chloromethane/benzene, 1:1), followed by preparative TLC (silica gel, ethyl acetate), 6%, mp 220–225 °C. ^{1}H NMR: δ 2.80 (3 H, d, J_{H-H} = 4.7 Hz, $NHCH_3$), 6.00 (1 H, br s, NH), 6.60–7.40 (12 H, m, 3 × C_6H_4), 11.30 (2 H, br s, 2 × OH). ^{31}P NMR: δ 49.6. MS, *m/e* 339 (M^+).

***N*,*N*′-Dimethyl-*N*,*N*′-diphenyl(2-hydroxyphenyl)phosphonic diamide (3a)**: purified by column chromatography (silica gel, ether/petroleum ether, 1:1), 51%, mp 122 °C. ^{1}H NMR: δ 3.08 (6 H, d, J_{P-H} = 9.4 Hz, 2 × NCH_3), 6.70–8.40 (14 H, m, 2 × C_6H_5, C_6H_4), 11.20 (1 H, br s, OH). ^{31}P NMR: δ 26.0. MS, *m/e* 352 (M^+). Anal. Found: C, 68.0; H, 5.7; N, 8.2.

***N*-Methyl-*N*-phenyl(2-hydroxyphenyl)[2-(methylamino)phenyl]phosphinic amide (3b)**: purified by column chromatography (silica gel, ether/petroleum ether, 1:1) followed by crystallization from ether/petroleum ether (1:1), 46%, mp 126 °C. ^{1}H NMR: δ 2.70 (3 H, d, J_{H-H} = 5.0 Hz, $NHCH_3$), 3.10 (3 H, d, J_{P-H} = 9.9 Hz, $PNCH_3$), 6.21 (1 H, m, NH), 6.50–7.30 (13 H, m, 2 × C_6H_4, C_6H_5), 11.20 (1 H, s, OH). ^{31}P NMR: δ 41.0. MS, *m/e* 352 (M^+). Anal. Found: C, 68.1; H, 5.7; N, 8.2.

(2-Hydroxyphenyl)bis[(*N*-methylamino)phenyl]phosphine oxide (3c): purified by crystallization from ether/petroleum ether (1:1), 25%, mp 246–247 °C. ^{1}H NMR: δ 2.80 (6 H, d, J_{H-H} = 4 Hz, 2 × $NHCH_3$), 6.30 (2 H, br s, 2 × NH), 6.50–7.50 (12 H, m, 3 × C_6H_4), 10.50 (1 H, br s, OH). ^{31}P NMR: δ 48.5. MS, *m/e* 352 (M^+). Anal. Found: C, 68.0; H, 6.0; N, 8.0.

Acknowledgment. We thank the C.S.I.R., University of Cape Town, and University of Pretoria for financial support.

Supplementary Material Available: ^{13}C NMR spectroscopic data of substrates **2** and **3** and their rearrangement products (Table S-I) (2 pages). Ordering information is given on any current masthead page.

Selectivity in the Base-Catalyzed Hydrolysis of *p*-Nitrophenyl Esters within a Reversed-Phase Liquid Chromatography Column

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The $^-$OH-catalyzed hydrolyses of *p*-nitrophenyl acetate (**1**) and hexanoate (**2**) were performed with excess $^-$OH on a reversed-phase liquid chromatography column of macroporous 10-μm poly(styrene–divinylbenzene) under HPLC conditions to give pseudo-first-order rate constants k_ψ. The maximum value of k_ψ^1/k_ψ^2 was ≥25, and the reactivity difference was attributed to different rates of desorption of **1** and **2** from the polymer surface into the mobile phase, where $^-$OH was localized. The results demonstrated that a polymer-based, reversed-phase HPLC column can impart selectivity to the reactions of an ionic, inorganic reagent with neutral, organic substrates that have comparable intrinsic reactivities but different relative hydrophilic/lipophilic characters.

Reversed-phase high-performance liquid chromatography (HPLC) columns are used routinely in analytical and preparative separations. However, they have been employed only infrequently as reaction media.[1] Recently, we reported a study[2] of the aromatic chlorination of a series of alkyl phenyl ethers by chlorine water on a reversed-phase column of an alkylsilane-bonded silica; substrate and regioselectivity were obtained. Herein, we report a study of the $^-$OH-catalyzed hydrolyses of *p*-nitrophenyl acetate (**1**) and hexanoate (**2**) to *p*-nitrophenoxide and acetate/hexanoate on a 15 cm × 4.1 mm (i.d.) column of macroporous 10-μm poly(styrene–divinylbenzene) (PRP-1)[3] under HPLC conditions.

