Structure-Property Relationships in the Basicity and Lipophilicity of Arylalkylamine Oxides

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Homologous *N*,*N*-dimethyl-phenylalkylamine oxides and *N*,*N*-dimethyl-diphenylalkylamine oxides were prepared. Their basicity and lipophilicity (octan-1-ol/H_2O) were compared to those of the parent amines. In contrast to the amines, the basicity of all *N*,*N*-dimethyl-arylalkylamine oxides showed very limited pK_a variations (range 4.65 – 5.01) with increasing chain length and number of Ph groups. The *N*-oxides in their neutral form had a log P^N value lower by 2.77 ± 0.34 ($n = 9$) units than that of the parent amine. The log P^C of the cationic *N*,*N*-dimethyl-diphenylalkylamines was lower than that of their neutral form, with a decrement *diff*(log P^{N-C}) that increased from 3.25 to 4.21 in the homologous series. Unexpectedly, the decrement *diff*(log P^{N-C}) for the *N*-oxides was much smaller than for the tertiary amines, being 0.23 for the aliphatic *N*,*N*-dimethyl-pentylamine oxide, 0.47 ± 0.13 for the phenylalkylamine oxides, and 0.80 ± 0.07 for the diphenylalkylamine oxides. In fact, the protonated *N*-oxides had log P^C values that were quite comparable to those of the protonated parent amines. Because of the differences in basicity, the difference in distribution coefficients at physiological pH (log $D^{7.4}$) between a tertiary arylalkylamine and its *N*-oxide was 0.82 ± 0.66 ($n = 9$). The pharmacokinetic implication is that *N*-oxygenation may have a smaller effect on the urinary excretion of tertiary amines than usually assumed.

1. Introduction. – Many reactions of metabolism facilitate the excretion of xenobiotics by transforming them into more polar (less lipophilic) metabolites. Thus, tertiary amines are an important group of xenobiotics (*e.g.*, most alkaloids) against which terrestrial animals had to evolve protection and elimination strategies.

N-Oxygenation is one of the major metabolic reactions of tertiary amines [1]. Depending on the physicochemical properties of the substrate, the reaction is catalyzed by cytochrome P450 and/or flavin-containing monooxygenases. Tertiary amines undergoing metabolic *N*-oxygenation are either strong bases (*i.e.*, alkylamines, arylalkylamines, and alicyclic amines) or moderate bases (*i.e.*, heteroaromatic and aromatic amines). The N-atom must also be sterically accessible, meaning, for example, that *N*,*N*-dimethyl-alkylamines are far better substrates than *N*,*N*-diethyl-alkylamines [1].

In pharmacokinetic terms, the *N*-oxygenation of drugs and other xenobiotics affects their distribution and excretion in a manner that is highly dependent on the changes in physicochemical properties produced by the metabolic reaction. It is recognized that the *N*-oxygenation of tertiary amines is accompanied by a decrease in basicity and lipophilicity [2]; however, the paucity of data available lacks systematic character [3]. In a recent study [4], we compared the lipophilicity of 4-substituted pyridines and their

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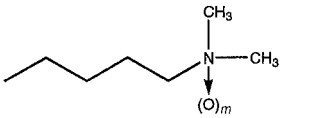
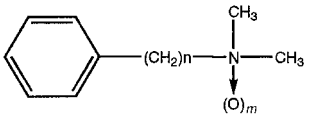
N-oxides, and found that the decrement in lipophilicity was proportional to the partial charge on the O-atom (H-bond acceptor basicity), itself inversely proportional to the electron-withdrawing capacity of the 4-substituent.

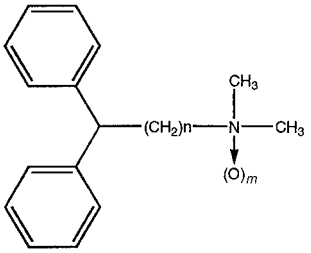
Here, we extend this work to basic tertiary amines, namely *N*,*N*-dimethyl-phenylalkylamines and *N*,*N*-dimethyl-diphenylalkylamines with varying chain lengths (*Fig. 1*). Many drugs contain one of these two structural motifs. *N*,*N*-Dimethylpentylamine (**1**) was included in the study to help assess the influence of the Ph ring(s). Besides the lipophilicity of the neutral form, we also succeeded in measuring the lipophilicity of the cationic form of several compounds. The data were then interpreted in terms of structure-property relationships, revealing the complexity of the intramolecular effects influencing the basicity and pH-lipophilicity profile of the compounds.



