Catalysis in Aprotic Solvents. Inter- and Intramolecular Hydrogen Bonding Complexation

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A mechanistic investigation is reported of aminolysis reactions of 2-hydroxy-5-nitro-α-toluenesulfonic acid sultone (1) in aprotic solvents. The *n*-butylaminolysis of 1 in acetonitrile and in toluene requires two and three molecules of amine, respectively. In the latter solvent, general bases strongly catalyze the reaction, and their catalytic constants are well correlated by the hydrogen bonding parameter pK_{HB}. These results are interpreted by a multistep mechanism where each intermediate can be stabilized via hydrogen bonding by general bases. The mechanistic features depend on the stability of the intermediates and on the solvent characteristics. When diamines such as polyoxyethylenediamines $H_2NCH_2(CH_2OCH_2)_nCH_2NH_2$ (**2**, $n = 2$; **3**, $n = 4$; **4**, $n = 6$) are used as nucleophiles for the reaction with sultone 1 in toluene, much higher reactivities are observed when compared to reactions of monoamines and alkylenediamines. This represents a novel type of intramolecular catalysis due to intramolecular hydrogen bonding complexation between oxygen atoms and the ammonium group of the reaction intermediates (Scheme III). In toluene 2-4 also display a large basicity.

Intramolecular catalysis is considered one of the most important factors which determine enzyme activity.[1] Moreover, it was suggested that the microenvironment of the active sites of the enzymes are better mimicked by aprotic solvents than by aqueous media because of hydrophobic properties of the enzymes' active sites.[2] Thus we have been engaged in studies[3] of intramolecular catalysis in aprotic solvents of chemical substrates as enzyme analogues.[4]

It was shown by Watson[2a] that in aprotic solvents the catalytic ability of general bases in aminolysis of carboxylic esters is closely correlated by the hydrogen bonding parameter[5] rather than by water basicity. In fact, amides are more effective catalysts than *n*-butylamine,[2a] a much stronger base in aqueous systems. More recently, Taft suggested a multiparameter equation where both water basicity, pK_A, and the hydrogen bonding parameter, pK_{HB},[5a] of the general base concur in varying degrees in determining the rates of reaction[6] (eq 1).

$$\log (k/k_o) = apK_{HB} + bpK_A + c \qquad (1)$$

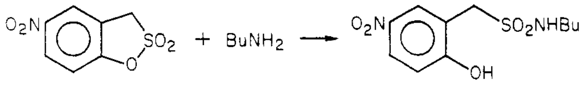
The a/b ratio indicates the relative importance of the two parameters and varies between 0.29 and >120 in the reactions studied so far according to the substrate, the nucleophile, and the solvent.[6]

We are now reporting the *n*-butylaminolysis of sultone 1 as a further example of intermolecular catalysis via hydrogen bonding and the reaction of sultone 1 with polyoxyethylenediamines 2-4 as a first example of its intramolecular version.

Results

Uncatalyzed Reactions. The kinetics governing the aminolysis of 2-hydroxy-5-nitro-α-toluenesulfonic acid sultone (1) by *n*-butylamine (eq 2) have been determined in acetonitrile and toluene at 25 °C.

A plot of $k_{obsd}/[BuNH_2]$ vs. $[BuNH_2]$ for the reactions in acetonitrile yields a straight line (Figure 1). Thus, the rate law and constants shown in eq 3 are derived.



