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Guanidine–Guanidinium Cooperation in Bifunctional Artificial Phosphodiesterases Based on Diphenylmethane Spacers; *gem*-Dialkyl Effect on Catalytic Efficiency

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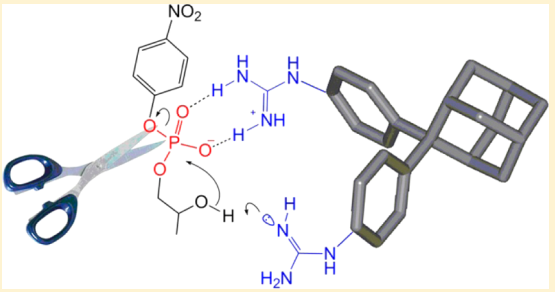
Supporting Information

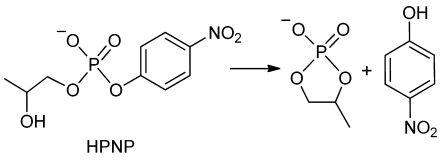
ABSTRACT: Diphenylmethane derivatives **1**–**3**, decorated with two guanidine units, are effective catalysts of HPNP transesterification. Substitution of the methylene group of the parent diphenylmethane spacer with cyclohexylidene and adamantylidene moieties enhances catalytic efficency, with *gem*-dialkyl effect accelerations of 4.5 and 9.1, respectively. Activation parameters and DFT calculations of the rotational barriers around the C–Ar bonds indicate that a major contribution to the driving force for enhanced catalysis is entropic in nature.



In the past two decades simple, nonpeptidic molecules that mimic structural and functional aspects of natural enzymes have received considerable attention.[1,2] The extreme reluctance of phosphodiester bonds to undergo hydrolytic cleavage has challenged many research groups to design and synthesize artificial catalysts capable of cleaving DNA, RNA, and their model compounds.[3−6]

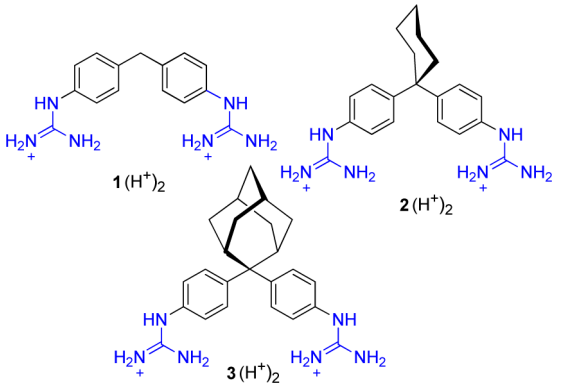
In the majority of cases, these artificial catalysts contain metal cations as catalytically active components, notably copper(II) and zinc(II).[3,4g] Less numerous are examples of catalysts devoid of metal centers.[3e,4−6] In a recent study,[6] the high catalytic efficiency of diguanidinocalix[4]arenes in the transesterification of 2-hydroxypropyl *p*-nitrophenyl phosphate (HPNP) was reported. It was shown that a necessary requisite for catalysis is the simultaneous presence, on the same molecular framework, of a neutral guanidine acting as a general base and a protonated guanidine acting as an electrophilic activator. In these bifunctional catalysts, as in many other catalysts of the same kind, an important role is played by the molecular scaffold connecting the catalytic groups. An efficient scaffold should keep the active functions at the proper distance as a result of a good compromise between preorganization and flexibility. Flexibility ensures good adaptability of the bifunctional catalyst to the altered substrate in the transition state, but the resulting entropic cost may greatly reduce catalytic efficiency.

With these ideas in mind, we have synthesized and investigated the catalytic activity of bifunctional catalysts **1**–**3** in the transesterification of HPNP (eq 1). Here we show that the efficiency of bifunctional catalysts based on diphenylmethane spacers is comparable to those of the more structurally elaborated *cone* 1,2- and 1,3-diguanidinocalix[4]arenes.[6] We also show that catalytic activity can be significantly improved when the methylene group in **1** is replaced by bulkier



HPNP (1)

cyclohexylidene or adamantylidene moieties as a manifestation of the *gem*-dialkyl effect[7,8] in supramolecular catalysis.