The HPLC reaction procedure for an individual ester, summarized in Figure 1, is as follows. First, at 23 ± 1 °C the column was equilibrated with a MeCN–H_2O mixture or H_2O. Then, at time (t) = 0, 5.0 μL of 0.030 M **1** (**2**) in MeCN was injected, and the eluant at a flow rate of 0.5 mL/min was changed to 100% H_2O, if necessary, to ensure immobilization of **1** (**2**) within the column by its sorption to the polymer. At t = 13 min, 2.0 mL of aqueous 0.50 M NaOH was injected, and the flow rate was either left at 0.5 mL/min or changed to a value between 0.30 and 4.0 mL/min. At t = 20 min, the flow rate was returned to 0.5 mL/min, and the MeCN content of the eluant was increased linearly to 60% (v/v) during 6 min for **1** or to 100% during 10 min for **2**, in order to elute unreacted ester. The same procedure was used for competition runs, except that at t = 0, 5.0 μL of a MeCN solution 0.015 M each in **1** and **2** was injected, and at t = 20 min the MeCN content was increased to 100% MeCN during 15 min. With these procedures, *p*-nitrophenoxide eluted first, followed by

Table I. Individual Hydrolyses of 1 and 2[a]

entry	substrate	equilibration solvent (v/v)	retention time of 1/2, min[b]	10^3k_ψ, s^{-1}[c]
1	1	H_2O	45.6	5.0 ± 0.3
2	1	10:90 MeCN–H_2O	45.3	4.3 ± 0.3
3	1	25:75 MeCN–H_2O	45.4	4.0 ± 0.3
4	1	40:60 MeCN–H_2O	41.7	11 ± 0.6
5	1	50:50 MeCN–H_2O	40.8	16 ± 0.8
6[d]	1	10:90 MeCN–H_2O	31.5	12 ± 0.6
7[d]	1	50:50 MeCN–H_2O	56.5	4.9 ± 0.3
8	2	H_2O	44.7	2.0 ± 0.2
9	2	25:75 MeCN–H_2O	44.5	1.4 ± 0.2
10	2	40:60 MeCN–H_2O	44.2	0.4 ± 0.1
11	2	50:50 MeCN–H_2O	44.4	0.4 ± 0.1
12	2	70:30 MeCN–H_2O	42.8	0.7 ± 0.1
13	2	80:20 MeCN–H_2O	40.7	0.9 ± 0.1

[a] The procedure of Figure 1 was used unless noted otherwise. [b] For each entry, the value represents the average of the retention times from t = 0 for the separate runs in the kinetic determination; average deviation 0.9 min for entry 6 and ≤0.3 min for the others. [c] Averages of duplicate determinations. [d] A modification of the program of Figure 1 was used; see the text for details.

(1) For examples, see: (a) Bolme, M. W.; Langer, S. H. *J. Phys. Chem.* **1983**, *87*, 3363. (b) Chu, A. H. T.; Langer, S. H. *Anal. Chem.* **1985**, *57*, 2197. (c) Tanaka, N.; Hosoya, K.; Iwaguchi, K.; Araki, M. *J. Am. Chem. Soc.* **1984**, *106*, 3057. (d) Xie, K. H.; Colgan, S.; Krull, I. S. *J. Liq. Chromatogr.* **1983**, *6*, 125 and references therein.

(2) Jaeger, D. A.; Clennan, M. W.; Leyden, D. E.; Murthy, R. S. S. *Tetrahedron Lett.* **1987**, *28*, 4805.

(3) Lee, D. P.; Kindsvater, J. H. *Anal. Chem.* **1980**, *52*, 2425.

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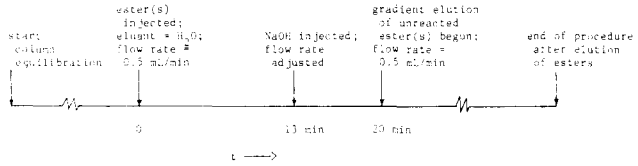

Figure 1. Summary of the HPLC reaction procedure.

