium borohydride and tetrabutylammonium borohydride were performed on a reversed-phase high-performance liquid chromatographic (HPLC) column of macroporous 10-μm poly(styrene–divinylbenzene) under HLPC conditions. In these reactions a lower concentration of tetrabutylammonium borohydride than of sodium borohydride was needed to effect the same extent of reduction, and modest substrate selectivity was obtained.

Reversed-phase high-performance liquid chromatographic (HPLC) columns are used routinely for analytical and preparative separations, but only infrequently as reaction media. For example, on alkylsilane-bonded silica columns, we have performed aromatic chlorinations of alkyl phenyl ethers by chlorine water,[1] Tanaka and co-workers.[2] nucleophilic substitution reactions and Langer and co-workers[3] esterifications. We have also reported hydroxide ion-catalyzed hydrolyses of *p*-nitrophenyl esters on a column of poly(styrene–divinylbenzene).[4] The use of a reversed-phase column as a chemical reactor offers a potential alternative to procedures such as phase transfer and micellar catalysis for reactions of water-insoluble organic substrates with water-soluble inorganic reagents, with the added possibility of reaction selectivity, as observed in our two studies above.[1,4] We report here a study of the reduction of propiophenone (**1**) and octanophenone (**2**) to 1-phenylpropan-1-ol and 1-phenyloctan-1-ol, respectively, with sodium borohydride (**3**) and tetrabutylammonium borohydride (**4**) on a 15 cm × 4·1 mm i.d. column of macroporous 10-μm poly(styrene–divinylbenzene) (PRP-1)[5] under HPLC conditions.

Two closely related HPLC reaction procedures were used for individual reactions of **1** and **2**. Procedure A, summarized in Figure 1 and similar to that used previously,[4] is as follows. The column was equilibrated at 23 ± 1 °C with an acetonitrile–water mixture or water alone. Then, at time $t = 0$, 5·0 μl of 0·50 M **1** (**2**) in acetonitrile was injected, and the eluent at a flow-rate of 0·7 ml min^{-1} was changed to 100% water, if necessary, to ensure immobilization of **1** (**2**) within the column by its sorption to the polymer. At $t = 4·5$ min, 2·00 ml of a solution of 0·010–1·25 M **3** (**4**) in 2·5 mM sodium hydroxide solution was injected, and the flow-rate was either left at 0·7 ml min^{-1} or changed to a value between 0·30 and 2·0 ml min^{-1}. At $t = 14·5$ min, the flow-rate was returned to 0·7 ml min^{-1}. At the same time, the eluent was linearly changed to 60% (v/v) acetonitrile during 3 min with **3**, or during 5 min with **4**, for reactions of **1**, or to 90% acetonitrile during 5 min for those of **2**. In procedure B, the events at $t = 4·5$ and 14·5 min were delayed by 3·5 min, i.e. they were performed at $t = 8·0$ and 18·0 min, respectively.

Procedure C was used for the competition runs and differed from procedure A as follows. At $t = 0$, 5·0 μl of 0·050 M **1** in acetonitrile was injected, followed by 5·0 μl of 0·050 M **2** in acetonitrile at $t = 1$ min. Then **3** (**4**) was injected at $t = 5·5$ min, and the eluent was changed at $t = 15·5$ min to 60% acetonitrile during 2 min, and at $t = 25$ min to 90% acetonitrile during 2 min.

With these procedures excess of **3** eluted with the void volume of the column (1·3 ml)[5] and excess of **4** at *ca* 20 min after its injection. In procedures A and B, the alcohol product eluted next, followed by **1** (**2**), as determined by a calibrated UV detector (254 nm) attached to the column outlet. In procedure C, 1-phenylpropan-1-ol and **1** eluted before 1-phenyloctan-1-ol and **2**.

