Reactivity of Cage-Like Amines toward *p*-Toluenesulfonyl Chloride and Diphenyl Chlorophosphate in Acetonitrile

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Abstract—The nucleophilic reactivity of amines of the norbornane, norbornene, and adamantane series toward *p*-toluenesulfonyl chloride and diphenyl chlorophosphate in acetonitrile at 25°C is determined mainly by the steric factor. Parameters characterizing spatial accessibility of the reaction center in the amine molecule have been determined. Cage-like substituents show no appreciable effect on the amine reactivity, as compared to common alkyl groups.

Cage-like amines, primarily of the norbornane, norbornene, and adamantane series, exhibit a wide spectrum of biological activity. 1-Aminoadamantane hydrochloride and 1-(1-aminoethyl)adamantane hydrochloride (amantadine and remantadine) have found application in medical practice as antiviral and anti-Parkinson agents [1, 2]. The biological activity of compounds of this group is believed to originate from the presence of a highly lipophilic bulky cage-like fragment which is capable of directly interacting with biological membranes containing a lipid layer, as well as with hydrophobic fragments of proteins [1]. Antiviral activity is typical of amines of the norbornene and norbornane series acyl derivatives of amines exhibit neurotropic (specifically analgetic, antispasmodic, antihypoxic, and tranquilizing), antiphlogistic, antiglycemic, and other kinds of biological activity [3, 4].

Although a considerable progress was achieved in the field of synthesis of cage-like amines and their acyl derivatives [5], quantitative aspects of their reactivity were studied very poorly. In the present work we used kinetic methods to estimate the nucleophilic reactivity of cage-like amines toward acyl halides. As electrophiles we selected *p*-toluenesulfonyl chloride and diphenyl chlorophosphate:

$$2RR'NH + AcylCl \longrightarrow AcylNRR' + RR'NH_2^+ + Cl^-, \quad (1)$$

R is a cage-like substituent; R' = H, Me; Acyl = *p*-MeC$_6$H$_4$SO$_2$, (PhO)$_2$PO.

For comparison, we also examined the kinetics of the reactions of common aliphatic amines RR'NH (where R, R' = H, Alk) with *p*-toluenesulfonyl chloride. The reactions were carried out in acetonitrile at 25°C under pseudozero-order conditions with respect to the reagent ([RR'NH] $\gg$ [AcylCl]); here, the concentration of AcylCl was 10^{-6} to 10^{-5} M. In this case, the conversion in reaction (1) is almost complete. The reaction rate was monitored by conductometry, following decrease in the electric resistance of the solution as a result of accumulation of ionic species. As a rule, the apparent pseudofirst-order rate constants k_τ (s^{-1}) did not change during the process, and average k_τ value calculated from 8–10 measurements was taken. In a few cases when k_t slightly decreased as the reaction progressed, the rate constants at the initial moment $k_{\tau=0}$ (s^{-1}) were determined by extrapolation of the curvilinear $k_\tau = f(\tau)$ dependences to the zero moment, assuming $k_{\tau=0} = k$ (cf. [6]).

The rate constants k are linearly related to the amine concentration [B] (Fig. 1). This relation suggests the overall second reaction order:

$$k = k_1[B]. \quad (2)$$

Here, k_1 (l mol^{-1} s^{-1}) is the second-order rate constant which characterizes the amine reaction with *p*-toluenesulfonyl chloride or diphenyl chlorophosphate. The fact that the straight lines shown in Fig. 1 include

points corresponding to different substrate concentrations provides an additional support for the first order of the reaction with respect to the substrate. Thus, from the kinetic viewpoint, reaction (1) is analogous to reactions of aliphatic amines with arenesulfonyl halides in a polar aprotic solvent [7] (unlike the reactions of alkylamines in weakly polar media, where autocatalytic effect of the two reaction products and the initial amine is observed [8]). Tables 1 and 2 contain the values of k_1 for cage-like aliphatic amines, calculated by Eq. (2) using the least-squares procedure.