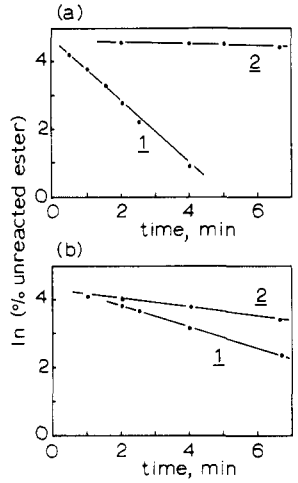

Figure 2. Pseudo-first-order plots of ln (% unreacted ester) vs reaction time for individual runs of 1 and 2 with different column equilibrations: (a) 50:50 MeCN–H_2O; (b) 100% H_2O.

Table II. Competitive Hydrolyses of 1 and 2

entry	equilibration solvent (v/v)	retention times, min[a] 1	2	10^3k_ψ, s^{-1} [b] 1	2
14	H_2O	44.9	49.7	4.0 ± 0.3	1.1 ± 0.2
15	50:50 MeCN–H_2O	41.2	49.8	13 ± 0.6	0.5 ± 0.1

[a] See footnote *b* of Table I; average deviation ≤0.2 min. [b] Averages of duplicate determinations.

unreacted 1 and/or 2, as determined by a calibrated UV detector (254 nm) attached to the column outlet. Acetate and hexanoate were not detectable.

The kinetics of the hydrolyses of 1 and 2 within the column were studied as a function of the eluant composition employed for column equilibration and were determined using adaptations of methods developed by Langer and co-workers[1a,b] and Bentley and Gream.[4] The use of different flow rates for the 7-min period from t = 13 to 20 min gave different contact/reaction times for an ester with the 2.0-mL aliquot of aqueous NaOH. Thus, flow rates of 0.30 and 4.0 mL/min correspond to reaction times of 6.7 and 0.5 min, respectively. Plots of ln (% unreacted ester) vs reaction time were uniformly linear and yielded observed pseudo-first-order rate constants, k_ψ. Two representative plots are illustrated in Figure 2, and all of the results are summarized in Tables I and II.

The second-order rate constants for the $^-$OH-catalyzed hydrolyses of 1 and 2 at 25 °C in H_2O containing 0.64 M MeCN are known,[5] and at [$^-$OH] = 0.50 M correspond to k_ψ's of 7.1 and 3.8 s^{-1}, respectively. The largest k_ψ's for 1 and 2 in the present study are 16 × 10^{-3} s^{-1} (entry 5) and 2.0 × 10^{-3} s^{-1} (entry 8), respectively, which are 444 and 1880 times less than those under homogeneous conditions.

The partitioning of an ester between the polymer phase and a mobile phase rich in H_2O overwhelmingly favors the former. Thus, an ester is effectively immobilized within the column during its reaction with an aliquot of aqueous

(4) Bentley, T. W.; Gream, G. E. *J. Org. Chem.* **1985**, *50*, 1776.
(5) Guthrie, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 897.

Table III. Analyses of Eluant in Control Runs

equilibration solvent	% vol MeCN in eluant[a,b] 16 → 18 min	18 → 21 min
10:90 MeCN–H_2O	2.9	1.2
25:75 MeCN–H_2O	6.1	1.8
50:50 MeCN–H_2O	8.2	2.1
80:20 MeCN–H_2O	9.1	2.2

[a] The sampling times are with respect to the HPLC reaction procedure of Figure 1. [b] Values are ±5%.

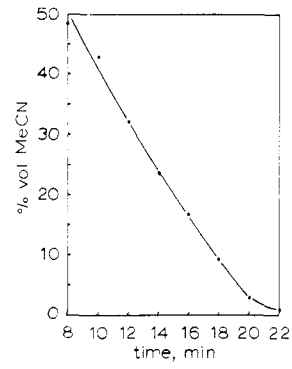

Figure 3. MeCN contents of 1-mL eluant samples collected at flow rate = 0.5 mL/min from the column equilibrated with 50:50 (v/v) MeCN–H_2O as a function of time in the reaction procedure of Figure 1. The indicated times represent the midpoints of the 2-min collection periods.

