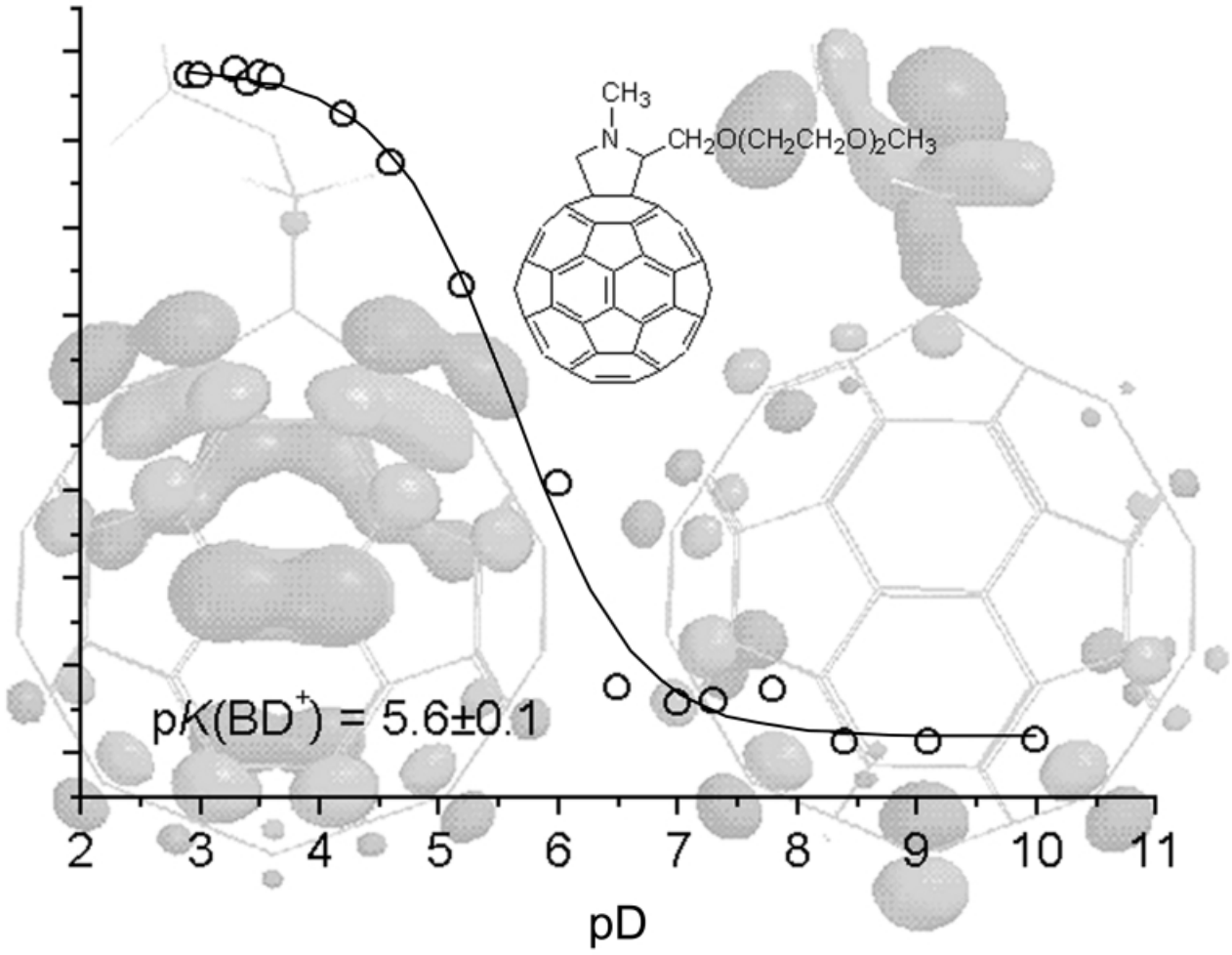
Basicity of Fulleropyrrolidines



The NMR titration curve of a fulleropyrrolidine, with a pK(BD$^+$) of 5.6 in 85% dioxane/water, is shown. The backdrop depicts the HOMO and HOMO(−4) surfaces (calculated at the PM3 level) of *N*-methylfulleropyrrolidine; this suggests a low basicity of the amino nitrogen.
For more details see the following pages.

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[60]Fullerene as a Substituent

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Abstract: The substituent effect of the dihydro[60]fullerenyl group and its hydrophobic parameters have been evaluated quantitatively. The substituent constant has been determined from the pK value of a fullerene-based, *para*-substituted benzoic acid **1** in 80% dioxane/water (v/v) by NMR spectroscopy. The resulting Hammett σ value of 0.06, consistent with a small electron-withdrawing effect of C_{60}, is a consequence of the fact that only inductive effects can be transmitted through the two tetracoordinate carbon atoms between the fullerene π system and the *para*-position of the benzoic acid moiety in **1**. The parameter π, which describes the hydrophobic character of the substituent C_{60}, has been evaluated as the difference between that of **1** and model compound **2**. The π value, which is larger than 3, indicates that the fullerene cage imparts high hydrophobicity to the molecule to which it is attached. Finally, we have evaluated how the fullerene spheroid influences the acid–base properties and nucleophilicity of the pyrrolidine nitrogen in a suitably functionalized fulleropyrrolidine. The fulleropyrrolidine **4** ($pK_{BD}^{+} = 5.6$) is six orders of magnitude less basic and 1000 times less reactive than its model **3** ($pK_{BD}^{+} = 11.6$). This may be related to through-space interactions of the nitrogen lone pair and the fullerene π system.

Keywords: basicity · fullerenes · fulleropyrrolidines · partition coefficient · substituent effects

Introduction

Following the discovery[1] and first macroscopic isolation[2] of fullerenes, major advances in the understanding of the basic principles of their chemical reactivity[3] have given rise to a large number of derivatives with attractive properties for biological applications[4] and as new materials.[5] However, the pace of development has left comparatively little time to collect data on the fundamental characteristics of the fullerene moiety as a substituent.

Monofunctionalization of C_{60}, the most widely studied fullerene, does not substantially alter its electronic and electrochemical properties. The UV/Vis absorption features of C_{60} are, in fact, mostly retained in its derivatives.[6] Only a slight shift of the reduction processes ($\approx$50–150 mV) to more negative potentials is observed in cyclic voltammetry of derivatives when compared to those for pristine C_{60}.[7]

On the contrary, little is known on how the fullerene substituent modifies the chemical properties of groups linked to it (is it electron withdrawing? And to what extent?) also with regard to its hydrophobic properties (to what extent?).

Recently, various calculations have been made on a number of physicochemical properties of C_{60}. Among these, log$P$ values for C_{60} have been calculated;[8] however, no conclusions could be drawn since experimental data were not available. The basic properties of C_{60} anions have also been studied:[9] this revealed that the basicity increases from the mildly basic monoanion to the highly basic C_{60}^{3-}.