While discussing the obtained results, it is reasonable to consider spatial accessibility of the reaction center in the amine molecule as the main factor. There is a hypothesis according to which the inductive effect of an alkyl group attached to a reaction center is almost equal to zero while change in the reactivity upon variation of alkyl substituents is determined exclusively by steric hindrances created by those substituents [10, 11]. Therefore, the reactivity of primary and secondary alkylamines depends only on the steric properties of the amine molecule and inductive effect of hydrogen atoms on the nitrogen. This assumption was convincingly proved by correlation analysis of more than 20 reaction series including reactions of primary and secondary alkylamines with various electrophiles, for which the attack by amine was reliably shown to be the rate-determining stage [11]. According to [11], the rate constants k for the above series are well described by two-parameter correlation (3):

$$\log k = \log k_0 + \delta E_N + \rho_H^* \; n_H \; \sigma_H^*. \qquad (3)$$

Here, E_N is a parameter which characterizes spatial accessibility of the amino group in an amine molecule; it is equal to the Taft steric constant E_S for an alkyl substituent which is isosteric to the given amine [12]; n_H is the number of hydrogen atoms on the nitrogen ($n_H = 1$ or 2); $\sigma_H^* = 0.49$ is the Taft inductive constant of the hydrogen atom; and the coefficients ρ_H and σ_H^* characterize the magnitude of the effect of the respective factor (steric and inductive) on $\log k$.

Let us consider the data in Table 1. For each substrate of both norbornane and norbornene series we observed only a small difference in the rate constants for the *exo* and *endo* isomers. In the reactions with *p*-toluenesulfonyl chloride, the ratio of k_1^{endo} to k_1^{exo} for amines **II** and **I** is 1.18, and for amines **V** and **IV** this ratio is equal to 1.27; in the reactions with diphenyl chlorophosphate, the corresponding ratios are 1.13 and 1.39, respectively (Table 1). Nevertheless, some tendency
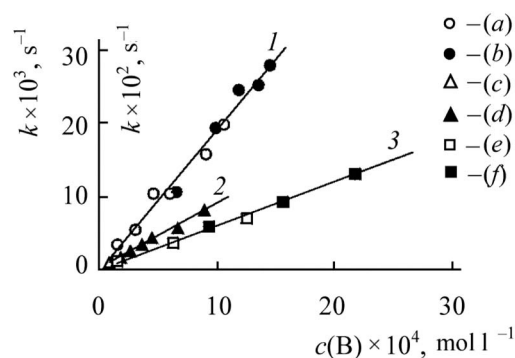

Fig. 1. Plots of the pseudofirst-order rate constants k versus amine concentration c_B for reactions of cage-like amines with *p*-toluenesulfonyl chloride (TSC) and diphenyl chlorophosphate (DPCP) in acetonitrile at 25°C: (*1*) **III** + TSC, c(TSC) = 1.22×10^{-1} (*a*), 2.41×10^{-5} M (*b*); (*2*) **VII** + DPCP, c(DPCP) = 2.48×10^{-6} (*c*), 2.48×10^{-5} M (*d*); (*3*) **XIII** + TSC, c(TSC) = 1.15×10^{-5} (*e*), 5.71×10^{-5} M (*f*). Plot *2* corresponds to the right *y* axis.

for the reactivity of cage-like amines to increase was revealed in going from the *exo* to the *endo* isomer.

The number of methylene units between the cage-like fragment and the amino group differently affects the rate constants k_1 for primary amines of the norbornene and adamantane series. The k_1 values for norbornene derivatives **V** and **VI** almost do not depend on the length of the $(CH_2)_n$ bridge, where $n = 1$ or 2 (Table 1). Here, we have a complete analogy with structurally related primary alkylamines (provided that the norbornenyl group is assumed to be formally equivalent to isopropyl): alkylamines in which the nitrogen atom is separated from the isopropyl group by one or more methylene units are characterized by almost equal E_N values [9] and hence by similar reactivities [11]. Amines of the adamantane series behave differently in reactions with *p*-toluenesulfonyl chloride. In going from 1-aminoadamantane (**IX**) to 1-aminomethyladamantane (**X**), the rate constant k_1 increases by a factor of ~40, and in going from amine **X** to 1-aminoethyladamantane (**XI**), by a factor of 2.5 (Table 1). Increase in the reaction rate upon introduction of the second methylene unit into adamantane derivatives (unlike amines of the norbornene series) is explained by the larger size of the adamantyl group.