$m=0$	$m=1$
1	**1a**



	$m=0$	$m=1$
$n=1$	**2**	**2a**
$n=2$	**3**	**3a**
$n=3$	**4**	**4a**
$n=4$	**5**	**5a**



	$m=0$	$m=1$
$n=0$	**6**	**6a**
$n=1$	**7**	**7a**
$n=2$	**8**	**8a**
$n=3$	**9**	**9a**

Fig. 1. *Structures of the investigated compounds*

2. Results and Discussion. – 2.1. *Basicity of Amines.* The pK_a values of the four phenyl-alkylamines, **2**–**5**, varied between 8.80 and 9.90 and increased linearly ($r^2 = 0.94$, *Eqn. 1*) with increasing distance between the amino and the Ph group (*Eqn. 1*, *Table 1*, and *Fig. 2*):

$$pK_a = 0.34\,(\pm 0.13)\cdot n\,CH_2 + 8.55\,(\pm 0.36) \qquad (1)$$
$$n = 4;\ r^2 = 0.94;\ s = 0.14;\ F = 30$$

where n is the number of CH_2 groups in the molecule. In this and the following equations, 95% confidence limits are given in parentheses, n is the number of compounds, r^2 the square of the correlation coefficient, s the standard deviation, and F is *Fischer*'s test.

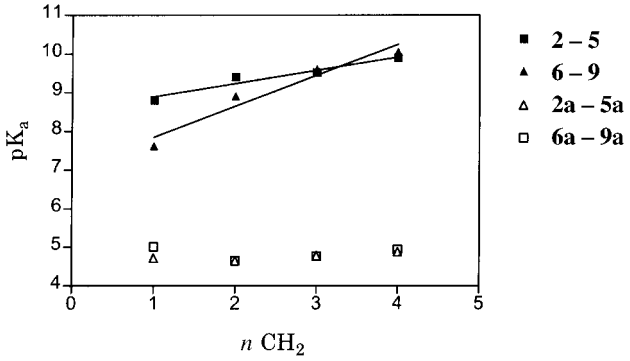


Fig. 2. *Basicity* (expressed as pK_a) *of amines and corresponding* N-*oxides as a function of chain length and number of Ph groups*

Very similar results have been reported for primary phenyl-alkylamines and pyridyl-alkylamines [5]. The same trend was seen here for the four diphenyl-alkylamines **6**–**9** (*Fig. 2*), but the effect of the benzhydryl group was stronger than that of the Ph group, with a range of 7.62 to 10.06 (*Eqn. 2*):

$$\mathrm{p}K_a = 0.80\,(\pm 0.28)\cdot n\ \mathrm{CH_2} + 7.04\,(\pm 0.79) \qquad (2)$$

$$n = 4;\ r^2 = 0.95;\ s = 0.30;\ F = 36$$

These intramolecular interactions are not novel and require no further discussion.

2.2. *Basicity of* N-*Oxides.* In sharp contrast to the tertiary amines **2**–**9**, the corresponding *N*-oxides **2a**–**9a** showed very limited pK_a dependence (range 4.65–5.01) on increasing chain length and number of Ph groups (*Fig. 2*). This is a clear indication that the strongly polar character of the N^+-O^- group and the resulting basicity of the O-atom are not strongly influenced by the aromatic groups. Indeed, the pK_a of the alkylamine *N*-oxide **1a** is 4.88, as compared to the average pK_a of all nine *N*-oxides (4.81 ± 0.13).

Because of the large pK_a differences between the tertiary amines, and the small pK_a differences between their *N*-oxides, the change in pK_a resulting from *N*-oxygenation (pK_a(amine) – pK_a(oxide)) varies considerably. It follows that the pK_a value of an arylalkyl- or alkylamine *N*-oxide cannot be deduced from that of the parent amine, but can be expected to be close to 4.8.

2.3. *Lipophilicity of Neutral and Protonated Tertiary Amines.* The octan-1-ol/H_2O log P^N values (experimental log *P* of the neutral amines) increased almost linearly in the two homologous series, the average increment per CH_2 unit being 0.39 ± 0.04 and 0.51 ± 0.27 in the monophenyl and diphenyl series, respectively (*Fig. 3,a*). The agreement with log *P* values calculated by the CLOGP algorithm [3] is good, with a slope not significantly different from 1, and an intercept equal to 0 (*Eqn. 3* and *Fig. 3,b*):

$$\log P^N = 1.23\,(\pm 0.28)\cdot \mathrm{CLOGP} - 0.25\,(\pm 0.79) \qquad (3)$$

$$n = 8;\ r^2 = 0.94;\ s = 0.28;\ F = 91$$

The phenyl-alkylamines in their cationic form were too hydrophilic for their log *P* (indicated as log P^C) to be measurable by potentiometry (log $P^C < -1$). In contrast, the cationic diphenyl-alkylamines were lipophilic enough to have a measurable log P^C. Here, the average increment per CH_2 unit was 0.19 ± 0.25 (*Fig. 3,c*).