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(2)

$$k_{obsd} = 0.15[BuNH_2] + 9.29[BuNH_2]^2 \qquad (3)$$

In toluene, a term which is first order in nucleophile could not be detected, and the process requiring two molecules of amine is of minor importance (intercept of Figure 2). The largest part of the reaction requires three molecules of amine. In fact, a plot of $k_{obsd}/[BuNH_2]^2$ vs. $[BuNH_2]$ yields a straight line, and the rate law and constants shown in eq 4 can be obtained.

$$k_{obsd} = 1.41 \times 10^{-3}[BuNH_2]^2 + 0.056[BuNH_2]^3 \qquad (4)$$

Intermolecular Catalysis. Very weak bases but strong hydrogen bond acceptors (Table I)[5a] do not catalyze the *n*-butylaminolysis of 1 in acetonitrile but are very effective catalysts in toluene. The overall rate equation becomes that shown in eq 5, where B is the added base.

$$k_{obsd} = k_2[BuNH_2]^2 + k_3[BuNH_2]^3 + k_B[BuNH_2][B] + k_B'[BuNH_2]^2[B] \qquad (5)$$

The values of k_2 and k_3 for the uncatalyzed reaction and those of k_B and k_B' for the catalyzed reactions at 25 °C are reported in Table I along with the pK_A and pK_{HB} values of the catalysts. The k_B value of the catalyzed reactions could be measured only for hexamethylphosphorotriamide (HMPT). In all other cases the intercept of the plot (see the Experimental Section) was always lower than the experimental error so that significant values cannot be reported. The k_B' values, on the other hand, could be easily measured. A plot (Figure 3) of $\log k_B'$ vs. pK_{HB} (the hydrogen bonding parameter) yields a straight line of slope 0.85.[7] Only *n*-butylamine deviates from the plot, but its lower reactivity cannot be ascribed to the fact that basicity was not considered. Inclusion of basicity as in eq 1 would, in fact, worsen the plot. Thus, the catalytic constants depend only on the hydrogen bonding parameter and not on the water basicity.

Intramolecular Catalysis. Since in toluene aminolysis of sultone 1 is very efficiently intermolecularly catalyzed by general bases which are strong hydrogen bond accep-

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[1] Bender, M. L. "Mechanisms of Homogeneous Catalysis from Protons to Proteins"; Wiley-Interscience: New York, 1971.

[2] (a) Su, C.-W.; Watson, J. W. *J. Am. Chem. Soc.* **1974**, *96*, 1854. (b) See ref 2, 4b, and 9 in ref 2a.

[3] Senatore, L.; Ciuffarin, E.; Isola, M.; Vichi, M. *J. Am. Chem. Soc.* **1976**, *98*, 5306.

[4] Stoddard, J. F. *Chem. Soc. Rev.* **1979**, *8*, 85; see footnote 136.

[5] (a) Taft, R. W.; Gurka, L. J.; Joris, L.; Schleyer, P. v. R.; Rakshys, J. W. *J. Am. Chem. Soc.* **1969**, *91*, 4801. (b) Kamlet, M. J.; Taft, R. W. *Ibid.* **1976**, *98*, 377. (c) Yokohama, T.; Taft, R. W.; Kamlet, M. J. *Ibid.* **1976**, *98*, 3233.

[6] Singh, T. D.; Taft, R. W. *J. Am. Chem. Soc.* **1975**, *97*, 3867.

[7] The use of β^{5b} instead of pK_{HB} leads to similar results except for the slope of the plot.

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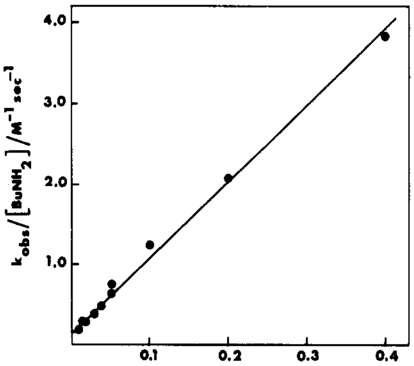

Figure 1. *n*-Butylaminolysis of sultone 1 in acetonitrile at 25 °C.

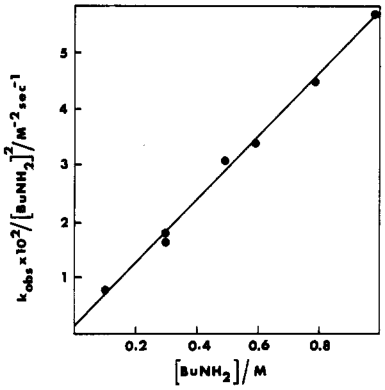

Figure 2. *n*-Butylaminolysis of sultone 1 in toluene at 25 °C.