Herein, we report on the quantitative evaluation of the substituent effect of C_{60}, on the determination of its hydrophobic parameters, and of its effect on the basic properties and on the nucleophilicity of a fulleropyrrolidine derivative.

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Results

Substituent effect: The most widely used parameter to measure the effect of a substituent is the Hammett constant σ,[10] which is evaluated by the measurement of its effect on the ionization constant of a substituted benzoic acid in water. The known extremely low solubility of C_{60} derivatives in water dictates the use of an organic solvent that contains water, and

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one for which the substituent effects on the ionization of benzoic acids are already available. To ensure adequate solubility, we prepared the fullerene-based benzoic acid derivative **1** that contains a triethylene glycol chain, and the reference compound **2**, which lacks the fullerene moiety. Methanofullerene **1** has been synthesized through the sequence described in Scheme 1. It is reasonably soluble in 80% dioxane/water (v/v), which was then chosen as the solvent for the study of the substituent effects (ρ for benzoic acids = 1.68).[11]

The studies of ionization equilibria are usually carried out by monitoring the change in UV spectra of the acid as a function of pH (or other scales of H^+ activity).[10] However, in the present case the use of UV spectroscopy is severely hampered because: 1) the UV spectrum is dominated by the strong absorption of the C_{60} group, rather distant from the site of ionization; 2) the strong absorption of the solvent dioxane which totally masks the region of interest. An alternative to UV is NMR spectroscopy,[12] where the change in the chemical shift of a suitable signal is monitored as a function of pH. This approach requires that the neutral and ionized forms undergo fast exchange on the NMR timescale, so that the measured chemical shift ν is the weighted average of the values for the neutral (ν_{HA}) and the ionized (ν_{A^-}) species: $\nu([HA] + [A^-]) = \nu_{HA}[HA] + \nu_{A^-}[A^-]$, in full analogy with the expression commonly adopted in UV measurements. This method has been widely adopted for studies in concentrated acids and bases, where similar problems apply.[12]

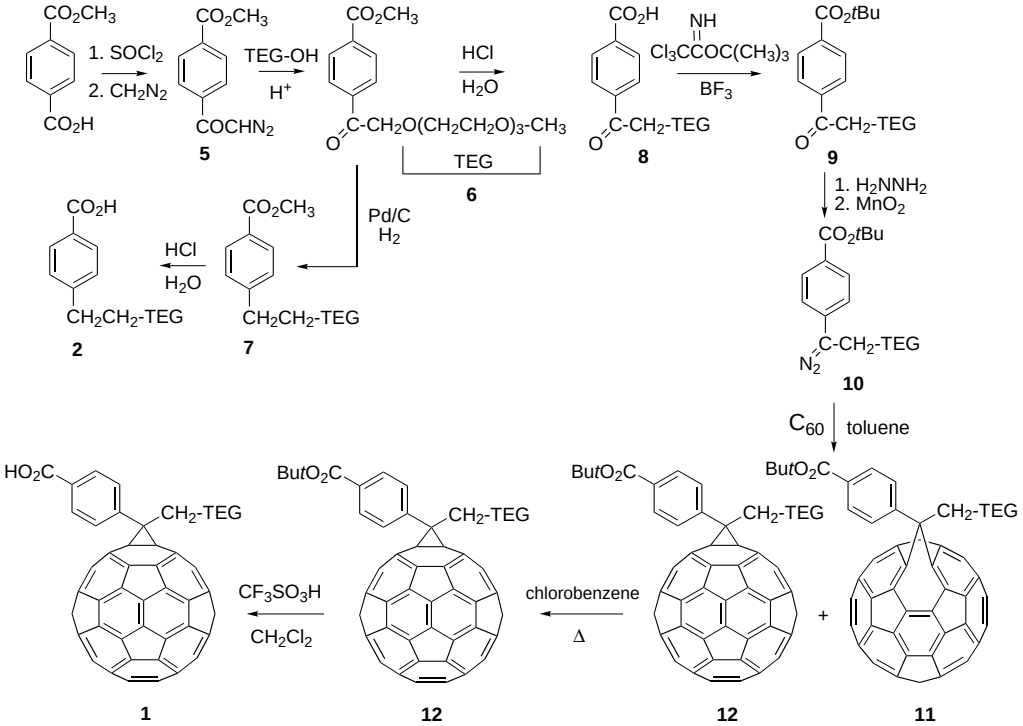
The most important problems connected to NMR measurements are: 1) the sensitivity is much lower than for UV measurements; 2) the need for a suitable signal from the species under investigation whose chemical shift can be easily detected and changes only as a consequence of the ionization process, and 3) the use of a reference signal whose chemical shift is insensitive to solvent and pH changes.

The problem of sensitivity was easily solved with the use of a 400-MHz instrument. However, since the NMR technique has rarely been applied to ionization equilibria in mixed organic solvents, the other two points were carefully examined.

The most obvious choice for the signal to be monitored is that of the aromatic protons which, in the present case of *p*-substituted benzoic acids, give rise to the familiar four-line pattern, whose splitting and appearance depend on the relative electron-withdrawing powers of the two substituents. *p*-Nitrobenzoic acid (PNBA) was chosen as a test acid for calibration purposes.

The problem concerning the reference for the chemical shifts has been thoroughly examined for concentrated acid solutions.[13] It was concluded that the best reference should have the same charge type and solvation characteristics as the ion being examined. In the present case, in which the solvent composition remains constant and dilute acid–base solutions are employed, the problem is expected to be of minor importance. Two substances were chosen as candidates, Me_4NCl and $MeSO_3Na$; both are ionic species not protonated under the conditions of interest.

A test determination of the ionization constant of *p*-nitrobenzoic acid was carried out in 60% dioxane. The pK_a values thus obtained were 5.97 and 5.96 with Me_4NCl and $MeSO_3Na$ as the reference compounds, respectively; all four aromatic signals yielded identical values. These values compare very well with the literature value of 5.99,[11] considering the different techniques, and point out that all four aromatic protons are suitable probes, and both standards work equally well. However, the Me_4NCl signal is close to that of dioxane



Scheme 1. Synthesis of **1** and **2**. See Experimental Section for details.

and its intensity is adversely affected because of the partial saturation occurring during measurements requiring saturation of the solvent signal. As a consequence, $MeSO_3Na$ was used as the standard in all subsequent measurements.

Measurements in 80% dioxane gave somewhat different results: PNBA yielded a pK_a value of 8.25, compared to a literature value of 8.15.[11] The origin of this discrepancy is probably related to the uncertainty in the correction for activity coefficients (see Experimental Section) as well as to the problem (i.e. reproducibility) arising in connection with the use of a glass electrode in highly nonaqueous media. Because all our measurements were carried out under identical conditions, pK differences will not be affected, although some uncertainty will result in the σ values. The resulting pK_a values are collected in Table 1.