Guanidinylation of the appropriate 4,4′-diaminodiphenyl derivative **4** was carried out with bis-Boc-thiourea and $HgCl_2$, followed by deprotection with hydrochloric acid in dioxane (Scheme 1). Whereas 4,4′-diaminodiphenylmethane (**4a**) was comercially available, the required cyclohexane and adamantane derivatives (**4b**[9] and **4c**,[10] respectively) were prepared according to slightly modified literature procedures.

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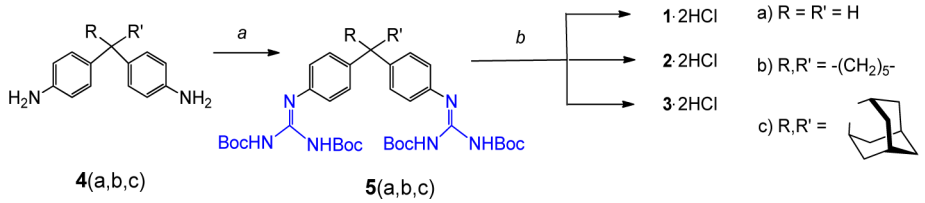
Scheme 1. Synthesis of Diguanidinylated Diphenylmethanes 1−3[a]



[a]Reagents and conditions: (a) BocNHC(S)NHBoc, $HgCl_2$, Et_3N, DMF; (b) 0.5 M HCl, 1,4-dioxane.

Determination of acidity constants of $\mathbf{1}(H^+)_2$−$\mathbf{3}(H^+)_2$ is a prerequisite for a meaningful investigation of their catalytic properties. A mixture of DMSO/H_2O 80:20 (v/v), hereafter referred to as 80% DMSO, was used as reaction medium in titration experiments. This mixture is well-known to be suitable for potentiometric measurements and for investigation of hydrolytic reactions of phosphodiesters[3o,5,6] and for dephosphorylation of ATP to ADP.[11] The pK_w for water autoprotolysis in 80% DMSO rises to 18.4,[12] and this implies that the pH value of a neutral solution is 9.2.

The chloride salts of diprotonated bases (2.0 mM) were potentiometrically titrated with a standard solution of Me_4NOH in 80% DMSO in the presence of 10 mM Me_4NClO_4. Analysis of the titration plots (Figures S1−S3 in Supporting Information) afforded the pK values listed in Table 1.

Table 1. Acidity Constants of Hydrochlorides of 1−3 in 80% DMSO, 25 °C[a]

	pK_1	pK_2
1·2HCl	9.13 ± 0.08	11.62 ± 0.08
2·2HCl	8.92 ± 0.07	11.54 ± 0.07
3·2HCl	8.78 ± 0.06	11.51 ± 0.08

[a]pK_i data from potentiometric titrations carried out on 2.0 mM substrate solutions in the presence of 10 mM Me_4NClO_4. Reported errors are standard deviations σ.

The catalytic activity of compounds **1**−**3** in the transesterification of HPNP was investigated under the same conditions used for the potentiometric titrations, namely, 80% DMSO containing 10 mM Me_4ClO_4 at 25.0 °C. In a first set of rate measurements, solutions of diprotonated catalysts were half-neutralized with 1 molar equiv of Me_4NOH. The resulting buffer solutions, in which the predominant species is the monoprotonated form of the catalyst, were used for the transesterification of HPNP. The results of the kinetic experiments are graphically shown in Figure 1 as plots of pseudo-first-order rate constants (k_{obs}, s^{-1}) for the spectrophotometrically determined liberation of *p*-nitrophenol versus total catalyst concentration (C_{cat}). Data points could be fitted in all cases to straight lines with zero intercept, showing that (i) the catalyst works under subsaturating conditions, i.e., binding of HPNP to the catalyst is in all cases too low to affect the kinetics in the investigated concentration range, and (ii) contributions from background hydrolysis to the overall rate are, as expected,[13] negligibly small.