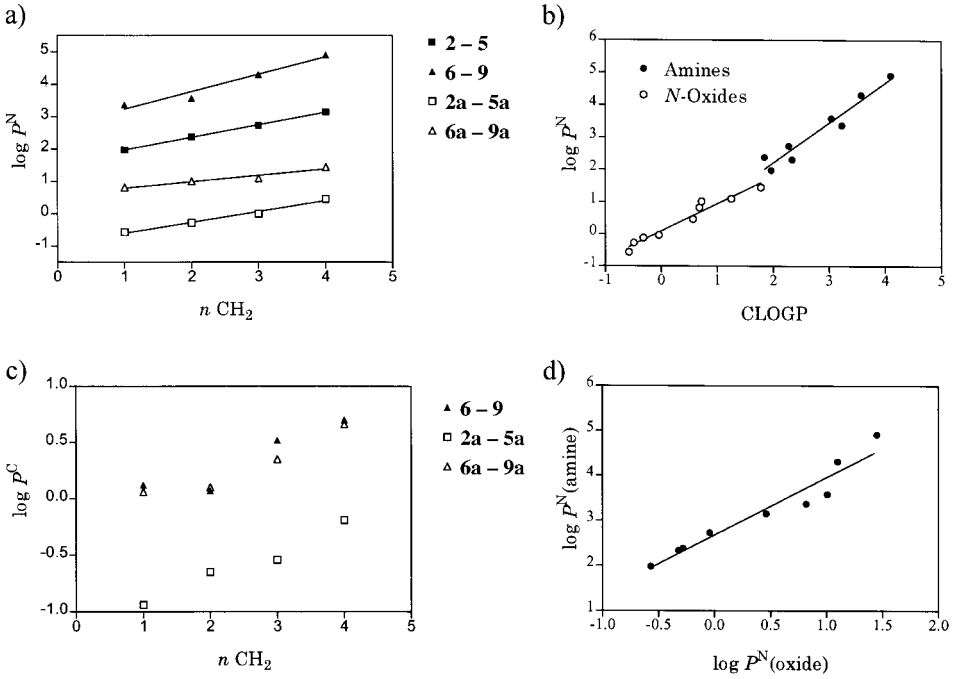


Fig. 3. *Lipophilicity plots:* a) *Variation in the log* P *value of neutral amines and corresponding* N-*oxides* (log P^N) *as a function of chain length and number of Ph groups.* b) *Linear relationships between calculated* (CLOGP) *and experimental* (log P^N) *data.* Amines are represented by a full circle (•), *N*-oxides by an empty circle (○). c) *Variation in the log* P *of cationic amines and corresponding* N-*oxides* (log P^C) *as a function of chain length and number of Ph groups.* d) *Linear relationships between the log* P^N *of amines and corresponding* N-*oxides*

An informative parameter in structure-property relationships is the decrement in lipophilicity resulting from protonation, designated as *diff*(log P^{N-C}). This decrement was not constant but increased from 3.25 to 3.51 to 3.79 to 4.21 in the homologous series of diphenyl-alkylamines. In fact, the decrement increased by 0.32 ± 0.09 per CH_2 unit. This clearly indicates that the effect of an increase in chain length on the lipophilicity of diphenyl-alkylamines is not felt similarly in the neutral and protonated amines.

2.4. *Lipophilicity of Neutral* N-*Oxides.* The log *P* values of the neutral *N*-oxides increased linearly in the two homologuous series (monophenyl compounds: $r^2 = 0.98$, increment $= 0.34 \pm 0.14$; diphenyl compounds: $r^2 = 0.94$, increment $= 0.21 \pm 0.13$) (*Fig. 3,a*). The linear relationship between these experimental data and values calculated by the CLOGP algorithm is shown in *Fig. 3,b*, and is described by *Eqn. 4:*

$$\log P^N = 0.84\,(\pm 0.15) \cdot \mathrm{CLOGP} + 0.09\,(\pm 0.13) \qquad (4)$$

$$n = 8;\ r^2 = 0.95;\ s = 0.17;\ F = 133$$

A parameter of high relevance here is the decrement in lipophilicity resulting from *N*-oxidation of the neutral amines ($\log P^N(\text{amine}) - \log P^N(\text{oxide})$) (*Table 1*). For compounds **1a**–**7a**, this decrement was 2.61 ± 0.11 ($n = 7$), but it became 2.77 ± 0.34 ($n = 9$), when the much larger decrement of compounds **8a** and **9a** was included. A plot (*Fig. 3,d*) of $\log P^N(\text{amine})$ *vs.* $\log P^N(\text{oxide})$ indicates a linear trend (*Eqn. 5*) with diaryl compounds being more dispersed than monophenyl compounds:

$$\log P^N(\text{amine}) = 1.28\,(\pm 0.28) \cdot \log P^N(\text{oxide}) + 2.68\,(\pm 0.21)$$
$$n = 8;\ r^2 = 0.93;\ s = 0.27;\ F = 97 \qquad (5)$$