Table 1. pK_a Values of benzoic acids in 60% and 80% dioxane/water at 30 °C.

Acid	60% Dioxane		80% Dioxane	
	ref. [11]	this work	ref. [11]	this work
benzoic acid	7.12	–	9.22	–
2	–	7.19	–	9.52 ± 0.09
p-nitrobenzoic acid	5.99	5.96	8.15	8.25 ± 0.01
1	–	–	–	9.42 ± 0.04

The -$(CH_2CH_2O)_4CH_3$ group, linked in the *para* position to the aromatic ring of **2**, renders the benzoic acid less acidic by 0.3 pK units. This is consistent with a small electron-donating effect of the methylene groups; the σ value of the group can be estimated as $\sigma = (9.22 - 9.52)/1.68 = -0.18$. The group linked to the *para* position in **1** includes the fullerene; overall, it is an acid-weakening group, but less than the -$(CH_2CH_2O)_4CH_3$ group ($\sigma = (9.22 - 9.42)/1.68 = -0.12$).

If we allow the additivity of the two parts of the substituent, we can then estimate that the fullerene moiety has an acid-strengthening effect of 0.1 unit. We can also estimate a σ value for the fullerene of $0.1/1.68 = 0.06$, indicating a small electron-withdrawing effect for the group.

Hydrophobicity parameters: The two parameters of interest are the partition coefficient P and the parameter π, which describes the hydrophobic character of the substituent.[14] The partition coefficient is evaluated by the expression $P = c_{octanol}/[c_{water}(1-\alpha)]$, where $c_{octanol}$ and c_{water} are the concentration of the substrate in equilibrated solutions in octanol and water, respectively, and α is the degree of dissociation of the acid in the aqueous phase. The partition coefficient gives an indication of the hydrophobicity of the whole molecule. The parameter π is given by $\pi = \log P_X - \log P_H$, where P_X and P_H are the partition coefficients for the substituted and unsubstituted substrate, respectively. A positive value for π means that the substituent prefers the octanol phase (hydrophobic), while a negative π value indicates hydrophilic character of the substituent.

The measurements for the relatively water-soluble compounds (benzoic acid, PNBA, and **2**), were carried out without difficulty. On the contrary, the extremely low aqueous solubility of **1** prompted us to determine $\log P$ values for the model compound **2** at two different concentrations to test for its consistency (Table 2). In any case, the solubility of **1** was close to the detection threshold of the HPLC technique we used; thus, only a very small peak with a signal-to-noise ratio (S/N) of about 2 could be obtained, at best. After checking with samples of known concentration, we set an upper limit for c_{water} of 6×10^{-9} mol L^{-1}. To confirm the presence of **1**, 5 mL of the aqueous phase after partitioning were concentrated to dryness under reduced pressure and the residue, dissolved in octanol, was checked by HPLC. A peak was clearly detected at the retention time of derivative **1** whose concentration, calculated for the 10 mL parent solution, qualitatively matched the upper limiting value estimated above. The results are reported in Table 2.

From the data for **2**, one can evaluate the hydrophobicity of the -$(CH_2CH_2O)_4CH_3$ group as $\pi = -0.60$. Therefore, we can only estimate a lower limit for the $\log P$ value for **1** as ≈ 4, which corresponds to a π value of > 3. Assuming additivity of the substituent effects, one can correct for the hydrophilic character of the -$(CH_2CH_2O)_4CH_3$ group and hence estimate the π value for the fullerene group itself as being larger than 4.

Basicity and reactivity of fulleropyrrolidines: One of the best methods to functionalize fullerenes is the cycloaddition of azomethine ylides.[15] This produces fulleropyrrolidines which are characterized by the presence of a pyrrolidine ring fused to a 6,6 ring-junction of C_{60}. The pyrrolidine nitrogen atom is close to the fullerene sphere: how are its basic and nucleophilic properties affected?

We are again faced with the problem of solubility. We synthesized, therefore, model compounds *N*-methyl-2-[2(2-methoxyethoxy)ethoxy]methylpyrrolidine (**3**) and *N*-methyl-2-[2(2-methoxyethoxy)ethoxy]methylfulleropyrrolidine (**4**), according to the sequences shown in Scheme 2.

Fulleropyrrolidine **4** is soluble (0.3 mg ml^{-1}) in an 85% dioxane/water mixture. The NMR spectrum of **4** in this solvent shows that the signals considered to be suitable for

Table 2. Hydrophobicity parameters.

Compound	pH[a]	pK_a[b]	α	$c_{octanol}$ [M]	c_{water} [M]	$\log P$	π[c]
benzoic acid	4.46	4.19	0.651	5.23×10^{-3}	0.25×10^{-3}	1.78	–
p-nitrobenzoic acid	4.21	3.41	0.863	4.63×10^{-3}	0.40×10^{-3}	1.93	0.15[d]
2	4.21	4.37	0.409	3.13×10^{-3}	0.35×10^{-3}	1.18	– 0.60
2	4.15	4.37	0.376	1.26×10^{-4}	0.14×10^{-4}	1.16	– 0.62
1	4.00	4.31	0.329	1.01×10^{-4}	$< 6 \times 10^{-9}$	> 4	> 3

[a] pH value of the aqueous phase after partitioning. [b] The pK_a values for benzoic and *p*-nitrobenzoic acid were taken from ref. [21]. Those for **1** and **2** were computed with the Hammett equation and the σ values obtained in the previous section. [c] $\pi = \log P_X - \log P_H$. [d] 0.02 (ref. [14]).

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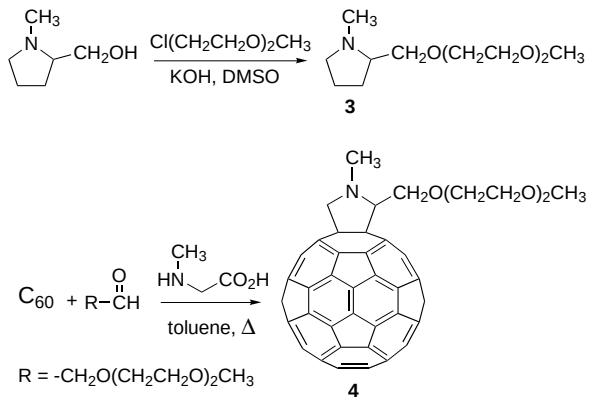

Scheme 2. Synthesis of **3** and **4**. See Experimental Section for details.

generating the chemical shift versus pH curve are close to the solvent signals. Therefore, solvent suppression by presaturation led to an excessive decrease in their intensity. To overcome this problem, we used perdeuterated solvents ([D_8]dioxane and D_2O), DCl as acid, and Me_4NCl as the internal reference. Obviously, the acidity constant is a pK_{BD}^+ value. The pK data are collected in Table 3, while Figure 1 shows the NMR titration curves of pyrrolidines **3** and **4**.