The double carbon–carbon bond is known to act as an electron-withdrawing moiety [13]. Therefore, norbornene amines **IV** and **V** were expected to be less reactive than the corresponding saturated norbornane derivatives **I** and **II**. However, according to the experimental data (Table 1), the rate constants k_1 are almost similar for a given electrophile and each pair of amines (**I** and **IV** or **II** and **V**). It seems reasonable to explain the

Table 1. Second-order rate constants k_1 for reactions of cage-like amines **I**–**XIV** (B) with *p*-toluenesulfonyl chloride (TSC) and diphenyl chlorophosphate (DPCP) (acetonitrile, 25°C) and parameters E_N for amines **I**–**XIV** and sterically related alkylamines
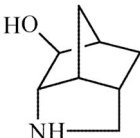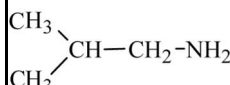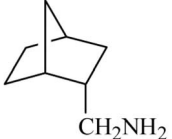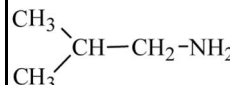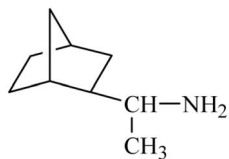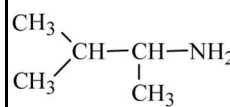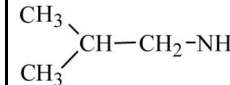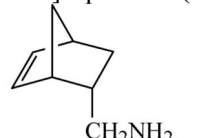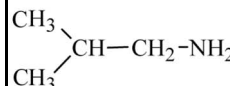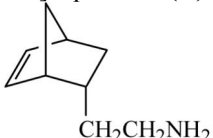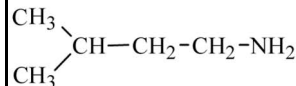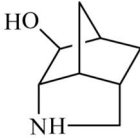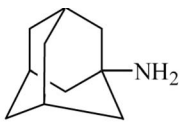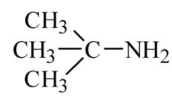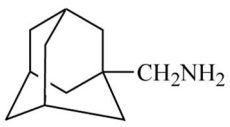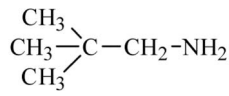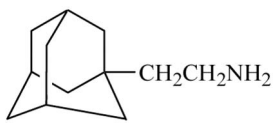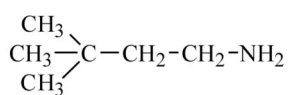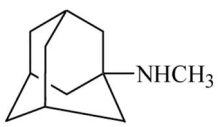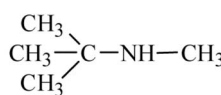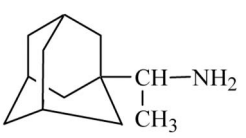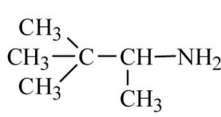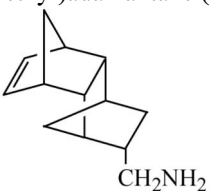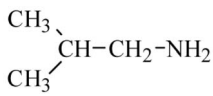
Amine	Electro-phile	$c_B \times 10^4$, M	k_1, l mol⁻¹ s⁻¹; r,[a] n[b]	$-E_N^B$	Alkylamine formula	$-E_N$ [9][c]
exo-2-Aminomethylbi-cyclo[2.2.1]heptane (**I**)	TSC	0.714–8.93	67.2±1.3, r =0.999, n = 6	0.31	$(CH_3)_2CH-CH_2-NH_2$	0.32
	DPCP	0.357–3.57	148±4, r =0.999, n = 5			
endo-2-Aminomethyl-bicyclo[2.2.1]heptane (**II**)	TSC	0.524–10.5	79.2±1.9, r =0.998, n = 8	0.27	$(CH_3)_2CH-CH_2-NH_2$	0.32
	DPCP	0.524–5.24	180±3, r = 0.999, n= 6			
2-(1-Aminoethyl)bicyclo-[2.2.1]heptane (**III**)[d]	TSC	1.51–14.5	19.1±1.0, r = 0.989, n=11	0.67	$(CH_3)_2CH-CH(CH_3)-NH_2$	0.97[d]
	DPCP	2.08–15.6	23.8±0.6, r = 0.998, n = 9			
exo-5-Aminomethyl-bicyclo[2.2.1]hept-2-ene (**IV**)	TSC	0.655–8.51	62.8±3.6, r = 0.992, n = 7	0.33	$(CH_3)_2CH-CH_2-NH_2$	0.32
	DPCP	0.655–6.55	148±3, r =0.999, n = 6			
endo-5-Aminomethylbi-cyclo[2.2.1]hept-2-ene (**V**)	TSC	0.664–7.31	79.7±2.5, r = 0.998, n = 6	0.27	$(CH_3)_2CH-CH_2-NH_2$	0.32
	DPCP	0.664–6.64	206±8, r = 0.997, n = 6			
endo-5-Aminoethylbi-cyclo[2.2.1]hept-2-ene (**VI**)	TSC	0.586–5.86	78.8±2.4, r = 0.998, n = 7	0.27	$(CH_3)_2CH-CH_2-CH_2-NH_2$	0.31
	DPCP	0.586–5.86	181±8, r = 0.996, n = 6			
exo-5-Aminomethyl-*exo*-2,3-epoxybicyclo[2.2.1]heptane (**VII**)	TSC	0.450–4.05	40.6±0.6, r = 0.999, n = 5			
	DPCP	0.899–8.99	88.0±3.5, r = 0.996, n = 7			