Interestingly, a $\log P^N(\text{amine}) - \log P^N(\text{oxide})$ value of only 1.91 had been found for pyridine *N*-oxide [4]. This value expresses the less polar character of aromatic *N*-oxides compared to aliphatic *N*-oxides, and it can be explained by resonance effects.

2.5. *Lipophilicity of Protonated* N-*Oxides.* All nine *N*-oxides were sufficiently lipophilic when protonated to yield a measurable $\log P^C$ value (*Table 1*). When measuring the $\log P$ values of ions, one should not neglect the possible influence of counterions. Such a phenomenon can best be seen when the $\log P$ value of an ion is strongly influenced by the ionic strength μ in the aqueous phase. To examine this effect, we compared the $\log P^N$ and the $\log P^C$ values of the *N*-oxides **5a** and **9a** at $\mu = 0.15$,

Table 1. *Physicochemical Properties of Tertiary Phenyl-alkylamines and Diphenyl-alkylamines and Corresponding* N-*Oxides*

	pK_a[a])	pK_a(amine) $-$ pK_a(oxide)	CLOGP[b])	$\log P^N$[c])	$\log P^C$[d])	*diff*($\log P^{N-C}$)[e]) Amine	*N*-oxide	$\log P^N$(amine) $-\log P^N$(oxide)[f])	$\log P^C$(amine) $-\log P^C$(oxide)[g])
1	10.30		2.00	2.33	NM[h])				
1a	4.88	5.42	−0.32	ND[i])	−0.55		0.23[j])	2.45[j])	
2	8.80		1.96	1.98	NM				
2a	4.72	4.08	−0.58	−0.57[k])	−0.94[k])		0.37	2.55	
3	9.40		1.84	2.38	NM				
3a	4.65	4.75	−0.49	−0.28[k])	−0.65[k])		0.37	2.66	
4	9.52		2.28	2.73	NM				
4a	4.78	4.74	−0.04	−0.04[k])	−0.54[k])		0.50	2.77	
5	9.90		2.89	3.15	NM				
5a	4.88	5.02	0.57	0.46	−0.19		0.65	2.69	
6	7.62		3.22	3.37	0.12	3.25			
6a	5.01	2.61	0.68	0.82	0.06		0.76	2.55	0.06
7	8.91		3.04	3.58	0.07	3.51			
7a	4.65	4.26	0.72	1.01	0.10		0.91	2.57	−0.03
8	9.60		3.57	4.31	0.52	3.79			
8a	4.77	4.83	1.25	1.10	0.35		0.75	3.21	0.17
9	10.06		4.10	4.91	0.70	4.21			
9a	4.94	5.12	1.78	1.45	0.66		0.79	3.46	0.04

[a]) Determined by potentiometry, SD < 0.01; $n = 3$. The average pK_a of all nine *N*-oxides 4.81 ± 0.13. [b]) Calculated with the CLOGP algorithm [3]. [c]) $\log P$ of the neutral species determined by potentiometry, SD < 0.05; $n = 4$. [d]) $\log P$ of the cationic species determined by potentiometry, SD < 0.05; $n = 4$. [e]) $\log P$ of the neutral form minus $\log P$ of the cationic form. This decrement is 0.47 ± 0.13 for the *N*-oxides **2a**–**5a**, and 0.80 ± 0.07 for the *N*-oxides **6a**–**9a**. [f]) This decrement is 2.61 ± 0.11 for compounds **1a**–**7a** ($n = 7$). It is 2.77 ± 0.34 ($n = 9$) for compounds **1a**–**9a** ($n = 9$). [g]) The average difference is 0.06 ± 0.08; $n = 4$. [h]) NM = not measurable by potentiometry ($\log P^C < -1$). [i]) ND = not determined. [j]) The CLOGP value was taken as $\log P^N$. [k]) Determined by the shake-flask method and used to check the potentiometric result (see text for details).

$\mu = 0.10$, and $\mu = 0.05$. As shown in *Table 2*, there were only minute fluctuations in pK_a and log P values. Also, the variations in log P^C values did not reveal any trend and remained within the experimental error. We conclude that ionic strength does not detectably affect the properties of the compounds under the present conditions.