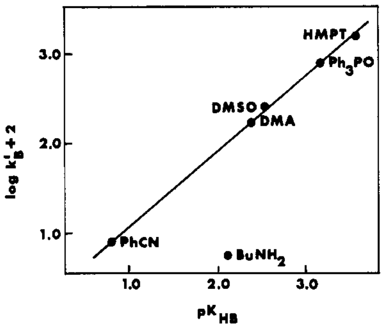

Figure 3. Correlation of the catalytic constants of general bases with their hydrogen bonding parameter for the *n*-butylaminolysis of sultone 1 in toluene at 25 °C.

Table I. Rate Constants for the Catalyzed *n*-Butylaminolysis of Sultone 1 in Toluene at 25 °C,[a] Hydrogen-Bonding Parameters, and Water Basicities

base	k_B, M^{-2} s^{-1}	k_B', M^{-3} s^{-1}	log k_B'	pK_{HB}[b]	pK_A[c]
PhCN		0.08	−1.10	0.79	−10.45[d]
$BuNH_2$	1.41×10^{-3}[e]	0.056[f]	−1.25	2.11	10.59[g]
DMA[h]		1.74	0.24	2.38	−0.36[i]
Me_2SO[j]		3.28	0.52	2.52	−1.80[i]
Ph_3PO		8.2	0.91	3.16	−2.10[i]
HMPT[k]	2.9	16.4	1.21	3.56	

[a] Refer to eq 5. [b] Reference 5a. [c] In water. [d] Reference 29. [e] k_2 in eq 5. [f] k_3 in eq 5. [g] Reference 12. [h] *N,N*-Dimethylacetamide. [i] Arnett, E. M.; Mitchell, E. J.; Murty, T. S. S. R. *J. Am. Chem. Soc.* 1974, *96*, 3875. [j] Dimethyl sulfoxide. [k] Hexamethylphosphorotriamide.

Table II. Rate Constants of Aminolysis Reactions of Sultone 1 in Acetonitrile at 25 °C

amine	k_1, M^{-1} s^{-1}	k_2, M^{-2} s^{-1}	pK_{A,CH_3CN}[a,b]
$BuNH_2$	0.15	9.29	18.26
1,2-diaminoethane	1.1	27.4	18.46
1,3-diaminopropane	12.2	45.1	19.70
1,4-diaminobutane	17.8	54.1	20.12
Oxa-2 (2)	2.8	25.7	
Oxa-4 (3)	6.6	29.2	

[a] Data from ref 8. [b] Second ionization constant.

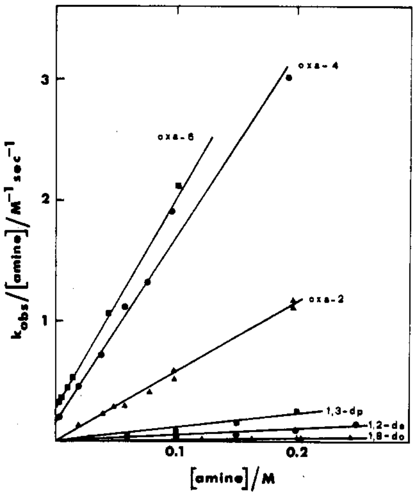

Figure 4. The reactions of sultone 1 with diamines in toluene at 25 °C.

tors, it was anticipated that amines possessing groups with hydrogen bonding ability should be very efficient nucleophiles because of intramolecular stabilization. Thus, we have prepared three polyoxyethylenediamines, 1,8-diamino-3,6-dioxaoctane (2), 1,14-diamino-3,6,9,12-tetraoxatetradecane (3), and 1,20-diamino-3,6,9,12,15,18-hexaoxaeicosane (4), which should presumably possess the intrinsic ability of intramolecularly complexing a protonated amino group.