Table 1. (Contd.)

Amine	Electro-phile	$c_B \times 10^4$, M	k_1, l mol^{-1} s^{-1}, r^a n^b	$-E_N^B$	Alkylamine formula	$-E_N$ [9]^c
exo-2-Hydroxy-4-azatri-cyclo[4.2.1.0^{37}]nonane (**VIII**)	TSC	0.298–2.74	289±11, r 0.998, n 4			
1-Aminoadamantane (**IX**)	TSC DPCP	2.64–26.4 2.56–20.0	1.06±0.09, r 0.986, n 6 0.977±0.062, r 0.992, n 6	1.47	(CH₃)₃C—NH₂	1.63
1-Aminomethyladamantane (**X**)	TSC	0.54–2.50	40.8±2.3, r 0.998, n 3	0.46	(CH₃)₃C—CH₂—NH₂	0.33
1-Aminoethyladamantane (**XI**)	TSC	0.253–2.32	103±6, r 0.997, n 4	0.20	(CH₃)₃C—CH₂—CH₂—NH₂	≥0.31^f
1-Methylaminoadamantane (**XII**)	TSC DPCP	27.8–81.6 89.2–315	0.200±0.011, r 0.996, n 5 0.0864±0.0072, r 0.990, n 5	2.96	(CH₃)₃C—NH—CH₃	3.21
l-(l-Aminoethyl)adamantane (**XIII**)	TSC DPCP	1.57–21.8 1.49–13.4	5.95±0.20, r 0.998, n 6 9.62±0.58, r 0.995, n 5	0.99	(CH₃)₃C—CH(CH₃)—NH₂	≥0.97^d
endo- Aminomethyltetracyclo -[6.2.1.1^{3,6}.0^{2,7}]dodec-9-ene (**XIV**)	TSC DPCP	1.10–8.27 0.509–5.09	93.4±2.8, r 0.998, n 6 193±6, r 0.998, n 7	0.22	(CH₃)₂CH—CH₂—NH₂	0.32

^{a} Linear correlation coefficient.
^{b} The number of points involved in the calculation of k_1.
^{c} Given are $-E_S$ values for alkyl radicals isosteric to the amines.
^{d} A mixture of *exo* and *endo* isomers.
^{e} Assumed on the basis of the fact that $-E_S$ values for hydrocarbon groups R(CH₂)₂CH₂ (R = H, Me, Et, *i*-Pr), which are isosteric to R(CH₂)₂NH₂, are equal to 0.31 [9].
^{f} The $-E_N$ value was assumed to be no less than $-E_S$ = 0.97 [9] for the CH₃CH₂CH(CH₃)CH₂ substituent, for alkyl groups at the third carbon atom weakly affect $-E_S$; for example, $-E_S$ values for CH₃CH₂CH₂CH₂, (CH₃)₂CHCH₂CH₂, and (CH₃)₃CCH₂CH₂ are 0.31, 0.32, and 0.33, respectively [9].