The kinetics of the reductions of **1** and **2** by **3** within

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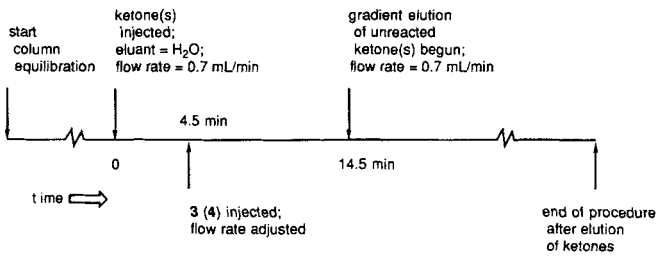

Figure 1. Summary of HPLC reaction procedure A

Table 1. Individual reductions of **1** and **2** with **3**[a]

Entry	Substrate	Equilibration solvent (v/v)	Retention times of **1**/**2** (min)[b] A	B	$10^3 k_\psi (s^{-1})$[c,d] A	B
1	**1**	H_2O	30·9		10 (84)	
2	**1**	20:80 MeCN–H_2O	30·8	33·3	3·7 (45)	3·1
3	**1**	40:60 MeCN–H_2O	29·4	32·2	4·7 (56)	4·3
4[e]	**1**	60:40 MeCN–H_2O	30·1		8·4 (76)	
5[f]	**1**	20:80 MeCN–H_2O	27·6		4·4	
6	**2**	H_2O		35·8		1·7
7	**2**	40:60 MeCN–H_2O	32·7	35·9	2·9 (36)	3·9
8	**2**	60:40 MeCN–H_2O	32·3	35·7	1·4	2·3
9	**2**	80:20 MeCN–H_2O	30·8	34·1	5·0 (60)	5·5

[a] Procedures A (Figure 1) and B in the text were used unless indicated otherwise. [**3**] = 0·75 and 1·25 M in the 2·00-ml aliquots of 2·5 mM NaOH for entries 1–5 and 6–9, respectively.
[b] For each entry the values represent the averages of the retention times in procedures A and B from $t = 0$ for the separate runs in the kinetic determinations; average deviation ±0·3 min.
[c] Averages of duplicate determinations; the estimated limits of error are ±10%.
[d] Each value in parentheses is the percentage reduction for the kinetic point in procedure A with flow-rate 0·7 ml min^{-1}.
[e] A different elution gradient was used; at $t = 14·5$ min, the acetonitrile content was increased to 45% during 3 min.
[f] A modification of procedure A was used; see the text for details.

the column were studied as a function of the eluent composition used for column equilibration and were determined with adaptations of procedures developed by Langer and co-workers[3] and Bentley and Gream.[6] In procedures A and B, the use of different flow-rates during the 10-min periods from $t = 4·5$ to 14·5 min and from $t = 8·0$ to 18·0 min, respectively, gave different contact/reaction times for a ketone with the 2·00-ml aliquot of aqueous **3**. Thus, flow-rates of 0·30 and 2·0 ml min^{-1} correspond to reaction times of 6·7 and 1·0 min, respectively. Plots of ln (% unreacted ketone) vs reaction time were uniformly linear and comparable to those in Figure 2 in Ref. 4. The resulting observed pseudo-first-order rate constants, k_ψ, are summarized in Table 1.

The above kinetic method could not be applied to the reductions with **4** since it did not elute with the void volume. Therefore, only percentage reductions to the alcohols are given in the summary in Table 2. Also, only percentage reductions are given for the competitive runs summarized in Table 3.

The second-order rate constant for the reduction of **1** by **3** in propan-2-ol at 25·0 °C is known,[7] and at [**3**] = 0·75 M, as used in entries 1–5 in Table 1, corresponds to $k_\psi = 5·87 \times 10^{-4}$ s^{-1}. In water, k_ψ should be greater.[8] In any event, the k_ψ values in Table 1 for reactions performed under the HPLC conditions are comparable to those obtained for homogeneous reactions in polar hydroxylic solvents.