The slopes of the straight lines are second -order rate constants (k_2, Table 2) based on the total catalyst concentration (C_{cat}).[14] In a second set of kinetic experiments, the catalytic efficiency was systematically investigated over a wide pH range. Partial neutralization of 2.0 mM solutions of

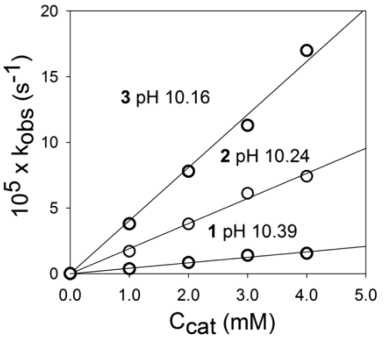


Figure 1. Plot of pseudo-first-order rate constants k_{obs} for the liberation of *p*-nitrophenol from 0.10 mM HPNP (80% DMSO, 25 °C, 10 mM Me_4NClO_4) catalyzed by **1**−**3** in 80% DMSO versus total catalyst concentration. The second-order rate constants k_2 in Table 1 were calculated from the slopes of the straight lines.

Table 2. Kinetic Parameters for the Transesterification of HPNP Catalyzed by 1−3 in 80% DMSO, 25°C[a]

	$10^2 \times k_2$ (s^{-1} M^{-1})[b]	$10^2 \times k_{cat}$ (s^{-1} M^{-1})[c]	k_{rel}[d]	EM (M)[e]
1·2HCl	0.42 ± 0.02	0.45 ± 0.03	1	0.45
2·2HCl	1.91 ± 0.06	2.04 ± 0.06	4.5	2.0
3·2HCl	4.04 ± 0.12	4.09 ± 0.08	9.1	4.1

[a]2.0 mM precatalyst, 10 mM Me_4NClO_4, reported errors are standard deviations σ. [b]Calculated from the slopes of the straight lines in Figure 1. [c]From best fit to eq 2 of rate data in Figure 2. [d]$k_{rel} = k_{cat}/k_{cat}^{1H+}$. [e]EM = k_{cat}/k_{inter}, calculated using $k_{inter} = (1.0 \pm 0.2) \times 10^{-2}$ M^{-2} s^{-1} from ref 6.

diprotonated catalyst with calculated amounts of Me_4NOH afforded a number of buffer solutions with pH values in the range of around 8−12, which were used for catalytic rate measurements. Pseudo-first-order rate constants (k_{obs}) for the transesterification of HPNP, corrected for background contributions[13] whenever appropriate (pH > 11), are shown in Figure 2. The bell-shaped pH−rate profiles could be fitted to a good precision to eq 2, based on the assumption that the monoprotonated forms of the catalysts (cat·H^+) are the only catalytically active species (eq 3).

$$k_{obs} = \frac{k_{cat}C_{cat}}{\frac{K_2}{[H^+]} + \frac{[H^+]}{K_1} + 1} \quad (2)$$

$$v = k_{cat}[catH^+][HPNP] \quad (3)$$

In eq 2, K_1 and K_2 are the known acidity constants from Table 1, while k_{cat} is the only adjustable parameter in a nonlinear least-squares fitting procedure. The best fit k_{cat} values, listed in Table 2, compare well with the corresponding k_2 values, calculated as the slopes of the straight lines in Figure 1.[15] To sum up, the kinetics fully confirm that compounds **1**−**3** are

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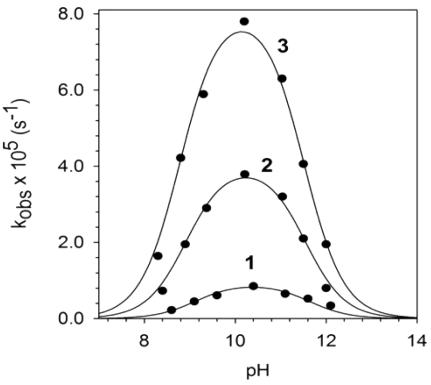

Figure 2. pH−rate profiles for the cleavage of 0.10 mM HPNP catalyzed by 2.0 mM **1**−**3** in 80% DMSO, 25.0 °C, 10 mM Me_4NClO_4. The rate constants measured at pH > 11 were corrected for background hydrolysis ($k_{bg} = 10^{(pH-17.2)}$, see ref 6).

catalytically active only in their monoprotonated forms, in agreement with previous conclusions[6] that bifunctional catalysis arises from the combined action of a neutral guanidine acting as a general base and a protonated guanidine acting as a general acid, as schematically depicted in Figure 3.