Table 2. *Influence of Ionic Strength on* pK_a *and log* P[a])

	0.05M KCl[b])			0.10M KCl[c])			0.15M KCl[d])		
	pK_a	log P^N	log P^C	pK_a	log P^N	log P^C	pK_a	log P^N	log P^C
5a	4.90	0.48	−0.35	4.84	0.45	−0.15	4.88	0.46	−0.19
9a	4.87	1.48	0.47	4.86	1.45	0.67	4.94	1.45	0.66

[a]) Determined by potentiometry, SD < 0.01; $n = 3$. [b]) $\mu = 0.05$. [c]) $\mu = 0.10$. [d]) $\mu = 0.15$.

As deduced from data in *Table 1*, the decrement in log P resulting from protonation, *diff*(log P^{N-C}), was much smaller for the *N*-oxides than for the tertiary amines. Indeed, this decrement was 0.23 for the aliphatic amine oxide **1a**, 0.47 ± 0.13 for the phenyl-alkylamine oxides **2a** to **5a**, and 0.80 ± 0.07 for the diphenyl-alkylamine oxides **6a**–**9a**. As a rule, the difference between the lipophilicity of neutral and cationic amines covers a range from 3 to 4 in the octan-1-ol/H_2O system [6]. Thus a normal value of *diff*(log P^{N-C}) (average value *ca.* 3.7) is observed for amines **6**–**9**, whereas the lipophilicity of the *N*-oxides decreases only modestly upon protonation.

This latter finding is postulated to be due to a polarity effect, and more specifically to the different manner in which protonation alters the polarity of amines and *N*-oxides. To test this hypothesis, we used quantum mechanics at the *ab initio* 6-31G** level to calculate ESP partial charges and N–O interatomic distances in the model compounds Me_3N, $Me_3N^+-O^-$, and their protonated forms. As seen in *Table 3*, neutral Me_3N is only slightly polar, but is transformed by protonation into a large cation rendered highly hydrophilic by a well-distributed positive charge. This change differs markedly from that occurring with $Me_3N^+-O^-$ (*Table 3*). Here, the *N*-oxide moiety is seen to be strongly polarized and highly polar, and protonation has only limited effect on the partial charges carried by the N- and O-atoms and on their interatomic distance. In other words, protonation cannot increase strongly the hydrophilicity of an already highly polar *N*-oxide.

Because of the vastly different effects of protonation on the log P of amines and the corresponding *N*-oxides, the difference in lipophilicity between the protonated amines

Table 3. *Charge Distribution and N–O Interatomic Distance in Model Compounds, as Calculated at the 6-31G** Level*

Model compounds	Atomic charges				Distance N–O [Å]
	Me	N	O	H	
Me_3N	0.14	−0.42			
$Me_3N^+-O^-$	0.02	0.71	−0.77		1.3665[a])
Me_3N^+-H	0.17	0.25		0.25	
Me_3N^+-OH	0.19	0.52	−0.54	0.47	1.3839[a])

[a]) The corresponding distance in Me_2N-OH is 1.3907 Å.

and their protonated *N*-oxides (0.06 ± 0.08; $n = 4$) is negligible (*Table 1*). It even appears that the protonated *N*-oxides **1a**–**5a** may be *more* lipophilic than the protonated form of their parent amines **1**–**5**. These observations point to the similarity of protonated amines, neutral *N*-oxides and protonated *N*-oxides as far as their polar intermolecular interactions are concerned.

2.6. *Distribution Coefficients (Apparent Lipophilicity) of the Amines and their N-Oxides.* Distribution coefficients (expressed as log *D*) can be calculated for an amine at any pH value knowing its pK_a, log P^N, and log P^C values. log *D* Values often yield better correlations with pharmacokinetic parameters than log *P*, presumably because the influence of all ionization states is taken into account. To obtain some pharmacokinetically relevant data from the results in *Table 1*, we calculated the log *D* values of the *N*-oxides at pH 2.0, 5.0, and 7.4 (*Table 4*). At pH 7.4, the tertiary amines are mostly protonated, whereas the *N*-oxides are mostly neutral. As a result, log $D^{7.4}$(amine) value is higher than log $D^{7.4}$(oxide) value by 0.82 unit ($n = 9$; SD = 0.66) (*Table 4*), whereas log P^N(amine) is higher than log P^N(oxide) by 2.77 units ($n = 9$; SD = 0.34) (*Table 1*). This comparison indicates, in pharmacokinetic terms, that *N*-oxygenation may have a smaller effect on the polarity and urinary excretion of tertiary amines than usually assumed.