The partitioning of a ketone between the polymer phase and a mobile phase rich in water overwhelmingly favors the former. Thus, **1** (**2**) is effectively immobilized within the column during its reaction with **3** (**4**). There are four possible reaction sites: (a) mobile phase outside the polymer beads; (b) liquid phase inside the pores of the beads; (c) liquid–polymer interface on the pore walls; and (d) bead interior. For reasons noted earlier,[4] it is unlikely that any **1** (**2**) resides at side d. Also, as

Table 2. Individual reductions of **1** and **2** with **4**[a]

Entry	Substrate	[4] (M)[b]	Equilibration solvent (v/v)	Retention time of **1/2** (min)[c]	Reduction (%)[d]
10	**1**	0·010	H_2O	29·8	43
11	**1**	0·025	20:80 MeCN–H_2O	29·7	52
12	**2**	0·20	H_2O	33·2	47
13	**2**	0·050	60:40 MeCN–H_2O	32·1	39
14	**2**	0·050	80:20 MeCN–H_2O	31·3	90

[a] Procedure A in the text was used with flow-rate 0·7 ml min^{-1} throughout.
[b] Contained in the 2·00-ml aliquot of 2·5 mM NaOH.
[c] From $t = 0$.
[d] Averages of duplicate runs; average deviation ±1%.

Table 3. Competitive reductions of **1** and **2**[a]

Entry	Reducing agent[b]		Equilibration solvent (v/v)	Flow-rate, (ml min^{-1})[c]	Reduction (%)[d]	
	Compound	Concentration (M)			**1**	**2**
15	**3**	0·75	H_2O	0·25	>99	50
16	**4**	0·050	H_2O	0·30	>99	30

[a] Procedure C in the text was used.
[b] Contained in the 2·00-ml aliquot of 2·5 mM NaOH.
[c] Used from $t = 5·5$ to 15·5 min.
[d] Averages of duplicate runs; average deviation ±3%.

reaction at site a cannot be readily distinguished from that at site b,[4] only the former is mentioned specifically in the following discussion. Thus, overall, a given reduction occurs at site a after desorption of **1** (**2**) from the polymer surface and/or at site c. Further, it is assumed that the reactivity of **1** (**2**) at site a is greater than that at site c. Desorption of a compound from a surface is a first-order process, and a bimolecular reaction on a sparsely covered surface is first order in each reactant.[9]

Based on control runs in our earlier study,[4] there was residual acetonitrile in the eluent during the reaction periods of procedures A–C, except when 100% water was used for column equilibration. It was also demonstrated that the greater the relative amount of acetonitrile used in the equilibration solvent, the greater was the amount left in the eluent during the reaction period.[4]

In Table 1 the value of k_ψ varied with the solvent used for column equilibration. In entries 1 and 6, it is proposed that **1** and **2** reacted at site c, with perhaps a small contribution from site a for **1**. On going from entry 1 to 2, $k_\psi^{1(A)}$ decreased. Since the solubility of **1** in the mobile phase in entry 2, containing residual acetonitrile, should be greater than that in the mobile phase in entry 1, an increase in $k_\psi^{1(A)}$ might have been expected as the result of more desorption of **1** from site c into the mobile phase. Apparently, any enhanced desorption was countered by solvent effects on the reactions at sites a and c. On going from entries 2 and 3 to 4, $k_\psi^{1(A)}$ increased. In entry 4, enhanced desorption due to the larger amount of residual acetonitrile has almost overcome the solvent effects. It is unclear why $k_\psi^{1(A)} > k_\psi^{1(B)}$ in entries 2 and 3, whereas $k_\psi^{2(B)} > k_\psi^{2(A)}$ in entries 7–9. With procedure B there should be less acetonitrile in the eluent during the reaction period. Perhaps the opposite trends reflect different blends of solvent effects on desorption and the rates of reactions at sites a and c. In entry 5, a modification of procedure A was used. At $t = 0$, the eluent was not changed to 100% water; instead it was left at 20% acetonitrile, the equilibration solvent, until the gradient elution was begun at $t = 14·5$ min. The lower k_ψ^1 for this entry compared with entry 1 is consistent with the proposed solvents effects.