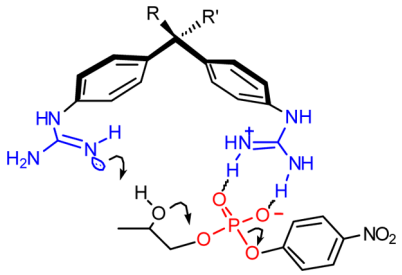

Figure 3. Suggested mechanism of HPNP cleavage catalyzed by $1H^+$−$3H^+$.

Catalytic rate constants and EM values (Table 2) are very similar to those reported for the 1,3- and 1,2-diguanidinocalix[4]arenes under the same conditions,[6] namely, $k_{cat} = 2.3 \times 10^{-2}$ M^{-1} s^{-1} (EM = 2.3 M) and $k_{cat} = 1.1 \times 10^{-2}$ M^{-1} s^{-1} (EM = 1.1 M), respectively, showing that even $1H^+$, despite its structural simplicity, can achieve high levels of catalytic efficiency in the cleavage of HPNP. Bulky substituents enhance the catalytic activity to a significant extent, the adamantane derivative $3H^+$ being nearly an order of magnitude more effective than the parent compound $1H^+$.

It has long been known that alkyl substituents frequently enhance rates and equilibria of processes involving the closing of rings from their noncyclic precursors. For historical reasons the effect is called the "*gem*-dimethyl (-dialkyl) effect" or Thorpe−Ingold effect.[7,8,16] Earlier explanations focused on the formation of small rings, in which the diminution of the internal angle would lead to a spreading apart of the external angle.[16] An additional, more general explanation was put forward by Hammond in terms of restriction of internal rotation caused by alkyl substituents in open chain compounds.[17] Good grounds for supporting Hammond's suggestion were provided a few years later by Allinger and Zalkow in quantitative terms.[18] Analysis of available quantitative data on the hypothetical gas-phase cyclization reactions of alkyl-substituted hexanes to cyclohexanes showed the entropy of formation of alkyl-substituted ring compounds to be in all cases less negative (more favorable) than that of the unsubstituted parent compound, as a consequence of steric hindrance to internal rotation caused by bulky substituents.[19]

To shed light on the origin of rate enhancement caused by bulky substituents, the temperature dependence of catalytic rates was investigated in the temperature range 25−55 °C. Analysis of rate data according to the Eyring equation afforded the activation parameters listed in Table 3 (see Supporting Information for details). Whereas the enthalpy of activation of the reaction of $1H^+$ and $2H^+$ are virtually identical, the corresponding value of the reaction of the adamantane derivative $3H^+$ is slightly larger, but the range of $\Delta H^{\ddagger}$, 1.4 kcal mol^{-1}, is only slightly larger than the sum of statistical errors, 1.1 kcal mol^{-1}. Since the possibility of nonrandom errors cannot be ruled out, it is difficult to say whether the slightly larger value of the adamantane derivative is a real phenomenon, or an experimental artifact. A different situation is observed with the entropy of activation.[20] Here the observed range of $\Delta S^{\ddagger}$, 9.1 cal K^{-1} mol^{-1}, is decidedly larger than the sum of statistical errors, 3.5 cal K^{-1} mol^{-1}. It appears therefore that there is an undeniable tendency for $\Delta S^{\ddagger}$ to become less negative (more favorable) when the catalytic efficiency increases in the order of $1H^+$ < $2H^+$ < $3H^+$. In other words the activation parameters indicate that the origin of rate enhancements caused by alkyl substituents is essentially entropic in nature.

Table 3. Activation Parameters for the Transesterification of HPNP Catalyzed by 1−3[a]

	$\Delta G^{\ddagger}$ (kcal mol^{-1})[b]	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal K^{-1} mol^{-1})
$1H^+$	20.65 ± 0.05	19.3 ± 0.5	−4.6 ± 1.5
$2H^+$	19.80 ± 0.03	19.6 ± 0.4	−0.5 ± 1.2
$3H^+$	19.35 ± 0.03	20.7 ± 0.6	4.5 ± 2.0

[a]See Supporting Information for details. [b]At 25 °C.

This view was strongly corroborated by DFT calculations carried out on simple model compounds with Gaussian 03 package[21] at the B3LYP 6-31g(d) level of theory. As shown in Table 4 an increase in steric bulk causes a marked increase in the height of the rotational barrier around the C−Ar bonds and hence a significant reduction of the entropy of internal rotation S°_{conf}. Although too much emphasis cannot be placed on exact figures, comparison with $\Delta S^{\ddagger}$ data (Table 3) shows that the driving force for enhanced catalysis of $2H^+$ and $3H^+$ relative to $1H^+$ is well commensurate to the reduction of conformational entropy caused by steric hindrance in the reactant state.