$H_2NCH_2(CH_2OCH_2)_nCH_2NH_2$

2, $n = 2$ (Oxa-2)
3, $n = 4$ (Oxa-4)
4, $n = 6$ (Oxa-6)

In acetonitrile the reactivity of polyoxyethylenediamines 2 and 3 is larger than that of *n*-butylamine in the reaction with sultone 1 but lower than that of alkylenediamines (Table II). Thus, it can be suggested that hydrogen bonding between the nitrogen atoms such as that already noticed by Coetzee[8] for a number of alkylenediamines in acetonitrile is a sufficient justification of the reactivity of 2 and 3 with respect to that of *n*-butylamine[9] without resorting to intramolecular effects of the amines' oxygen atoms. The lower reactivities of 2 and 3 relative to those of 1,3-diaminopropane and 1,4-diaminobutane is expected because of the larger number of atoms separating the two amino groups and because of inductive effects of the oxygen atoms. A limited intramolecular effect of the oxygen atoms of polyoxyethylenediamines in acetonitrile may be suggested by the observation that 3, a diamine with four oxygen atoms, is more reactive than 2 which has only two oxygen atoms, the larger number of atoms separating the two amino groups notwithstanding (8 and 14, respectively).

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(8) Coetzee, J. F.; Padmanabham, G. R. *J. Am. Chem. Soc.* **1965**, *87*, 5005.

(9) This was already suggested by Watson for the nucleophilicity of 1,3-diaminopropane in the reaction with *p*-nitrophenyl acetate in chlorobenzene.[10]

(10) Anderson, H.; Su, C.-W.; Watson, J. W. *J. Am. Chem. Soc.* **1969**, *91*, 482.

Table III. Rate Constants of Aminolysis Reactions of Sultone 1 in Toluene and Chlorobenzene with p*K* Values of Amines in Toluene at 25 °C

amine	k_1, M^{-1} s^{-1}	k_2, M^{-2} s^{-1}	k_3, M^{-3} s^{-1}	reactivity ratio[b]	−p*K*
$BuNH_2$		1.41×10^{-3}	5.6×10^{-2}	0.057	1.84
1,2-diaminoethane		0.51		4.18	
1,3-diaminopropane		1.14		9.34	
1,8-diaminooctane		0.122		1.00	
Oxa-2 (2)		5.87		48	3.24
Oxa-4 (3)	0.15	15.3		138	5.01
Oxa-6 (4)	0.28	17.5		166	5.43
1,3-diaminopropane[a]	0.113	6.47			
Oxa-4 (3)[a]	2.01	32.4			

[a] In chlorobenzene. [b] Reactivity ratio at 0.1 M amine concentration.

Table IV. Acid Dissociation Constants of Protonated Polyoxyethylenediamines in Water at 25 °C

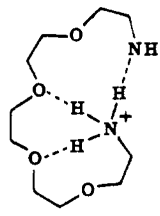
	pK_A	
amine	first step[a]	second step[b]
Oxa-2 (2)	8.74	9.68
Oxa-4 (3)	8.82	9.71
Oxa-6 (4)	8.91	9.75

[a] $K_{A_1} = [H_2NCH_2(CH_2OCH_2)_nCH_2NH_3^+][H^+]/[H_3N^+\text{-}CH_2(CH_2OCH_2)_nCH_2\text{-}NH_3^+]$. [b] $K_{A_2} = [H_2NCH_2(CH_2\text{-}OCH_2)_nCH_2NH_2][H^+]/[H_2NCH_2(CH_2OCH_2)_nCH_2\text{-}NH_3^+]$.

While the results in acetonitrile proved to be negative or insufficient to justify the expected intramolecular hydrogen bonding interaction for polyoxyethylenediamines, the picture is completely reversed in aprotic, *apolar* toluene (Table III, Figure 4). In this solvent both the basicity and the reactivity of polyoxyethylenediamines are much higher than those of *n*-butylamine, indicating strong intramolecular catalysis by the oxygen atoms. The reported rate constants in toluene for the reaction of 1,2-diaminoethane and 1,3-diaminopropane with sultone 1 in toluene have an estimated maximum error of 30% due to uncertainty in the infinity value of the kinetics because of partial precipitation experienced after 50–75% reaction.