NaOH. A priori, there are four possible reaction sites for an ester: (a) mobile phase outside the polymer beads; (b) liquid phase inside the pores of the beads; (c) liquid–polymer interface on the pore walls; (d) the bead interior. However, site d is not a reasonable possibility because $^-$OH is not readily extracted into organic media, even with lipophilic cations.[6,7] Furthermore, it is likely that little, if any, ester resides at site d.[8]

The reaction of ester sorbed at site c must be preceded first by the transport of $^-$OH from the mobile phase into the pores and then by its mass transfer from the liquid phase to the pore walls. Since pseudo-first-order kinetics were uniformly observed, the rates of both processes at all of the flow rates used in a given kinetic measurement must be greater than the intrinsic rate of reaction at site c. The reaction of ester at site b must be preceded by its desorption from the pore walls into the liquid phase. In view of the above comparisons of k_ψ, the rate of desorption is likely less than the intrinsic rate of reaction at site b. Furthermore, the observation of pseudo-first-order kinetics dictates that the rate of transport of $^-$OH into the pores at each flow rate must be greater than the rate of desorption. In the context of this model, reaction at site a cannot be readily distinguished from that at site b, and only the former is mentioned specifically in the following discussion. Thus, overall, a given hydrolysis reaction occurs at site a after desorption and/or at site c.[7] 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]

(6) Ford, W. T.; Tomoi, M. In *Advances in Polymer Science*; Springer-Verlag: New York, 1984; Vol. 55, p 53.
(7) This discussion is an adaptation of that by Tomoi and Ford for polymer-supported catalysis (Tomoi, M.; Ford, W. T. *J. Am. Chem. Soc.* **1981**, *103*, 3821 and references therein).
(8) The properties of PRP-1 and XAD-2 (Rohm and Haas) are qualitatively similar.[3] For a wide variety of organic solvents, XAD-2 takes up about the same volume per gram of dry resin (Wilks, A. D.; Pietrzyk, D. J. *Anal. Chem.* **1972**, *44*, 676). This near constancy indicates that solvent goes largely into the macropores and not into the polymer network. Thus, XAD-2 does not swell much in any solvent.

The presence of residual MeCN in the eluant during the reaction period after MeCN–H_2O equilibration was demonstrated by control runs utilizing the program of Figure 1 with the following modifications: at t = 0, no ester was injected; at t = 13 min, 2.0 mL of H_2O rather than 0.5 M NaOH was injected at flow rate = 0.5 mL/min; at t = 20 min, no MeCN–H_2O gradient was begun. Over various periods, samples of eluant were collected and analyzed by gas-liquid chromatography (GLC) for their MeCN contents. The results are summarized in Table III and Figure 3. The former indicates that the greater the amount of MeCN used in the equilibration, the greater the amount left in the eluant during the sampling periods. The latter indicates that the residual MeCN content from a column equilibrated with 50:50 (v/v) MeCN–H_2O decreases to about zero at t = 22 min, i.e., after 11 mL (8.5 void volumes) of H_2O have passed through the column after equilibration. Without dilution, a 2.0-mL aliquot of aqueous NaOH injected at t = 13 min will elute from t = 15.6 → 19.6 min at flow rate = 0.5 mL/min, and with dilution, the elution period will be extended. Thus, the analyses of Table III fairly represent the MeCN contents of the mobile phase during the reaction period at flow rate = 0.5 mL/min, and it is assumed that similar results would be obtained at other flow rates.

The value of k_ψ varied with the solvent used for column equilibration. In entries 1 and 8, it is proposed that **1** and **2** reacted almost exclusively at site c. In entries 2 and 3, k_ψ^1 decreased slightly relative to entry 1. Since the solubilities of **1** in the mobile phases of entries 2 and 3, containing residual MeCN, should be greater than that in the mobile phase of entry 1, increases in k_ψ^1 might have been expected as the result of greater rates of desorption of **1** from the polymer surface into the mobile phase. However, any enhanced desorption was countered by solvent effects on the reactions at sites a and c; the rate of $^-$OH-catalyzed hydrolysis of **1** is less in MeCN–H_2O than in H_2O.[10] Comparable explanations account for the changes in k_ψ^2 on going from entry 8 to entries 9–13.

The larger values of k_ψ^1 obtained in entries 4 and 5 compared to entries 1–3 reflect increased contributions from reaction in the mobile phase due to the greater amounts of residual MeCN. This statement is supported by the results of entries 6 and 7, which used modified versions of the program of Figure 1. In entry 6, **1** was injected at t = 0 onto the column equilibrated with 10% MeCN–H_2O without a change of the eluant to 100% H_2O. At t = 6 min, the NaOH aliquot was injected, and the flow rate was adjusted as in the standard program. At t = 13 min, the flow rate was returned to 0.5 mL/min, and the MeCN content of the eluant was increased linearly to 60% during 6 min in order to elute unreacted **1**. In entry 7, a 30-min, rather than a 13-min, 100% H_2O wash starting at t = 0 was employed, and all other events of the standard program were displaced by 17 min. On the basis of the results of Figure 3, the extended H_2O wash totally eliminated residual MeCN from the mobile phase before the reaction. Note that the values of k_ψ in entries 6 and 7 are comparable to those in entries 4 and 5 and entries 1–3, respectively. Thus, the presence of MeCN in the mobile phase has a marked effect on k_ψ.