Table 3. pK_{BH}^+ Values for substituted pyrrolidines in dioxane/water at 30 °C.

Compound	80% Dioxane/water pK_{BH}^+	85% [D_8]Dioxane/D_2O pK_{BD}^+
N-methylpyrrolidine	11.7 ± 0.1	
3	11.1 ± 0.1	11.6 ± 0.1
4		5.6 ± 0.1

The basic strength of *N*-methylpyrrolidine compares well with literature data for other tertiary amines in 80% dioxane/water, for example cyclohexyldimethylamine ($pK_{BH}^+ = 11.08$) and triethylamine ($pK_{BH}^+ = 11.39$).[16] The decrease in pK upon going from *N*-methylpyrrolidine to derivative **3** shows a small electron-withdrawing effect of the -CH_2-OR substituent (cf. σ_p for $CH_2OCH_3 = 0.03$). On the contrary, the difference of six orders of magnitude between the basicity of pyrrolidine **3** and that of fulleropyrrolidine **4** is impressive.

The reactivity of pyrrolidine **3** and that of fulleropyrrolydine **4** has been compared in the Menschutkin reaction with methyl iodide in $CDCl_3$. The solvent was chosen to allow monitoring of the reaction by NMR spectroscopy. Compound **3** reacts at 25 °C with a rate constant of 2.1×10^{-3} L mol^{-1} s^{-1}, whereas the rate constant for fulleropyrrolidine **4** is, under the same conditions, 4.2×10^{-6} L mol^{-1} s^{-1}, that is, the reaction of the fullerene derivative is retarded by 1000-fold.

Discussion

The low σ value (0.06) evaluated for the fullerene as a substituent is, at first sight, surprising given the fact that the fullerene core is a well-known electron acceptor.[7] However,

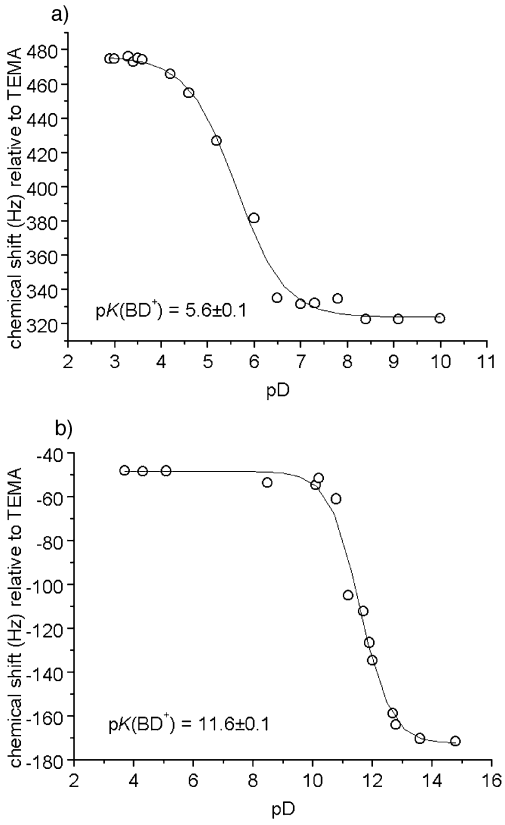

Figure 1. Chemical shift variations, relative to Me_4NCl (TEMA), of a methylene proton at position 5 of the pyrrolidine ring in a) **1** and b) **2** versus pD (85% [D_8]dioxane/D_2O at 30 °C).

in **1** the fullerene π system is separated from the *para* position of the benzoic acid ring by the two tetracoordinate carbon atoms that bear the three-membered ring, so that only inductive effects can be transmitted to the reacting center. Therefore, it is not surprising that the polar effect is minimal.

With regards to the hydrophobic character, the estimated value ($\pi > 3$) is largely positive which implies that the fullerene substituent favors, relative to H, the octanol phase and hence has a strong hydrophobic character. The magnitude of π can be compared with that of cyclohexyl (2.51) and ferrocenyl (2.46) groups,[14] while log$P$ is similar to that of pyrene (4.88).[14]

By itself, the value of 4 for log$P$ appears to be inconsistent with the large size and functionalities (mainly C–C bonds) of the fullerene derivative; thus, for example, Abraham et al.[8] estimated a much larger log$P$ value (12.6) for the partition between water and water/wet 1-octanol for fullerene. However, one must bear in mind that the value obtained in this work is only a lower limit for log$P$ or π because of the extremely unfavorable water/octanol partition of **1** despite the added hydrophilic group.

In addition, it is worth mentioning that in polar solvents hydrophilic fullerene monoadducts can form supramolecular aggregates.[17] Similar aggregation phenomena have been demonstrated for C_{60} itself in solvents having a dielectric permittivity (ε) larger than ≈13 (ε values for water and 1-octanol are 78.3 and 10.3, respectively).[18] This occurrence introduces the additional difficulties that a) the nature of the

dissolved species is solvent-dependent, and b) the solubility of such aggregates might differ substantially from that of the monomeric species. Therefore, it is worthwhile to make an independent estimation of the relative magnitude of $\log P$ values of **1** and **2** as follows: assuming $\log P = 12.6$ for **1**, as proposed by Abraham, and a value of 1.2 for **2**, the Gibbs energies of transfer (octanol → water) can be estimated as $\Delta G_t^{o\rightarrow w} = 2.303\,RT\log P = 17$ and 2 kcal mol^{-1} for **1** and **2**, respectively. This difference can be accounted for as follows: the energetics of transfer of both solutes is dictated by a) cavitation energies and b) solute–solvent interactions. The latter term can be further dissected into polar contribution (i.e. dipole–dipole and hydrogen-bonding interactions) and dispersive contributions (mainly the result of the solute and solvent polarizabilities). Polar contributions can be assumed equal for **1** and **2**, since both species share the same number and type of suitable functionalities. Conversely, their polarizabilities (α) are substantially different: an HF/3-21G calculation yields average volume polarizabilities of $\alpha = 88$ and 24 Å^3 for **1** and **2**, respectively (the value for **1** compares favorably with the value for C_{60} itself, $\alpha = 86$ Å^3).[19] The polarizability of water (1.45 Å^3) is also substantially smaller than that of 1-octanol (17 Å^3, estimated from that of di-*n*-butyl ether[20]). From the classical expression for the dispersive interaction of two spherical particles with given α and ionization potential I, [Eq. (1)], it is qualitatively apparent

$$E = -\frac{2}{3}\alpha_1\alpha_2\frac{I_1 I_2}{I_1 + I_2}\frac{1}{r_{12}^6} \qquad (1)$$

that the interaction between the most polarizable solute–solvent pair (i.e., **1** and 1-octanol) would be the most stabilizing. However, a quantitative assessment is hampered by the need of estimating the approach distance (difficult to define for nonspherical particles), and by the difficulty in accounting for the complex collective phenomena taking place in a bulk medium.