The basicity of 2–4 was measured in water and in toluene. The expectation of a large basicity in water was not fulfilled. In fact, the pK_A value (Table IV) of the second ionization constant of protonated polyoxyethylenediamines is lower than those of alkylenediamines (pK_A = 9.9–10.8)[11] and monoalkylamines (p$K_A \approx 10.5$)[12] and similar to that of methoxyethylamine (pK_A = 9.72).[13] Clearly, intramolecular stabilizing effects which should produce pK_A values larger than those of monoalkylamines are absent or negligible in water where the ammonium ion and the ethereal oxygens become heavily solvated and water acts as a competitive inhibitor of complexation.

In toluene the basicity of polyoxyethylenediamines is much higher than that of *n*-butylamine. It has been measured according to the method of Pearson.[14] The p*K* values reported in Table III refer to equilibrium constants for ion-pair formation between 2,4-dinitrophenol and the amines.[14,15] The ion pair may be in equilibrium with a hydrogen bonded complex[16,17] of 1:1 or 1:2 composition.[18] Apart from these unavoidable complications in aprotic, apolar solvents, the p*K* values in toluene clearly point out that the monoprotonated form of polyoxyethylenediamines derives considerable stability from intramolecular hydrogen bonding. Moreover, the stability constants for ion-pair formation of 2 and 3 relative to that of *n*-butylamine cannot be justified by intramolecular hydrogen bonding between the two nitrogen atoms only. In fact, the Δp*K* (1.4) on going from *n*-butylamine to 2, which is due to both nitrogen and oxygen participation, is lower than the Δp*K* (1.77) between 2 and 3, which is due only to the two extra oxygen atoms. Two more oxygen atoms, for a total of six, produces a smaller further stabilization (Δp*K* = 0.42), indicating that the amine with four oxygen atoms can assume a conformation sufficiently free from steric strain to allow a good interaction between the ammonium ion and the ligands as in 5. Ammonium ions are, in fact, complexed via hydrogen bonding by crown ethers and noncyclic crown-type polyethers.[19] Therefore, it did not appear unlikely that an ammonium ion could be intramolecularly complexed as illustrated in 5 for 3.[20]



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It would have been desirable to obtain a direct comparison of the p*K*s in toluene of the alkylenediamines. Unfortunately in this solvent the p*K* could not be measured for these amines because of precipitation of the monoprotonated species.

Discussion

Uncatalyzed Reactions. The results (eq 3) for the *n*-butylaminolysis of sultone 1 in acetonitrile are best explained by the reversible formation of an intermediate followed by a rate-determining proton-transfer step to either a second molecule of amine or, for a minor fraction, to the solvent itself (eq 6).[21] The suggestion that *n*-butylamine dimer is responsible for the second-order term

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[11] Bertsch, C. R.; Fernelius, W. C.; Block, B. P. *J. Phys. Chem.* **1958**, *62*, 444.

[12] Hall, H. K., Jr. *J. Am. Chem. Soc.* **1957**, *79*, 5441, 5444.

[13] Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622.

[14] Pearson, R. G.; Vogelson, D. C. *J. Am. Chem. Soc.* **1958**, *80*, 1038.

[15] It was assumed that the first and the second ionization constant of diamines are sufficiently different in toluene as they are in acetonitrile[8] so that any mutual interference on the p*K* values can be disregarded.

[16] Baba, H.; Matsuyama, A.; Kokubun, H. *Spectrochim. Acta, Part A* **1969**, *25A*, 1709.

[17] Moulik, S. P.; Chatterjee, A. K.; Sen Gupta, K. K. *Spectrochimica Acta, Part A* **1973**, *29A*, 365.