On going from entry 6 to entries 7–9, $k_\psi^{2(B)}$ increased, opposite to the decreases uniformly obtained for k_ψ^1 on going from entry 1 to entries 2–4. Presumably for **2** there are greater solvent effects on desorption than on the reactions at sites a and c. The decreases in $k_\psi^{2(A)}$ and $k_\psi^{2(B)}$ on going from entry 7 to 8 are unclear but could reflect different blends of solvent effects as suggested above for the trend in $k_\psi^{1(A)}$ and $k_\psi^{1(B)}$ compared with $k_\psi^{2(A)}$ and $k_\psi^{2(B)}$.

The extents of reduction in Tables 1 and 2 are comparable, even though the concentrations of **4** used in the latter are considerably lower than those of **3** in the former. This greater efficiency with **4** derives from at least two related factors. First, since **4** did not elute in the void volume of the column after its injection, it partitioned from the mobile phase onto the polymer surface to a greater extent than did **3**. Therefore, the effective concentrations of **4** at site c in the runs of Table 2 were probably comparable to, or greater than, those of **3** in the runs in Table 1, even though the formal concentrations of **4** were lower. Second, the greater retention of **4** by the column resulted in longer reaction/contact times for **1** (**2**) with **4** than with **3**.

The competition runs in Table 3 were performed under conditions which, based on the results in Tables 1 and 2, maximized the reactivity difference between **1** and **2**. The selectivity with **4** was greater than with **3**.

The retention times for **1** were the same in entries 1 and 2 of Table 1, even though different equilibration solvents were used. This invariance suggests that **1** was immobilized at the same point along the length of the column. Analogous statements pertain to **2** in entries 6–8 in Table 1, and to **1** in entries 10 and 11 in Table 2. The decrease in retention time for **1** on going to entry 3 in Table 1 is consistent with the use of an equilibration solvent containing more acetonitrile. Hence there is a greater fraction of residual acetonitrile in the eluent that carries **1** further down the column before its immobilization. Equivalent statements apply to **2** in entry 9 in Table 1 and entries 13 and 14 in Table 2. Also, note that a single retention time was obtained in each entry in Table 1, even though different flow-rates were used during a 10-min period in procedures A and B after the injection of **3**. This fact suggests that **1** (**2**) remains immobilized during its reaction with **3** (**4**). In Table 1, with acetonitrile–water (40 : 60) the retention times decreased for **1** in entry 3 but not for **2** in entry 7. This difference reflects the greater lipophilicity of the latter. It is reasonable that the retention time of **2** decreased only with a greater fraction of acetonitrile, as in entry 9.

In Table 1, **1** is uniformly more reactive than **2** with a given equilibration solvent, and the greatest reactivity differences were obtained with 100% water and acetonitrile–water (60 : 40) equilibration. In entry 6, $k_{\psi}^{2(A)}$ was not determined, but it is probably less than $k_{\psi}^{2(B)}$, since $k_{\psi}^{2(A)} < k_{\psi}^{2(B)}$ in entries 7–9. Hence with 100% water equilibration, $k_{\downarrow}^{1(A)}/k_{\psi}^{2(A)} \geqslant 5{\cdot}9$, and with acetonitrile–water (60 : 40) equilibration in entries 4 and 8, $k_{\downarrow}^{1(A)}/k_{\psi}^{2(A)} = 6{\cdot}0$. However, these rate constant ratios are minimum values since [**3**] in the 2·00-ml aliquot was greater in the reductions of **2**. Quantitative rate comparisons cannot be made for the reductions of **1** and **2** with **4** in Table 2, but it is qualitatively apparent that the former is more reactive. In entries 10 and 12 with 100% water equilibration, comparable extents of reduction were obtained, but the [**4**] used for **2** was 20 times greater than that for **1**. In the competition runs in Table 3, essentially complete conversions of **1** were obtained with only 50% and 30% reductions of **2** with **3** and **4**, respectively.