In fact, however, the strongest factor operating in the transfer appears to be the cavitation energy. According to the scaled particle theory (SPT),[21] this term depends primarily on the relative diameter of solute and solvent molecules, so that the most endergonic process is the creation of a cavity in a solvent whose molecules are very different in diameter from those of the solute. The Gibbs energies of transfer (octanol → water) can be simply derived from the solvation (gas → solvent) energies. Thus, even allowing for a fairly wide uncertainty in the molecular diameters, according to the SPT the $\Delta G_t^{o\rightarrow w}$ is much less favorable for **1** than for **2** by ≈ 20 kcal mol^{-1}, which is in the same range as the difference in the experimental $\Delta\log P$. This arises mainly because the cavitation energy of **1** in water is very unfavorable (owing to the very large difference in size between water and **1**).

Hence, our calculated estimate agrees with that calculated by Abraham: both data point to an extremely high hydrophobic character of the fullerene sphere. The experimental result only yields a lower limit for $\log P$. The large experimental difficulties, including aggregation of fullerene in water, do not allow for a better estimate.

The pK_{BD}^+ values of compounds **3** and **4** differ by 6 units! (For other weak acids, such as RCO_2H and $ArNH_3^+$, the difference between pK_{BD}^+ and pK_{BH}^+ is of the order of 0.2–0.6 units; obviously the same 6 pK units difference will probably hold in the pH scale for **3** and **4**). Similar results have been recently reported by D'Souza et al., who ascribed the differences to inductive effects.[22a] Siegel et al. determined the relative basicity of *N*-methylfulleropyrrolidine and *N*,*N*-dimethylaniline by means of a competitive titration NMR method in a fully nonaqueous medium (CS_2/$CDCl_3$).[22b] These measurements indicated the two bases to have essentially equal pK values; however, even assuming that solvent effects on the proton-transfer equilibrium are the same, it is not possible to derive a quantitative assessment of the basicity of the fullerene derivative, owing to the large uncertainty associated with measuring acid strengths in nonaqueous, nonpolar media.

Polar effects cannot be responsible for this large decrease in basicity (see above and compare with the σ value of 0.06). On the other hand, steric effects can also be discarded on the following grounds: although the basicity of aliphatic and aromatic nitrogen bases is indeed affected by steric hindrance (the hindered species being less basic), the known basicity differences amount to only 1–2 pK units.[23] Furthermore, such relatively large effects are only encountered when the nitrogen atom lies within a cavity formed by the bulky substituents, for example in the cases of 2,4- versus 2,6-di-*tert*-butylpyridine, or piperidine versus *cis*-2,6-di-*tert*-butylpiperidine. Even then, the observed steric effects have been demonstrated to be connected with the solvation of the protonated base rather than with protonation itself.[23b] In contrast, the optimized structure of *N*-methylfulleropyrrolidine using the PM3 semiempirical method (Figure 2) shows

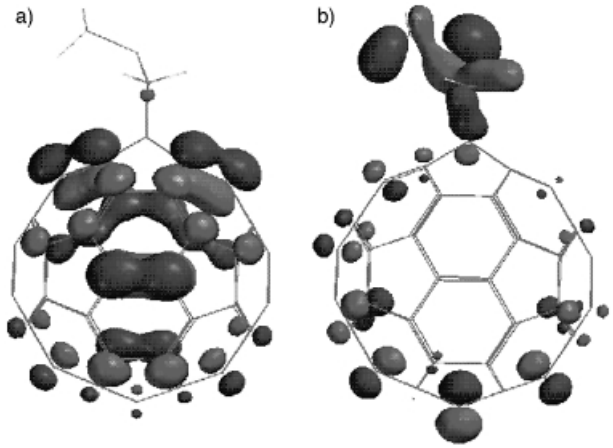

Figure 2. a) HOMO and b) HOMO(−4) surfaces of *N*-methylfulleropyrrolidine calculated with the PM3 semiempirical method.

that the pyrrolidine ring is in the envelope conformation, with the lone pair in the axial position pointing toward the fullerene sphere. The nitrogen atom is therefore far away from the fullerene core, so that the solvation of the ammonium ion can be expected to be free of any steric influence.

Conversely, it is well known that the aqueous basicity of anilines ($pK_{BH}^+ \approx 4-5$) is much lower than that of aliphatic amines ($pK_{BH}^+ \approx 10-11$). In this case, the effect stems from an

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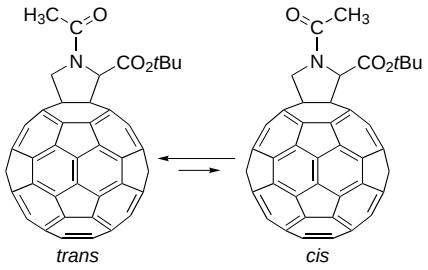
intrinsically lower basicity of anilines (in the gas phase, cyclohexylamine is more basic than aniline by 11 kcal mol^{-1}), the solvation energy of the respective ammonium ions being similar.[24] This is commonly ascribed to a participation of the nitrogen lone pair to the benzene resonance; we suggest that the lower basicity of the fulleropyrrolidine derives from a similar effect. In fact, PM3 calculations show that the HOMO frontier orbital of *N*-methylfulleropyrrolidine (Figure 2a) is localized almost exclusively on the fullerene. Only the HOMO(−4) molecular orbital, shown in Figure 2b, displays electron density on the pyrrolidine nitrogen. Therefore, it appears that the nitrogen lone pair lies in a lower energy orbital and, as such, is not readily available for protonation. This is also consistent with the reduced nucleophilic reactivity: the 1000-fold decrease in reaction rate on going from pyrrolidine to its fullerene derivative is of the expected order of magnitude.

There are other examples of through-space interactions between the fullerene π system and orbitals of the added functional group. In spiromethanofullerenes, for instance, a similar effect has been called *periconjugation*.[25] Another example has been reported in the EPR study of radical anions of fulleropyrrolidine **4** by Brustolon and co-workers.[26] A further case of nitrogen lone pair delocalization into the fullerene core is that of fulleroproline **13** for which we measured the kinetic parameters of the *trans* → *cis* isomerization.[27]



13

The activation enthalpy for the isomerization process is about 7 kcal mol^{-1} lower than that of the proline analogue. This means that in **13** the nitrogen lone pair is less available for conjugation with the carbonyl with a consequent loss in the C–N double-bond character.