3. Conclusions and Perspectives. – This study sheds light on some intramolecular interactions influencing the basicity of arylalkylamine oxides, and especially their lipophilicity in the neutral and protonated state.

Table 4. *Distribution Coefficients of Amines and Corresponding* N-*Oxides*[a])

	log $D^{2.0}$	log $D^{5.0}$	log $D^{7.4}$	log $D^{7.4}$(amine) – log $D^{7.4}$(oxide)
1	–[b])	–[b])	– 0.57	
1a	– 0.55	0.39	– 0.32	– 0.25
2	–[b])	–[b])	0.56	
2a	– 0.90	– 0.67	– 0.57	1.13
3	–[b])	–[b])	0.38	
3a	– 0.64	– 0.38	– 0.28	0.66
4	–[b])	–[b])	0.61	
4a	– 0.53	– 0.19	– 0.06	0.67
5	– 1.04	– 0.96	0.65	
5a	– 0.18	0.29	0.46	0.19
6	0.12	0.84	2.94	
6a	0.06	0.58	0.82	2.12
7	0.07	0.22	2.06	
7a	0.10	0.87	1.01	1.05
8	0.52	0.58	2.12	
8a	0.35	0.94	1.10	1.02
9	0.70	0.76	2.26	
9a	0.66	1.24	1.45	0.81

[a]) Calculated according to the following equation:

$$D = P^N \cdot \left(\frac{1}{1 + 10^{pK_a - pH}}\right) + P^C \cdot \left(\frac{10^{pK_a - pH}}{1 + 10^{pK_a - pH}}\right).$$

[b]) Not calculable due to the non-availability of a log P^C value.

The lack of variation in the pK_a values of monophenyl-alkylamine *N*-oxides and diphenyl-alkylamine oxides, as well as the weak log *P* differences between their neutral and cationic forms, suggest that the ionizable and strongly polarized *N*-oxide moiety has an overwhelming influence on these physicochemical properties. From a pharmacokinetic perspective, the next step is to investigate the partitioning and intermolecular interactions of *N*-oxides in anisotropic media such as micelles and artificial membranes (liposomes). Work is in progress along these lines.

Experimental Part

General. Anal. grade octan-1-ol was purchased from *Fluka Chemie* (Buchs, CH). M.p.: *Büchi 530* apparatus, uncorrected. ^{1}H-NMR Spectra: *Bruker AC-200*, in (D_6)DMSO, at 200 MHz. Elemental analyses: within 0.4% unless indicated otherwise, obtained from *REDOX* (I-Cologno Monzese).

N,N-*Dimethylamines* **1** [7], **2** [8], **3** [8], **4** [8], **5** [8], **6** [9], **7** [10], **8** [11] were synthesized according to published methods.

N,N-*Dimethyl-4,4-diphenylbutylamine hydrochloride* (**9**) was synthesized according to the procedure for **8** [11]: 0.25 g (11.0 mmol) of Na and 1.29 g (22.0 mmol) of K were vigorously stirred at reflux temp. under N_2 in dry THF (60 ml) until the Na/K alloy was formed (ca 4 h). To the cooled suspension, a soln. of diphenylmethyl methyl ether [12] (2.30 g, 11.0 mmol) in dry THF (15 ml) was added dropwise at r.t. The mixture was stirred for 16 h, then cooled to 0°, and a soln. of 3-chloro-*N,N*-dimethylpropylamine (2.67 g, 22.0 mmol) in dry THF (10 ml) was added slowly. The mixture was further stirred for 3 h, the reaction was quenched by slow dropwise addition of H_2O (10 ml), THF was distilled under vacuum, and the residue was dissolved in Et_2O. The product was extracted with 4N HCl, the aq. phase was washed with Et_2O, made alkaline with 6N NaOH, and extracted with AcOEt. The org. phase was dried ($MgSO_4$) and evaporated to afford the crude product, which was purified by flash chromatography (FC) (silica gel; CH_2Cl_2/MeOH 9.5:0.5) to obtain an oil (30%) which was characterized as the hydrochloride. M.p. 145–148° (i-PrOH /Et_2O). ^{1}H-NMR ((D_6)DMSO): 1.64–1.56 (*m*, 2 H); 2.15–2.03 (*m*, 2 H); 2.66 (*s*, 6 H); 3.07 (*t*, 2 H); 3.97 (*t*, 1 H); 7.15–7.36 (*m*, 10 H); 10.65 (br., 1 H); ^{13}C-NMR: 22.5; 31.7; 41.9; 50.1; 56.3; 126.3; 127.7; 128.5; 144.8. Anal. ($C_{18}H_{23}N \cdot HCl$): C, H, N.