Table 4. Barrier Height (V_o)[a] for the Rotation around the C−Ar Bonds and Corresponding Contribution[b] to the Entropy of Internal Rotation in Model Compounds[c]

model compound	V_o (kcal mol^{-1})	S_{conf} per rotor (cal K^{-1} mol^{-1})	S°_{conf} (cal K^{-1} mol^{-1})
diphenylmethane	0.53	7.6	15.2
1,1-diphenylcyclohexane	5.65 (ax)	5.5	12.6
	1.42 (eq)	7.1	
2,2-diphenyladamantane	9.88	4.9	9.8

[a]Calculated by B3LYP 6-31g(d) DFT methods. [b]Calculated using Pitzer treatment of internal rotations. [c]See Supporting Informations for details.

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In conclusion, the data reported in this work show that compounds $1H^+-3H^+$ are effective catalysts of HPNP transesterification. EM values of 0.45−4.0 M indicate a high degree of synergism[22] displayed by neutral and protonated guanidinium units of the bifunctional catalyst in the stabilization of the transition state. The catalytic advantage of the diphenylcyclohexane and diphenyladamantane derivatives over the parent diphenylmethane compound provides, to the best of our knowledge, the first example of the operation of the *gem*-dialkyl effect in supramolecular catalysis as a means of fine-tuning catalytic activity. Activation parameters and DFT calculations suggest that this effect is an essentially entropic phenomenon, in that the bulky cyclohexane and adamantane moieties significantly reduce the conformational mobility around the C−Ar bonds and, consequently, the cost in entropy required to reach the transition state, without reducing the adaptability of the catalyst to the altered HPNP substrate in the transition state.

EXPERIMENTAL SECTION

Instruments and General Methods. NMR spectra were recorded on a 300-MHz spectrometer. Chemical shifts are reported as δ values in ppm from tetramethylsilane added as an internal standard. Mass spectra were performed by an electrospray ionization time-of-flight spectrometer.

Materials. DMSO purged 30 min with argon and mQ water were used in the preparation of 80% DMSO. HPNP was prepared as reported in the literature.[23] Other solvents and reagents were commercially available and used without any further purification.

4,4′-Bis[*N*,*N*′-di(*tert*-butoxycarbonyl)guanidine]diphenylmethane (5a). A stirring solution of 4,4′-diaminodiphenylmethane (495 mg, 2.50 mmol) and bis-Boc-thiourea (1.40 g, 5.07 mmol) in 6 mL of dry DMF (Aldrich, 99.8%) was cooled to 0 °C with an ice bath, and then Et_3N (1.75 mL, 12.6 mmol) and $HgCl_2$ (1.36 g, 5.04 mmol) were added. After 2 h, the reaction was quenched by adding AcOEt (30 mL), and the HgS precipitate was filtered. The solvent was removed, and the residue chromatographed (SiO_2, hexane/AcOEt 10:1). Compound **5a**, obtained as a white solid (648 mg 0.950 mmol, 38% yield), showed the same spectroscopic properties as those reported in the literature.[24]

4,4′-Diguanidinediphenylmethane Bis-hydrochloride (1·2HCl). A solution of compound **5a** (180 mg, 0.264 mmol) in 15 mL of a 1:1 mixture of dioxane and 0.5 M hydrochloric acid was stirred for 2 days at room temperature. Evaporation of the solvent gave compound **1**·2HCl as a white solid (89 mg, 0.251 mmol, 95% yield) that showed the same spectroscopic properties as those reported in the literature.[24]

1,1-Bis(4-aminophenyl)cyclohexane (4b). Excess aniline (10 mL, 110 mmol) was added to a solution of cyclohexanone (3.0 g, 30.6 mmol) in 11 mL of 35% hydrochloric acid, and the mixture was stirred at 150 °C for 48 h. After cooling, the solution was made basic with aqueous NaOH to pH 13, and the oily layer was separated and distilled to remove unreacted aniline. The residue was chromatographed (SiO_2, hexane/AcOEt from 10:1 to 3:1), and compound **4b**, obtained as a pale yellow solid (4.91 g, 18.4 mmol, 60% yield), showed the same spectroscopic properties as those reported in the literature.[9]