Experimental Section

Instrumentation: ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC200, AC250 and AM400 spectrometers. Chemical shifts are given relative to tetramethylsilane. UV/Vis absorption spectra were collected on a Perkin-Elmer Lambda5 spectrophotometer. FT-IR spectra were collected on a Perkin-Elmer 1720X spectrophotometer. MALDI (matrix-assisted laser desorption ionization) mass spectra were obtained in positive linear mode at 15 kV acceleration voltage on a Reflex time-of-flight mass spectrometer (Bruker), with 2,5-dihydroxybenzoic acid as the matrix. GC-MS analyses were performed on a Hewlett-Packard electron-impact mass spectrometer 5970 coupled with a gas chromatograph 8890 equipped with a 30 m × 0.25 mm Alltech EC-1 column. The exact mass determination was performed on a VG ZAB 2F instrument (70 eV, 200 μA). Isocratic elutions (see partition coefficient measurements) were performed on a Shimadzu HPLC unit (Shimadzu LC-8A pump, 20 μL injections, SCL-8A system controller, SPD-6A spectrophotometric detector at $\lambda = 254$ or 340 nm (derivative **1**)). Reactions were monitored by thin-layer chromatography on Macherey-Nagel plates (Polygram SIL G/UV$_{254}$, 0.2 mm thickness). Flash column chromatography was performed on 230–400 mesh silica gel (Macherey-Nagel). Reaction yields were not optimized and refer to pure, isolated products. PM3 and ab initio calculations were performed with Spartan 4[28] and Gaussian 98,[29] respectively.

Materials: C_{60} was purchased from Bucky-USA (99.5%). All other reagents were purchased from Aldrich. Fulleropyrrolidine **4**[30] was prepared as reported in the literature.

2-[2-(2-Methoxyethoxy)ethoxymethyl]-1-methylpyrrolidine (3): 1-Methyl-2-pyrrolidine-methanol (2.0 g, 17 mmol) and bis(ethyleneoxy)methyl chloride (4.7 g, 34 mmol) were added to a suspension of KOH (3.8 g) in DMSO (33 mL). The mixture was stirred at room temperature for 2.5 h. Brine (100 mL) was added followed by extraction of the aqueous phase with CH_2Cl_2. The crude oily residue, obtained after concentration of the organic phase, was distilled (b.p. 170 °C, 2 mmHg) to yield derivative **3** (1.2 g; 34%). An analytical sample was obtained by further bulb-to-bulb distillation. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.48–1.94$ (m, 4H), 2.10–2.20 (dd, 1H), 2.30–2.42 (dd, 1H), 2.36 (s, 3H), 2.98–3.08 (td, 1H), 3.34 (s, 3H), 3.32–3.65 (m, 8H); ^{13}C NMR (62.5 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 57.29$, 58.49, 64.25, 70.04, 70.10, 70.19, 71.48; HR-MS calcd for $C_{11}H_{23}NO_3$ 217.1672; found 217.1639 (±0.005).

Methyl 4-(2-Diazoacetyl)benzoate (5): Terephthalic acid monomethyl ester (1.0 g, 5.6 mmol) was dissolved in freshly distilled thionyl chloride (10 mL) and 3 drops of DMF. The mixture was heated to reflux temperature for 3 h, then excess thionyl chloride was removed in vacuo. Crude methyl 4-chlorocarbonylbenzoate (m.p. 54–56 °C; ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS) $\delta = 3.98$ (s, 3H), 8.18 (s, 4H); ^{13}C NMR (62.5 MHz, $CDCl_3$, 25 °C, TMS) $\delta = 52.7$, 130.0, 131.2, 136.0, 136.5, 165.2, 168.0) was dissolved in diethyl ether (20 mL) and added to a solution of diazomethane in diethyl ether (≈16 mmol) cooled on an ice-bath. When the addition was complete (15 min), the cooling bath was removed and the solution was stirred at room temperature for 3 h. The solvent and excess diazomethane were removed with a stream of nitrogen. The residue was purified by flash chromatography (SiO_2, eluent: toluene/ethyl acetate 1:1, $R_f = 0.7$) to yield **5** as yellow crystals (860 mg; 76%). M.p. 107–109 °C; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 3.95$ (s, 3H), 5.95 (s, 1H), 7.82 (m, 2H), 8.12 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$, 25 °C, TMS): δ 52.1, 54.7, 126.4, 129.5, 133.3, 139.7, 165.8, 185.1; IR (neat): $\tilde{\nu} = 2366$, 1717, 1680 cm^{-1}; GC-MS (70 eV): *m*/*z* (%): 163 (100) $[M - CHN_2]^{+\bullet}$.

Methyl 4-(2-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}acetyl)benzoate (6): Triethylene glycol monomethyl ether (TEG-OH) (1.4 mL, 8.1 mmol) followed by 5 drops of $BF_3 \cdot Et_2O$ were added to a solution of **5** (850 mg, 4.17 mmol) in diethyl ether (120 mL). The solution was left standing for two days at room temperature. Aqueous workup afforded an oily residue which was purified by flash column chromatography (SiO_2, toluene/ethyl acetate 1:1) to yield **6** (820 mg; 58%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 3.36$ (s, 3H), 3.50–3.80 (m, 12H, triethylene glycol), 3.96 (s, 3H), 8.0 (m, 2H), 8.12 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 51.8, 58.3, 69.7, 69.8, 70.1, 70.2, 71.1, 73.7, 127.2, 129.1, 133.4, 137.3, 165.4, 195.4; IR (neat): $\tilde{\nu} = 1724$, 1704, 1281, 1108 cm^{-1}; GC-MS (70 eV): *m*/*z* (%): 340 (10) $[M]^{+\bullet}$.

Methyl 4-(2-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}ethyl)benzoate (7): Pd/C (≈15 mg) was added to a solution of **6** (580 mg, 1.71 mmol) in ethanol (20 mL) and the mixture was stirred under hydrogen atmosphere (1 atm) for four days. After filtration of the catalyst, the solvent was evaporated in vacuo and the product purified by flash column chromatography (SiO_2, ethyl acetate/methanol 95:5) to yield **7** (320 mg; 58%) as a clear oil. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 2.92$ (t, 2H), 3.37 (s, 3H), 3.55 (m, 2H), 3.5–3.8 (m, 14H), 3.89 (s, 3H), 7.28 (m, 2H), 7.94 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$, 25 °C, TMS): δ 36.23, 51.96, 58.99, 70.31, 70.47, 70.53, 70.58, 71.59, 71.90, 128.90, 129.59, 144.59, 167.02; IR (neat): $\tilde{\nu} =$ 1700, 1224, 1111 cm^{-1}; GC-MS (70 eV): *m*/*z* (%): 326 (10)$[M]^+$.