Table 2. Rate constants k_1 for reactions of aliphatic amines **XV–XXIV** with *p*-toluenesulfonyl chloride (acetonitrile, 25°C) and parameters E_N of amines **XV–XXIV**

Amine k_1	l mol⁻¹ s⁻¹	$-E_N$, [9]
Methylamine (**XV**)	174 ± 13	0.08
Allylamine (**XVI**)	21.8 ± 1.3	0.43
Butylamine (**XVII**)	70.3 ± 1.3	0.31
Isobutylamine (**XVIII**)	59.2 ± 1.8 (131 ± 4)[a]	0.32
tert-Butylamine (**XIX**)	1.29 ± 0.02	1.63
Cyclohexylamine (**XX**)	7.52 ± 0.55	0.89
Diethylamine (**XXI**)	8.06 ± 0.51	2.00
Dipropylamine (**XXII**)	7.13 ± 0.29 (3.59 ± 0.23)[a]	2.03
Dibutylamine (**XXIII**)	4.06 ± 0.77	2.08
Diisopropylamine (**XXIV**)	(9.96 ± 0.25)×10⁻⁵	5.01

[a] The rate constant k_1 for the reaction with diphenyl chlorophosphate.

absence of electron-withdrawing effect of the double bond in amines **IV** and **V** by its remoteness from the reaction center. Oxidation of the double bond in **IV** to oxirane ring (amine **VII**) leads to decrease in the rate constant k_1 for reactions with both electrophiles. Presumably, this is caused by a stronger negative inductive effect of the oxirane oxygen atom, as compared to the double bond.

In reactions with both TSC and DPCP, the rate constant k_1 decreases in going from primary amine, 1-amino-adamantane (**IX**), to secondary amine, 1-methylamino-adamantane (**XII**). Naturally, this is due to lesser spatial accessibility of the reaction center in the secondary amine, as compared to the primary one. The steric factor is also
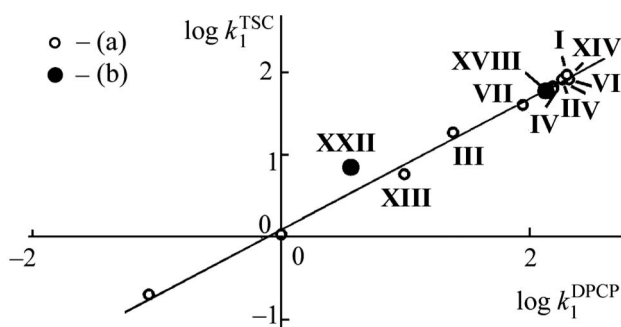

Fig. 2. Correlation between log k_1^{TSC} and log k_1^{DPCP} for the reactions of (a) cage-like amines and (b) with *p*-toluenesulfonyl chloride (TSC) and diphenyl chloro-phosphate (DPCP) in ac-etonitrile at 25°C. The numbers of points correspond to compound nos. in Tables 1 and 2.

responsible for an appreciable reduction in k_1 in going from 2-aminomethyl-norbornanes **I** and **II** to 2-(1-amino-ethyl)norbornane (**III**). Accessibility of the amino group in compound **III** is reduced as a result of replacement of methylene hydrogen atom by a methyl group. An analogous pattern is observed in the reactions of amines **X** and **XIII** of the adamantane series with *p*-toluenesulfonyl chloride (Table 1).

As repeatedly noted above, the effects of the structure of cage-like amines on their reactions with *p*-toluenesulfonyl chloride and diphenyl chlorophosphate are essentially similar. A statistical substantiation of this statement is given by the existence of linear correlation (4) between log k_1 values for the reactions with both re-agents (Fig. 2):

$$\log k_1^{TSC} = (0.09 \pm 0.03) + (0.80 \pm 0.02) \log k_1^{DPCP};$$
$$\text{(4)}$$
$$r = 0.998, s_0 = 0.06, n = 11.$$

In the general case, equations like (4) indicate that the reactivity of compounds in both reaction series is con-trolled by the same factors and that the ratios between the efficiency of these factors in one reaction series and the corresponding factors in the other reaction series are similar. The existence of correlation (4) for the reaction series under study provides an indirect proof for the as-sumption that the reactions of cage-like amines with TSC and DPCP involve transition states having similar bipyramidal structures. Taking into account that the slope of correlation (4) is close to unity and that the intercept on the *y* axis is small, the substrate selectivity of cage-like amines for the examined acyl chlorides is low. At the point corresponding to log k_1^{TSC} = log k_1^{DPCP} = 0.45, the reactivity of the amines is inversed: those amines for which log k_1^{TSC} > 0.45 are more reactive toward diphenyl chlorophosphate than toward *p*-toluenesulfonyl chloride; the reverse pattern is observed for amines **IX** and **XII** for which log k_1^{TSC} < 0.45.