1,1-Bis[4-(*N*,*N*′-di(*tert*-butoxycarbonyl)guanidinephenyl)cyclohexane (5b). The reaction was carried out according to the same procedure used for the preparation of compound **5a**, starting from compound **4b** (310 mg, 1.16 mmol) and 2 molar equiv of bis-Boc-thiourea. A pure sample of **5b** was obtained by flash column chromatography (SiO_2, hexane/AcOEt 10:1) as a colorless oil (455 mg, 52% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.63 (br s, 2 H), 10.25 (br s, 2 H), 7.49 (d, 4H, J = 9 Hz), 7.21 (d, 4H, J = 9 Hz), 2.22 (m, 4 H), 1.50 (m, 6H), 1.51 (d, 36 H, J = 9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.4 153.2 145.0 134.0 127.7 121.8 83.6 77.4 45.7 37.1 28.1 28.0 26.3 22.8 14.1. HR ES-MS m/z: $[M + H]^+$ calcd for $C_{40}H_{59}N_6O_8^+$ 751.4394; found 751.4378.

1,1-Bis[4-guanidinephenyl)cyclohexane Bis-hydrochloride (2·HCl). A solution of compound **5b** (210 mg, 0.280 mmol) in 15 mL of a 1:1 mixture of dioxane and 0.5 M hydrochloric acid was stirred for 2 days at room temperature. Evaporation of the solvent gave compound **2**·2HCl as a colorless glassy solid (115 mg, 0.272 mmol, 97% yield). ^{1}H NMR (300 MHz, D_2O): δ 7.45 (d, 4H, J = 9 Hz), 7.18 (d, 4H, J = 9 Hz), 2.28 (m, 4 H), 1.49 (m, 6H). ^{13}C NMR (75 MHz, D_2O): δ 156.9 132.2 129.2 126.5 132.5 46.1 36.7 26.3 23.1 HR ES-MS: m/z calcd for $C_{20}H_{28}N_6Cl^+$ $[M + 2H + Cl]^+$ 387.2064, found 387.2067.

2,2-Bis(4-aminophenyl)adamantane (4c). Aniline hydrochloride (5.1 g, 39 mmol) was added to a solution of 2-adamantanone (2.0 g 13 mmol) in 7 mL of aniline, and the mixture was stirred at 160 °C for 60 h. After cooling, the solution was made basic with aqueous NaOH, and the oily layer was separated and distilled under vacuum to remove unreacted aniline. The crude product was treated with active carbon to remove the dark color and chromatographed (SiO_2, hexane/AcOEt from 10:1 to 3:1). Compound **4c**, obtained as a pale yellow solid (1.78 g, 18.4 mmol, 43% yield), showed the same spectroscopic properties as those reported in the literature.[10]

2,2-Bis[4-(*N*,*N*′-di(*tert*-butoxycarbonyl)guanidinephenyl)-adamantane (5c). The reaction was carried out according to the same procedure used for the preparation of compound **5a**, starting from compound **4c** (210 mg, 0.66 mmol) and 2 molar equiv of bis-Boc-thiourea. A pure sample of **5c** was obtained by flash column chromatography (SiO_2, hexane/AcOEt 20:1) as a colorless oil (517 mg, 46% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.60 (br s, 2H), 10.19 (br s, 2H), 7.45 (d, 9 Hz, 4H), 7.32 (d, 9 Hz, 4H), 3.18 (s, 2H), 2.09−1.97 (m, 4H), 1.83−1.65 (m, 8H), 1.50 (s, 18H), 1.48 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5 153.3 153.2 144.9 133.5 126.2 122.1 83.5 79.5 50.0 37.9 33.2 31.9 28.1 28.0 27.4 HR ES-MS: m/z calcd for $C_{44}H_{63}N_6O_8^+$ $[M + H]^+$ 803.4707, found 803.4720.