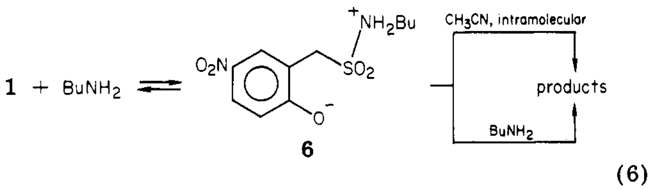
[18] Romanowsky, H.; Sobczyk, L. *J. Phys. Chem.* **1975**, *23*, 2535.

[19] Timko, J. M., Helgeson, R. C.; Newcomb, M.; Gokel, G. W.; Cram, D. J. *J. Am. Chem. Soc.* **1974**, *96*, 7097.

[20] Structure 5 is the structure suggested by space-filling models on the hypothesis that it is more stable than others which are less strained but have only two hydrogen bonds.

[21] This mechanism and the discussion which follows is based on the assumption that the reaction of sultones with nucleophiles is a nucleophilic substitution and not an elimination–addition mechanism involving a sulfene intermediate. This assumption is substantiated by previous studies by Kaiser,[22] Williams,[23] and Houk.[24]

[22] Kaiser, E. T. *Acc. Chem. Res.* **1970**, *5*, 145.



(6)

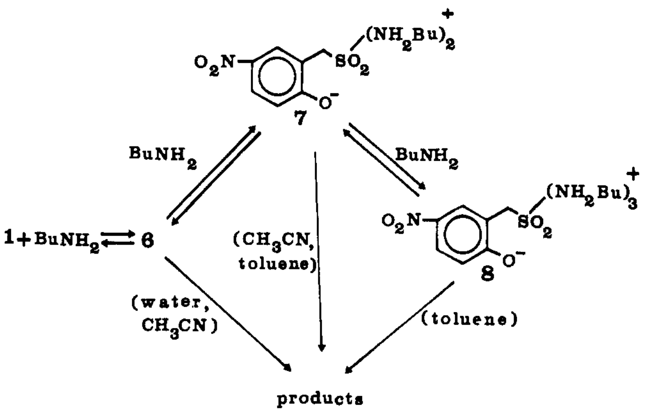
would be very unlikely and unprecedented in acetonitrile. Intramolecular catalysis by the phenoxide oxygen can also be suggested in order to account for the term first order in amine. This process would require rotation about the C–S bond.

The formation of an intermediate such as 6 in fast equilibrium with the reagents has been postulated[23,25] in all nucleophilic substitutions of sultones studied so far.[26,27] However, the intermediate could not be kinetically detected because, water being the reaction medium, transfer of the proton to the solvent was faster than to a second molecule of amine so that the kinetics were all first order in nucleophile. In acetonitrile on the other hand, a much less basic solvent than water,[29] solvent participation is minimal, and the greatest part of the reaction proceeds instead with two molecules of amine, the second acting as a general base.

In toluene, where solvent participation is absent or very low, a solvent-catalyzed path cannot be detected, and the largest part of the reaction requires three molecules of amine. Thus, a mechanism must be envisaged where three amine molecules react with the substrate before the rate-determining step. Such a mechanism in our opinion should be general enough to explain also the data in water and in acetonitrile, provision being made for the different solvent characteristics.

Third-order terms in nucleophile have been so far found in reactions of carbonyl compounds with imidazole in aprotic solvents.[30,31] Because of its ability to form linear complexes in solution, it was suggested that imidazole trimer is the reactive species.[32] Formation of trimer was never detected for n-butylamine[33] so that the third-order term in nucleophile detected in toluene cannot be linked to an abundance of trimer in solution (a concentration factor) but, if this is the case, can be linked to its large reactivity.

Scheme I



We believe that the results for the n-butylaminolyses of sultone 1 in water,[23] acetonitrile, and toluene are best explained by a multistep mechanism (Scheme I). Intermediates 7 and 8 in Scheme I must be considered abbreviated notations to indicate two and three species, respectively, in equilibrium, with the positive charge localized on any of the nitrogen atoms of the amino groups which are linked via hydrogen bonds. It appears risky if not impossible to speculate about the structure of the intermediates leading to products.