The above qualitative analysis of the kinetic data led us to conclude that the main factor determining the reac-tivity of cage-like amines is spatial accessibility of the reaction center, the amino nitrogen atom. Therefore, we made an attempt to estimate on a quantitative level steric structure parameters of cage-like amines, i.e., E_N. This problem may be solved by comparing the reactivity of common aliphatic amines for which the corresponding parameters E_N are known with that of cage-like amines. In this case, it is necessary to assume that the nucleo

philic reactivity of cage-like amines is also described by Eq. (3) and that cage-like and aliphatic amines of the same type (such as primary and secondary) with similar spatial accessibilities of the amino group are characterized by similar reactivities. Treatment of k_1 values for aliphatic amines (Table 2) by Eq. (3) leads to the following correlation:

$$\log k_1^{\text{TSC}} = (5.53 \pm 0.39) + (1.56 \pm 0.07)E_{\text{N}} - (3.28 \pm 0.38)\ 0.49 n_{\text{H}};$$

$$R = 0.996,\ s_0 = 0.19,\ n = 10. \tag{5}$$

By substituting k_1 and n_{H} values for cage-like amines into Eq. (5) we calculated the corresponding parameters E_{N} (Table 1).*

Naturally, the parameters E_{N} determined in such a way require for an additional checking by applying to other reaction series. One of such series may consist of reactions of cage-like and aliphatic amines with diphenyl chlorophosphate. Here, inclusion of the data for amines **I**–**VI**, **IX**, **XII**–**XIV** (Table 1), **XVIII**, and **XXII** (Table 2) gives correlation (6):

$$\log k_1^{\text{DPCP}} = (5.94 \pm 0.22) + (1.84 \pm 0.05)E_{\text{N}} - (3.27 \pm 0.21)0.49\ n_{\text{H}};$$

$$R = 0.999,\ s_0 = 0.064,\ n = 12. \tag{6}$$

However, verification in such a way cannot be regarded as reliable, for $\log k_1^{\text{TSC}}$ and $\log k_1^{\text{DPCP}}$ values for cage-like amines are linearly related to each other through Eq. (6) which also covers alkylamines **XVIII** and **XXII** included in correlation (4) (Fig. 2). We believe it more reasonable to compare the calculated E_{N} values for cage-like amines with E_{N} of aliphatic amines which can be considered to be steric analogs of the former. Here, we can assume that 2-norbornyl and 5-norbornenyl substituents correspond to isopropyl group and that 1-adamantyl moiety is spatially analogous to *tert*-butyl. The structures of these model aliphatic amines and their respective parameters E_{N} are also given in Table 1.

The E_{N} values for cage-like amines **I**, **II**, **IV**–**VI**, **IX**, **XII**, and **XIII** and sterically related alkylamines are fairly similar: the difference in E_{N} does not exceed 10–20%. The difference observed for amines **III**, **X**, **XI**, and **XIV** is more significant: it approaches 40–50%. It is difficult

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* The parameters E_{N} for amines **VII** and **VIII** were not calculated, for the procedure used for the calculation should distort their values because of inductive effect of the oxygen atom.

to rationalize these findings unambiguously. A probable reason may be both insufficient similarity between cage-like amines and the corresponding model and large errors in the calculation of E_{N} from the kinetic data obtained for only one reaction series [Eq. (5)].

On the whole, we can state that cage-like substituents do not bring appreciable specificity to the nucleophilic reactivity of amines in comparison with common alkyl groups.

EXPERIMENTAL

The procedures for conductometric measurements and calculation of the apparent rate constants k_τ were described previously [6]. *p*-Toluenesulfonyl chloride was heated in a boiling mixture of carbon tetrachloride with petroleum ether (1 : 1) with addition of charcoal A; after cooling, the crystals were separated and dried in a vacuum desiccator. Diphenyl chlorophosphate was synthesized and purified by the procedure reported in [14]. Saturated amines **I** and **II** were prepared as described in [15], and unsaturated stereoisomeric amines **IV** and **V** were obtained as reported in [16]. Amine **VI** was synthesized according to the procedure described in [17]. Epoxy amine **VII** [18] and tricyclic amine **VIII** [19] were prepared by known methods. Amines of the adamantane series were synthesized by the procedures described in [20]. Liquid amines were purified by distillation of the dry crude products, and crystalline amines, by recrystallization from appropriate dry solvents. Liquid aliphatic amines **XVI**–**XXIV** were purified via conversion into the corresponding hydrochlorides; the free bases were dried over potassium hydroxide and distilled over metallic sodium. Methylamine of analytical grade was dried over potassium hydroxide. Acetonitrile was purified by the procedure described in [21].

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