The greatest reactivity differences observed between **1** and **2** in the HPLC reactions with borohydride are probably greater than the intrinsic reactivity difference in water by factors of *ca* 3 with **3** and *ca* 6 with **4**. At 25 °C in propan-2-ol, the relative reactivity ratio for acetophenone and **1** in reactions with **3** is 1·00 : 0·56,[7] and the reactivity of **2** should be somewhat, but not much, less than that of **1**. In the hydroxide ion-catalyzed hydrolysis of $RCO_2C_6H_4NO_2$-*p*, another reaction involving rate-determining nucleophilic attack at a carbonyl carbon, the relative reactivity ratio with R = Me, n-C_5H_{11}, n-C_7H_{15} and n-C_9H_{19} was 1·00 : 0·53 : 0·55 : 0·23.[10] The greater reactivity of **1** under a given set of HPLC reaction conditions probably derives from its greater propensity to desorb from the polymer surface with a resultant greater contribution from reaction at site a in comparison with that at site c. A reactivity difference between alkyl phenyl ketones in reduction by borohydride has also been obtained in a surfactant-based organized medium. In a water-in-oil microemulsion containing **3**, the reactivity ratio for **1** and octadecanophenone was 1·0 : 0·056.[11] This result was attributed to a difference in the partitioning of the two ketones between the oil pseudo-phase and the interphase, the reaction site.

In summary, it has been shown that a reserved-phase HPLC column can be used as a chemical reactor in real time (i.e. with continuous eluent flow) for the reduction of ketones to alcohols by borohydride. In these reactions a lower concentration of **4** than of **3** was needed to effect the same extent of reduction, and modest substrate selectivity was obtained for compounds with comparable intrinsic reactivities but different relative hydrophilic/lipophilic characters.

EXPERIMENTAL

General procedures and materials. The HPLC reactions were performed on a 15 cm × 4·1 mm i.d. stainless-steel column packed with 10-μm poly(styrene–divinylbenzene) (PRP-1) from Hamilton. The characteristics of the column have been reported.[5] A Beckman Model 344 gradient liquid chromatograph, an Altex Model 210 injector fitted with a 2·00-ml sample loop and a Beckman Model 165 variable-wavelength detector (254 nm) were used. A column inlet filter (2 mm) was inserted between the injector and column, and a back-pressure regulator was attached to the detector outflow. The pump pressure did not exceed 2000 psi. The PRP-1 column was washed with 2·0 ml of 2% hydrochloric acid after each run. Quantitations

were performed on a Hewlett-Packard Model 3390A reporting integrator. HPLC-grade water and acetonitrile (J. T. Baker) were used. Compounds **1**, **3** and **4** were used as received (Aldrich); **2** (Aldrich) was purified by HPLC on a 25 cm × 10 mm i.d. column of 7-μm LiChrosorb RP-18 (EM Science) with 100% acetonitrile as eluent.

HPLC kinetic measurements. Reactions were performed at room temperature (23 ± 1 °C) with the procedures given in the text. The extent of reaction was determined by comparison of the peak area for unreacted ketone with that for ketone in a blank.[6] Rate constants were obtained by least-squares analysis. The product alcohols, 1-phenylpropan-1-ol and 1-phenyloctan-1-ol, were identified by comparison with the retention times of authentic materials.[12] Even though the volume of the aliquot of **3** will increase as it moves through the column owing to dilution by the eluent, the initial volume was used in calculations. It is likely, at least for runs where little or no acetonitrile was used in the equilibration solvent, that **1** (**2**) was absorbed by the polymer at or near the head of the column, where minimal dilution of the aliquot has occurred. The volume of the line between the injector and the column inlet was 0·02 ml.

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