4-(2-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}ethyl)benzoic acid (2): A suspension of ester **7** (420 mg, 1.29 mmol) in aqueous HCl (10%, 80 mL) was heated to reflux temperature for 2 h then the solvent was removed in vacuo. The product, dissolved in CH_2Cl_2 (15 mL) was filtered through a pad of

celite. Evaporation of the solvent afforded the benzoic acid derivative **2** in nearly quantitative yield as a deliquescent solid that was used for acidity and partition coefficient measurements without further purification. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 2.96$ (t, 2H), 3.38 (s, 3H), 3.5–3.9 (m, 14H), 7.32 (m, 2H), 8.01 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 36.26$, 58.99, 70.28, 70.43, 70.50, 70.54, 71.54, 71.87, 127.40, 129.03, 130.18, 145.43, 171.40; IR (KBr): $\tilde{\nu} = 1712$, 1249, 1107 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{24}O_6 \cdot 0.5\,H_2O$ (321.4): C 59.79, H 7.84; found: C 59.38, H 7.74.

4-(2-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}acetyl)benzoic acid (8): The hydrolysis of the ester function of benzoate **6** (470 mg, 1.38 mmol) was performed as previously described for derivative **7**. Benzoic acid **8** (440 mg, 98%) was isolated and used for the next reaction without further purification. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 3.38$ (s, 3H), 3.5–3.9 (m, 12H, triethylene glycol), 4.88 (s, 2H), 8.0 (m, 2H), 8.15 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 58.83$, 61.38, 70.12, 70.24, 70.28, 70.38, 70.63, 70.78, 71.71, 72.34, 74.28, 127.75, 130.14, 133.96, 138.12, 168.42, 196.05; IR (KBr): $\tilde{\nu} = 1684$, 1700 cm^{-1}; EI-MS (70 eV): m/z: 326 $[M]^{+\bullet}$.

***tert*-Butyl 4-(2-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}acetyl)benzoate (9)**: A solution of *tert*-butyl-2,2,2-trichloroacetimidate (750 mg, 3.4 mmol) in *n*-hexane (7 mL) at room temperature was added to a solution of acid **8** (440 mg, 1.35 mmol) in CH_2Cl_2 (7 mL). One drop of $BF_3 \cdot Et_2O$ was added and the mixture stirred at room temperature for 20 h. After addition of solid Na_2CO_3, the solution was filtered through a pad of celite and then evaporated under reduced pressure. The product was purified by flash column chromatography (SiO_2, eluent: ethyl acetate) to yield **9** (190 mg; 37%) as a clear oil. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.62$ (s, 9H), 3.38 (s, 3H), 3.48–3.82 (m, 12H, triethylene glycol), 4.85 (s, 2H), 7.95 (m, 2H), 8.08 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 28.1$, 59.0, 70.47, 70.53, 70.79, 70.91, 71.9, 74.4, 81.8, 127.7, 129.6, 136.1 137.7, 164.7, 196.2; IR (neat) 1705–1715 (br) cm^{-1}; GC-MS (70 eV): m/z (%): 263 (20) $\{M - [(OCH_2CH_2)_2OCH_3]\}^{+\bullet}$.

Homofullerene 11: The hydrazone of **9** was prepared by dissolving **9** (80 mg, 0.21 mmol) in absolute ethanol (7 mL). Excess anhydrous hydrazine (0.1 mL) was added and the mixture was stirred at reflux temperature for 1.5 h. The solvent was removed on the rotary evaporator and excess hydrazine under high vacuum (0.1 torr) at 40 °C. The oily residue was dissolved in chloroform (10 mL), and dry $MgSO_4$ (200 mg) was added followed by portionwise addition of MnO_2 (200 mg). After stirring at room temperature for 10 min, the resulting yellow solution containing diazo derivative **10** (IR (neat): $\tilde{\nu} =$ 2052 ($\nu_{N=N}$), 1708 ($\nu_{C=O}$) cm^{-1}) was filtered through a pad of celite in order to remove all solids. Because of the instability towards SiO_2 and concentration, the diazo compound was added directly to a solution of C_{60} (100 mg, 0.14 mmol) in toluene (120 mL). The solution was stirred at room temperature for 1.5 h. The solvents were removed in vacuo and the residue was purified by flash column chromatography (SiO_2, eluent: toluene → toluene/ethyl acetate 75:25). Yield: 45 mg (30%); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.63$ (s, 9H), 3.37 (s, 3H), 3.4–3.7 (m, 12H, triethylene glycol), 4.83 (s, 2H), 8.09 (m, 2H), 8.17 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 28.2$, 50.8, 59.0, 61.1, 70.4, 70.5, 70.6, 70.7, 71.3, 71.8, 81.2, 125.3, 128.2, 129.0, 129.26, 129.3, 131.0, 131.4, 132.4, 134.9, 137.15, 137.2, 138.0, 138.3, 138.7, 139.4, 140.41, 140.45, 141.31, 141.38, 142.11, 142.16, 142.29, 149.32, 142.82, 142.94, 142.97, 143.09, 143.15, 143.50, 143.54, 143.7, 143.8, 143.9, 144.2, 144.8, 145.1, 145.2, 147.3, 150.2, 165.0; UV/Vis (cyclohexane): $\lambda_{max} = 214$, 260, 332, 423 nm; MALDI MS $C_{80}H_{30}O_6$ (1086): m/z: 1087 $[M+H]^+$.

Methanofullerene 12: Homofullerene **11** was converted quantitatively to methanofullerene **12** according to the literature[31] by heating overnight a 0.5 mM solution of **11** in 1,2-dichlorobenzene. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.64$ (s, 9H), 3.37 (s, 3H), 3.55 (m, 2H), 3.59–3.68 (m, 6H), 3.70 (m, 2H), 3.80 (m, 2H), 4.83 (s, 2H), 8.05 (m, 2H), 8.16 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 28.22$,, 50.79, 59.05, 70.55, 70.68, 70.72, 71.41, 71.84, 71.92, 81.27, 129.26, 131.94, 132.96, 137.74, 137.98, 140.46, 140.81, 141.04, 142.08, 142.14, 142.95, 143.0, 143.04, 143.14, 143.76, 144.16, 144.46, 144.56, 144.67, 144.71, 144.80, 145.03, 145.10, 145.20, 145.71, 147.32, 148.01, 165.44; UV/Vis (cyclohexane): $\lambda_{max} = 216$, 264, 327, 430 nm; MALDI MS $C_{80}H_{30}O_6$ (1086): m/z: 1109 $[M+Na]^+$.