The retention times of Table I are of interest. The value for **1** is essentially the same in entries 1–3, even though different equilibration solvents were used. This invariance suggests immobilization of **1** at the same point along the length of the column. Analogous statements apply to **2** in entries 8–11. The decreases in retention time for **1** and **2** on going to entries 4 and 5 and to entries 12 and 13, respectively, are consistent with greater amounts of residual MeCN in the eluant, which carry **1** (**2**) farther down the column before immobilization. Also, note that a single retention time was obtained in each entry, even though different flow rates were used from t = 13 → 20 min in the individual runs of a kinetic determination. This fact strongly suggests that desorption is the rate-limiting factor for reaction at site a.

Table II contains the results of competition runs. Three of the four k_ψ values were less than the corresponding values in the individual runs of Table I (entry 14 vs 1 and 8; entry 15 vs 5 and 11). The differences perhaps reflect a concentration-dependent distribution of **1**/**2** among the sorption sites on the pore walls.

In Tables I and II, **1** is uniformly more reactive than **2** under the same conditions. With 100% H_2O equilibration, which presumably results in near exclusive reaction at site c, the values of k_ψ^1/k_ψ^2 are 2.5 (entries 1 and 8) and 3.6 (entry 14). Both are similar to the value of 1.9 observed in homogeneous aqueous solution.[5] The maximum value of k_ψ^1/k_ψ^2 in Table I is 46 (entries 5 and 11) and in Table II is 25 (entry 16) with 50:50 MeCN–H_2O equilibration. Here the substantially greater reactivity of **1** results from its greater rate of desorption from the polymer surface into the mobile phase. Reactivity differences between **1** and **2** have also been obtained in surfactant-based organized media. In a reversed micellar system of bis(2-ethylhexyl) sodium sulfosuccinate (Aerosol OT) in octane containing water pools, k_ψ^1/k_ψ^2 = 33 for imidazole-catalyzed hydrolysis at 25 °C.[11] This result was attributed to a difference in the partitioning of **1** and **2** between the octane pseudophase and the water pools, wherein imidazole was localized. In aqueous micellar sodium dodecyl sulfate and hexadecyltrimethylammonium bromide, k_ψ^1/k_ψ^2 = 33 (maximum) and 0.72, respectively, for $^-$OH-catalyzed hydrolysis at 25 °C.[12] The interpretation of these results involved the partitioning of substrate and $^-$OH between the micellar and aqueous pseudophases. In another system involving multiple phases, selectivity was found in anhydride formation from PhCOCl and carboxylate ions of different hydrophilic/lipophilic characters in mixtures of CH_2Cl_2–H_2O.[13]

In summary, it has been shown that a polymer-based reversed-phase HPLC column can impart selectivity to the reactions of an ionic, inorganic reagent with neutral, organic substrates that have comparable intrinsic reactivities but different relative hydrophilic/lipophilic characters.

Experimental Section

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, Hamilton). PRP-1 is stable from pH 1 to 13 and has the following characteristics: specific surface area = 415 m^2/g; average pore diameter = 75 Å; pore volume = 0.79 cm^3/g. The void volume of the column was 1.30 mL.[3] A Beckman Model 332 gradient liquid chromatograph, an Altex Model 210 injector fitted with a 2.00-mL sample loop, and a Beckman Model 153 UV detector (254 nm) were used. A column inlet filter (2 μm) was inserted between the injector and column, and a back-pressure regulator

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(10) Baranskii, V. A.; Eliseeva, G. D.; Zhdankovich, E. L.; Voronkov, M. G. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1984**, 2476.
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(13) Fife, W. K.; Xin, Y. *J. Am. Chem. Soc.* **1987**, *109*, 1278.

was attached to the outflow of the detector. The GLC analyses were carried out at 85 °C with He as the carrier gas on a 6 ft × $^1/_8$ in. aluminum column packed with 50–80 mesh Porapak Q (Waters) installed in a Varian Aerograph Model 2700 chromatograph (thermal conductivity detection). Both HPLC and GLC quantitations were performed on a Hewlett-Packard Model 3390A reporting integrator. HPLC grade H_2O and MeCN (J. T. Baker) were used for all reactions. 1 (Aldrich) was recrystallized from EtOH, mp 76–77 °C (lit.[14a] mp 79.5–80 °C), and 2 was prepared by the literature procedure, bp 140–145 °C (ca. 20 mmHg) [lit.[14b] bp 174–175 °C (10 mmHg)].