General Procedure for the Synthesis of the N,N-Dimethylphenyl-alkylamine N-*Oxides* **1a**–**5a.** The amine (50 mmol) in MeOH was treated dropwise under stirring at 0° with 30% H_2O_2 (150 mmol), and the resulting mixture was stirred at r. t. until the reaction was complete (TLC detection; CH_2Cl_2/MeOH 9:1). The solvent was evaporated, the residue dissolved in H_2O, and the resulting soln. was made alkaline with 37% NH_4OH and washed with AcOEt. The aq. phase was evaporated under vacuum and the residue dried in a desiccator under vacuum over P_4O_{10} and dissolved in MeOH. The soln. was saturated with gas. HCl, evaporated under vacuum, and the residue was crystallized.

N,N-*Dimethylpentylamine* N-*Oxide Hydrochloride* (**1a**). Yield: 30%. Very hygroscopic oil that solidified in the desiccator; crystallized from dry MeOH/Et_2O. ^{1}H-NMR ((D_6)DMSO): 0.90 (*t*, 3 H); 1.29–1.36 (*m*, 4 H); 1.70–1.80 (*m*, 2 H); 3.46 (*s*, 6 H); 3.62–3.70 (*m*, 2 H); 12.69 (br., 1 H). ^{13}C-NMR: 13.83; 21.78; 21.89; 27.73; 55.25; 67.91. Anal. ($C_7H_{17}NO \cdot HCl \cdot 1.75\ H_2O$): C, H, N.

N,N-*Dimethylbenzylamine* N-*Oxide Hydrochloride* (**2a**). Yield: 60%. Hygroscopic white solid. M.p. 108–110° (dry MeOH/Et_2O). ^{1}H-NMR ((D_6)DMSO): 3.17 (*s*, 6 H); 4.95 (*s*, 2 H); 7.49–7.65 (*m*, 5 H); 12.90 (br., 1 H). ^{13}C-NMR: 54.81; 70.18; 128.43; 128.66; 130.26; 133.06. As picrate, m.p. 157–159° ([13]: 158–158.5°).

N,N-*Dimethyl-2-phenylethylamine* N-*Oxide Hydrochloride* (**3a**). Yield: 75%. White solid. M.p. 156–158° (dry i-PrOH). ^{1}H-NMR ((D_6)DMSO): 3.15 (*t*, 2 H); 3.55 (*s*, 6 H); 3.96 (*t*, 2 H); 7.32–7.37 (*m*, 5 H); 12.94 (br., 1 H). ^{13}C-NMR: 28.49; 55.48; 66.33; 127.03; 128.79; 129.10; 136.20. Anal. ($C_{10}H_{15}NO \cdot HCl$): C, H, N.

N,N-*Dimethyl-3-phenylpropylamine* N-*Oxide Hydrochloride* (**4a**). Yield: 45%. White solid. M.p. 90–91° (dry i-PrOH/Et_2O). ^{1}H-NMR ((D_6)DMSO): 2.11–2.15 (*m*, 2 H); 2.66 (*t*, 2 H); 3.46 (*s*, 6 H); 3.64–3.72 (*m*, 2 H); 7.22–7.34 (*m*, 5 H); 12.71 (br., 1 H). ^{13}C-NMR: 24.09; 31.57; 55.36; 67.77; 126.30; 128.39; 128.55; 140.45. Anal. ($C_{11}H_{17}NO \cdot HCl \cdot 0.25\ H_2O$): C, H, N.

N,N-*Dimethyl-4-phenylbutylamine* N-*Oxide Hydrochloride* (**5a**). Yield: 50%. White solid. M.p. 112–114° (dry THF). ^{1}H-NMR ((D_6)DMSO): 1.57–1.69 (*m*, 2 H); 1.76–1.85 (*m*, 2 H); 2.65 (*t*, 2 H); 3.46 (*s*, 6 H); 3.67–3.75 (*m*, 2 H); 7.20–7.35 (*m*, 5 H); 12.70 (br., 1 H). ^{13}C-NMR: 21.92; 27.66; 34.60; 55.33; 67.81; 126.01; 128.46; 141.66. Anal. ($C_{12}H_{19}NO \cdot HCl \cdot 0.2\ H_2O$): C, H, N.

General Procedure for the Synthesis of the N,N-*Dimethyl-ω-diphenyl-alkylamine* N-*Oxides* **6a**–**9a**. A soln. of 3-chloroperbenzoic acid (6.3 mmol) in dry toluene was added slowly to a stirred soln. of the amine (5 mmol) in dry toluene (20 ml) kept at 0°. The mixture was stirred at r. t. until all of the amine was oxidized (TLC detection). Toluene was evaporated under vacuum, the residue was dissolved with Et_2O, and the resulting soln. was saturated with gas. HCl. The precipitated hydrochloride was filtered and crystallized.