Methanofullerene 1: Trifluoromethanesulfonic acid (0.2 mL) was added to a solution of methanofullerene **12** (30 mg, 0.28 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred at room temperature overnight. After the solvent had been evaporated at reduced pressure, the residue was transferred in a centrifuge tube with the aid of diethyl ether, washed thoroughly with the same solvent and then with acetonitrile to give **1** (25 mg, 86%) as a brownish solid; ^{1}H NMR (250 MHz, $CDCl_3/CS_2$ 2:1, 25 °C, TMS): $\delta = 3.38$ (s, 3H), 3.55 (m, 2H), 3.63 (m, 6H), 3.70 (m, 2H), 3.82 (m, 2H), 4.86 (s, 2H), 8.13 (m, 2H), 8.28 (m, 2H); ^{13}H NMR (62.5 MHz, $CDCl_3/CS_2$ 2:1, 25 °C, TMS): $\delta = 50.71$, 59.06, 70.46, 70.59, 70.65, 70.71, 71.31, 71.56, 71.88, 129.18, 129.89, 132.48, 137.62, 137.84, 140.74, 140.94, 141.64, 141.87, 141.96, 142.83, 142.87, 142.92, 143.0, 143.61, 144.09, 144.36, 144.41, 144.52, 144.65, 144.83, 144.99, 145.06, 145.49, 147.00, 147.61, 192.35; IR (KBr): $\tilde{\nu} = 2864$, 1720, 1681, 1105, 526 cm^{-1}; UV/Vis (octanol): $\lambda_{max} =$ 219, 256, 322, 428 nm; MALDI MS $C_{76}H_{22}O_6$ (1031): m/z: 1054 $[M+Na]^+$.

Acidity measurements: 1,4-Dioxane was freed from peroxides by percolation through activated neutral alumina. Stock solutions were prepared by dissolving the acid in the dioxane/water solution (0.1 M in $NaClO_4$) containing CH_3SO_3Na; the final concentrations were 10^{-3} M for *p*-nitrobenzoic acid, 5×10^{-3} M for **2** and CH_3SO_3Na. The stock solution of **1** was prepared by dissolving the acid in dioxane and adding the required amount of water containing $NaClO_4$ and CH_3SO_3Na (final concentration 5×10^{-4} M). 16–24 aliquots were then brought to the desired pH by addition of dilute NaOH or HCl in the same solvent. The pH-meter was calibrated with a standard buffer solution; no difference was observed if the glass electrode was conditioned in 3 M KCl or in 80% dioxane. pH-Meter readings (B values) were corrected to pH values as recommended by van Uitert and Fernelius[32] as $pH = B + \Delta$ with 0.1 mol kg^{-1} as the molality of the electrolyte, and $x = 0.45$ as the mole fraction of the organic solvent. The value of Δ ($= \log U_H^o + \log 1/\gamma$) was estimated by interpolation of the published values of $\log U_H^o$ and $\log 1/\gamma$ so that for the 80% dioxane/water solution a value of $\Delta = 2.52$ was calculated. However, the uncertainty related to the sparse values for interpolation, and the steepness of the curve of Δ versus x limits the accuracy of Δ to ± 0.1. ^{1}H NMR measurements were carried out on a Bruker AM400 instrument operating at 400 MHz without a lock. The probe temperature (30 °C) was checked with a sample of neat ethylene glycol. Typically, for each measurement 32–128 transients were accumulated in 32 K data points. Chemical shifts in Hz are referenced to internal CH_3SO_3Na. The strong resonance of the solvent was suppressed by multiple presaturation (40 cycles, 55 ms each with total irradiation time of 2.2 s). The total acquisition time was 15–20 min per sample. The resulting values of chemical shift as a function of pH were fitted to Equation (2) where $I = [HA]/[A^-]$ and $\log I = -pH + pK_a$.

$$\nu = \frac{I\nu_{HA} + \nu_{A^-}}{1 + I} \qquad (2)$$

The values of pK_a, ν_{HA}, and ν_{A^-} were optimized by nonlinear least-squares fitting. The calculated limiting chemical shifts (ν_{HA} and ν_{A^-}) were then used to calculate $\log I$ values; those between -1 and 1 were used to calculate pK values which were eventually averaged to yield the recommended values, along with their standard deviations.

Basicity measurements: The general procedure is the same as described for the acidity measurements, except that the solvent was 85% $[D_8]$dioxane/D_2O and hence $\Delta = 3.29$; pH readings were corrected to pD by adding 0.40.[16] The chemical shifts were referenced to internal Me_4NCl. All measurements were carried out at 30 °C. Data were processed as described for the acidity measurements.

Kinetic measurements: The reactions were carried out in $CDCl_3$ as the solvent at 25 °C. Stock solutions of CH_3I, compounds **3** and **4** in $CDCl_3$ were prepared and thermostatted at 25 °C. Aliquots were transferred into a NMR tube and the initial concentration determined by integrating the CH_3 signal against that of $CHCl_3$ present as impurity in the deuterated solvent. The $CHCl_3$ concentration, determined by integration of a known solution of a standard (cubane dimethyl ester) is 2.51×10^{-2} M. The starting concentration of the reactants was evaluated as $c_X = c_S(A_X/A_S)$, where c_X and c_S are the concentrations of the reactant and of $CHCl_3$, respectively, and A_X and A_S the integrated area of the CH_3 signal for the reagent and of the methine proton for chloroform. The concentrations were: a) 1.4×10^{-2} M for **3** and 8.0×10^{-2} M for CH_3I and b) 4×10^{-3} M for **4** and 4.8×10^{-1} M for CH_3I. Rate constants were evaluated by the usual plots of concentration versus time.

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Partition coefficients measurements: Deionized water was shaken with distilled octanol for five minutes. Octanol-saturated water was boiled for 30 min to remove CO_2 and was kept under N_2 atmosphere during the cooling process. The substrate (Table 2) was dissolved in octanol. The octanol solution (10 mL) and water (10 mL) were stirred vigorously for 1.25 h under a nitrogen atmosphere. The phases were left standing for 10 min so that they could separate. The pH was measured (Metrohm 632 pH-meter) for the aqueous phase and the concentration of the substrate determined in both phases by means of HPLC with the aid of external standards (CH_3CN solutions of naphthalene for benzoic and *p*-nitrobenzoic acid; β-naphthol for compound **2** and benzo[α]pyrene for compound **1**. 1 ml of CH_3CN standard solution was added to 1 mL of the octanol or aqueous phase after partitioning). Isocratic elution was performed on a Shimadzu HPLC station (see instrumentation). Conditions for benzoic acid, *p*-nitrobenzoic acid and **2**: column Techsphere, ODS (C_{18}), 250 × 4.6 mm, 5μ, flow 1 mL min^{-1}. Eluent: CH_3CN/H_2O 65:35, 0.05% TFA (benzoic and *p*-nitrobenzoic acid); CH_3CN/H_2O 35:65, 0.05% TFA (derivative **2**). Conditions for derivative **1**: column Vydac 201TP510 (C_{18}), 150 × 4.6 mm, 5 μ, flow 1 mL min^{-1}. Eluent: $CH_3CN/CHCl_3$ 60:40, 0.05% TFA.

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