1,1-Bis[4-guanidinephenyl)adamantane Bis-hydrochloride (3·HCl). The reaction was carried out according to the same procedure used for the preparation of compound **1** starting from compound **5c** (300 mg 0.280 mmol). Compound **3**·2HCl was obtained as a colorless colorless glassy solid (115 mg, 0.272 mmol, 97% yield). ^{1}H NMR (300 MHz, D_2O): δ 7.55 (d, 9 Hz, 4H), 7.16 (d, 9 Hz, 4H), 3.28 (s, 2H), 1.95−1.55 (m, 8H). δ156.1 148.1 131.2 127.4 126.1 50.6 37.4 32.8 31.3 27.1 HR ES-MS: m/z calcd for $C_{24}H_{31}N_6^+$ $[M + H]^+$ 403.2610, found 403.2615; m/z calcd for $C_{24}H_{32}N_6^{+2}$ $(M + 2H^+)$ 202.1344, found 202.1346.

Potentiometric Titrations. Potentiometric titrations were performed by an automatic titrator equipped with a combined microglass pH electrode. Experimental details and procedure for the electrode calibration were the same as previously reported.[6] Potentiometric titrations were carried out under a nitrogen atmosphere, on 6 mL of 2 mM solutions of the compound, in the presence of 10 mM Me_4NClO_4, (80% DMSO, 25 °C). A 50 mM Me_4NOH solution in 80% DMSO was added to the titration vessel in small increments. Analysis of titration plots was carried out by the program HYPERQUAD 2000.[25]

Kinetic Measurements. Kinetic measurements of HPNP transesterification were carried out by UV−vis monitoring of *p*-nitrophenol liberation at 400 nm on either a double beam or on a diode array spectrophotometer. Rate constants were obtained by an initial rate method, error limits on the order of ±5%. A typical kinetic run is reported in Supporting Information.

Theoretical Calculations. DFT calculations were carried out at the B3LYP/6-31G(d)//B3LYP/6-31G(d) level of theory (GAUSSIAN-03 package). Barriers for the rotation around the C−Ar bonds were determined by difference of the energies, corrected for the zero-point vibrational energy, of the ground state and transition state (opt=ts keyword) for the rotation. Vibrational analysis confirmed all stationary points to be minima (no imaginary frequencies) or first-order saddle points (one imaginary frequency) in the case of transition states of the rotation. The contributions of the internal rotation to entropy were calculated using Pitzer treatment.[26] Further details are reported in Supporting Information.

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■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra, details of the DFT calculations, plots of potentiometric acid−base titrations, and a typical kinetic run. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(13) Rate constants for the background hydrolysis of HPNP are available from a previous investigation, $k_{bg} = 10^{pH-7.20}$ from ref 6. From this equation we calculate $k_{bg} = 0.95 \times 10^{-7}$ s^{-1} at pH 10.16 and $k_{bg} = 1.60 \times 10^{-7}$ s^{-1} at pH 10.39. These values show that in the given pH range background contributions to the liberation of p-nitrophenol are 2 to 3 orders of magnitude lower than catalytic rates.

(14) As noted by a reviewer, the acceleration effect of alkyl substituents is somewhat larger than actually measured, because the basicity of the guanidine moiety acting as a general base decreases in the order **1** > **2** > **3**. Combination of ΔpK_1 values of hydrochlorides of **2** and **3** relative to **1** (Table 1) with Brönsted slope of 0.7 for this reaction (ref 5) leads to corrected krel values of 6.3 and 16.0 for **2** and **3**, respectively.

(15) The small differences between the two sets of values arise from the fact that the experiments on which k_2 values are based were carried out at pH values at which the mole fractions of the monoprotonated forms of the catalysts are maximal but still slightly lower than unity in all cases.

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(19) In addition to the entropy effect, a favorable enthalpy effect of alkyl substituents may arise from a lower number of gauche interactions in alkyl-substituted ring compounds compared to their open chain precursors (see ref 18). However, these enthalpy effects are irrelevant to the present work, for the obvious reason that no gauche interactions are present in catalysts **1**−**3**.

(20) The fact that $\Delta S^{\ddagger}$ data in Table 3 do not show the large and negative values expected for bimolecular reactions is no surprise. It is well known that for reactions between ions of unlike charge there is a large and positive contribution to $\Delta S^{\ddagger}$ arising from release of some frozen solvent molecules on going from reactants to transition state. For a thorough discussion of reactions between ions, see: Frost, A. A., Pearson, R. G. *Kinetics and Mechanism*, 2nd ed.; John Wiley & Sons: New York, 1961; Chapter 7.

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