N,N-*Dimethyldiphenylmethylamine* N-*Oxide Hydrochloride* (**6a**). TLC: petroleum ether/AcOEt 7:3. Yield: 61%. White solid. M.p. 184–186 ° (H_2O). ^{1}H-NMR ((D_6)DMSO): 3.46 (*s*, 6 H); 6.43 (*s*, 1 H); 7.42–7.68 (*m*, 10 H); 13.14 (*s*, 1 H). ^{13}C-NMR: 55.78; 81.50; 128.02; 129.12; 129.72; 133.76. Anal. ($C_{15}H_{17}NO \cdot HCl$): C, H, N.

N,N-*Dimethyl-2,2-diphenylethylamine* N-*Oxide Hydrochloride* (**7a**). TLC: CH_2Cl_2/MeOH 7:3. Yield: 79%. White solid. M.p. 125–129° (H_2O). ^{1}H-NMR ((D_6)DMSO): 3.41 (*s*, 6 H); 4.55 (*d*, 2 H); 4.90 (*t*, 1 H); 7.19–7.53 (*m*, 10 H); 12.91 (*s*, 1 H). ^{13}C-NMR: 45.01; 56.43; 71.24; 127.00; 127.80; 126.95; 142.25. Anal. ($C_{16}H_{19}NO \cdot HCl \cdot 0.5\ H_2O$): C, H, N.

N,N-*Dimethyl-3,3-diphenylpropylamine* N-*Oxide Hydrochloride* (**8a**). TLC: CH_2Cl_2/MeOH 7:3. Yield 86%. White solid. M.p. 158–160° (acetone). ^{1}H- NMR ((D_6)DMSO): 2.60–2.67 (*m*, 2 H); 3.48 (*s*, 6 H); 3.46–3.58 (*m*, 2 H); 4.05 (*t*, 1 H); 7.21–7.42 (*m*, 10 H); 12.64 (*s*, 1 H). ^{13}C-NMR: 27.52; 47.61; 55.44; 67.31; 126.60; 127.52; 128.68; 143.66. Anal. ($C_{17}H_{21}NO \cdot HCl$): C, H, N.

N,N-*Dimethyl-4,4-diphenylbutylamine* N-*Oxide Hydrochloride* (**9a**). TLC: AcOEt/MeOH/37% NH_4OH 8.5:1:0.5. Yield: 74%. White solid. M.p. 148° (i-PrOH). ^{1}H-NMR ((D_6)DMSO): 1.5–1.7 (*m*, 2 H); 2.0–2.1 (*m*, 2 H); 3.35, 3.36 (2*s*, 6 H); 3.66–3.74 (*m*, 2 H); 4.02 (*t*, 1 H); 7.19–7.37 (*m*, 10 H); 12.46 (*s*, 1 H). ^{13}C-NMR: 21.02; 31.32; 49.97; 55.30; 67.75; 126.3; 127.66; 128.58; 144.68. Anal. ($C_{18}H_{23}NO \cdot HCl$): C, H, N.

Potentiometric Determination of Protonation Constants. Potentiometric titrations were performed with the *PCA101* apparatus [14] (*Sirius Analytical Instruments Ltd.*, Forrest Row, East Sussex, UK) as described in [15].

Determination of Lipophilicity Parameters. Potentiometry was the main technique used to determine the pH-lipophilicity profiles of parent amines and *N*-oxides. The *PCA101* and the new *GlpKa* instruments (*Sirius Analytical Instruments Ltd.*) were used. At least four separate titrations of *ca.* 1 mM for each compound, containing various volumes of octan-1-ol (from 1 ml of org. solvent/15 ml of H_2O to 8 ml of org. solvent/8 ml of H_2O), were performed in the pH range 2 to 11.5. The titrations were carried out under Ar at 25.0 ± 0.1° [14–16].

Because the pH-metric technique cannot reliably determine partition coefficients of markedly hydrophilic compounds, log *P* values below −0.5 were confirmed with the classical shake-flask procedure [17].

Ab initio *Quantum-Mechanical Calculations.* The geometries of compounds Me_3N, $Me_3N^+-O^-$, Me_3N^+-H, Me_3N^+-OH (*Table 3*) were optimized by *ab initio* calculations at the 6-31G** level with the Spartan 5.0 software [18] with the standard convergence criteria. All calculations were run on a *Silicon Graphics Origin 2000* workstation. The ESP partial atomic charges were also calculated [19].

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