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 ester with that for ester in a blank.[4] Rate constants were obtained with least-squares analysis as described in the text, and the limits of error were estimated with the use of the Student's t test.[15] Even though the volume of the NaOH aliquot will increase as it moves through the column due to dilution by the eluant, the initial volume was used in calculations. It is likely, at least for runs where little or no MeCN was used in the equilibration, that ester was sorbed 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 column inlet was 0.02 mL. The results are summarized in Tables I and II. Comparable results for selected entries were obtained on a second, identical column.

The pump pressure did not exceed 2000 psi. The activation volume for the $^-$OH-catalyzed hydrolysis of 1 in H_2O at 24.5 °C is −3 cm^3/mol.[16] At 2000 psi, k_ψ in H_2O would experience about a 2% increase compared to atmospheric pressure. Thus, it is unlikely that the lesser reactivity for 1 under the HPLC reaction conditions as compared to homogeneous conditions[5] resulted from the elevated pressure, and the same is assumed for 2.

GLC Eluant Analyses. The procedures given in the text were used. The retention times for H_2O and MeCN were 1.0 and 5.8 min, respectively. The MeCN content was calculated from the peak area ratios for the sample and 5:95 (v/v) MeCN–H_2O. The results are summarized in Table III and Figure 3. With literature data[17] the pseudo-first-order rate constant for hydrolysis of MeCN in 0.5 M NaOH at 25 °C is calculated to be 7.7×10^{-9} s^{-1}. Thus, MeCN was effectively inert during the reaction procedure.

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Conformation and Internal Mobility of 10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene Derivatives in Solution. Conformational Analysis of Highly Flexible Structures

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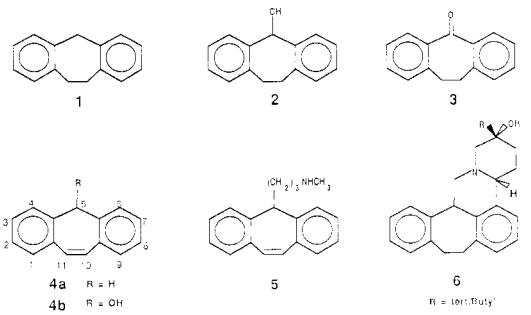
The ground-state conformations and internal mobilities of 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (**1**), of the 5-hydroxy derivative **2**, and of 10,11-dihydrodibenzo[*a*,*d*]cyclohepten-5-one (**3**) as well as of their mono tricarbonylchromium complexes **1m–3m** are analyzed. It is shown that with use of the lanthanide induced shift method, together with empirical force-field calculations (**1–3**) and X-ray analysis (**1m–3m**), the conformations and interconversion modes of these highly flexible structures (with interconversion barriers less than 29 kJ mol^{-1}) can be analyzed. In solution, **2** and **3** adopt at room temperature a conformation similar to that of **1** and **3**, respectively, in the solid state. π-Complexation with tricarbonylchromium does not change the structure of the tricyclic system to a very significant degree, although the $Cr(CO)_3$ unit is located either on the convex (**1**, **3**) or on the concave (**2**) face of the ligand. In solution, a predominant conformation of **2m** with the tricarbonylchromium unit on the concave face is found.

This paper reports the results of a conformational analysis whose aim was to study the conformations of **1–3** in solution and to quantify the effects induced by π-complexation on the ground-state conformations and internal mobility of the tricyclic cycloheptene system. 5*H*-Dibenzo[*a*,*d*]cycloheptene (**4a**) and 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (**1**) are common substructures of a variety of pharmacologically and clinically active compounds[1] such as protryptyline (**5**) or butaclamol (**6**). In order to investigate structure–activity relationships, systematic conformational analyses have been previously



reported using X-ray spectroscopy,[2] quantum mechanical calculations,[1b] and other methods.[3] Models,[4] including

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