Scheme I takes into account the different solvent characteristics and the inaccessibly high energies required in toluene for the formation of free ions.[6] Two competing processes may be suggested for the product yielding step. The first is diffusion out of the solvent cage of the protonated dimer, but this would not avoid free-ion formation. The second and in our opinion more likely process is rotation about the C–S bond followed by intramolecular catalysis by the phenolic oxygen.

It may perhaps seem surprising at first sight that rotation about a bond and ion-pair formation are slower processes than cyclization. It is known, however, that halide ions form charge-transfer complexes with sulfonyl sulfur in aprotic solvents.[35] Thus, it seems plausible that the negatively charged oxygen of intermediates 6–8 interacts with sulfur, thus raising the barrier to rotation. The positive charge on nitrogen induces a positive charge on sulfur, thus favoring the interaction.

Intermolecular Catalysis. In the previous section it was suggested that in toluene three molecules of nucleophile are linked via hydrogen bonds. Experiments performed in the presence of hydrogen bond acceptor (HBA) general bases indicate that the energetics of hydrogen bonded complex formation are dominant in the transition state of these reactions as shown by the linearity of the plot (Figure 3) of log k_B' (the catalytic constant) vs. pK_{HB} (the hydrogen bonding parameter). Only n-butylamine deviates from the plot. The deviation can be tentatively linked to the possibility that n-butylamine is at the same

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(23) Deacon, T.; Steltner, A.; Williams, A. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1778.

(24) Houk, K. N.; Strozier, R. W.; Hall, J. A. *Tetrahedron Lett.* **1974**, 897.

(25) Berg, W.; Campbell, P.; Kaiser, E. T. *J. Am. Chem. Soc.* **1972**, *94*, 7933.

(26) A preequilibrium leading to an addition intermediate is also possible,[23] but the kinetics or the conclusions are in no way affected. A referee has suggested that an addition–elimination mechanism is more likely in view of the evidence recently presented by Engberts[26b] and since collapse of an addition intermediate to reagents is obviously much faster than any process involving transfer of a proton. However, even though it is an appealing possibility, we cannot support this hypothesis with our own data which, contrary to those of Engberts, do not give any indication of the charge distribution in the transition state. The same referee suggests that the third-order term in toluene may be explained by a chain of molecules (either three amine molecules or two amine molecules and one other hydrogen bond acceptor) which transfer the proton from the attacking amine nitrogen to the departing phenolic oxygen. This hypothesis is also appealing in view of the analogy with the mechanism proposed by Taft and Singh[6] for the aminolysis of esters in low-dielectric, aprotic solvents. However, space-filling models indicate that while three amine molecules can in fact hydrogen bond the nucleophile and leaving group, when the third order term is due to two amine molecules and one other hydrogen bond acceptor which *does not possess* a hydrogen on the accepting atom, the distance is too great for a sort of Grotthus chain "transport". Since this mechanism is limited to a single case we prefer the more general one proposed by us which also takes into account the data in acetonitrile and in water. (b) Graafland, T. G.; Wagenaar, A.; Kirby, A. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1979**, *101*, 6981.

(27) In a few specific examples general-base-catalyzed hydrolysis was also suggested.[22,23,28]

(28) Kaiser, E. T.; Lo, K.-W.; Kudo, K.; Berg, W. *Bioorg. Chem.* **1971**, *1*, 32.

(29) Arnett, E. M. *Prog. Phys. Org. Chem.* **1963**, *1*, 223.

(30) Rivetti, F.; Tonellato, U. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1176.

(31) Rogne, O. *J. Chem. Soc., Chem. Commun.* **1975**, 25.

(32) Another explanation relative to the imidazolynolysis of benzoyl fluoride suggests general-acid catalysis but cannot be applied to sultones.[31]

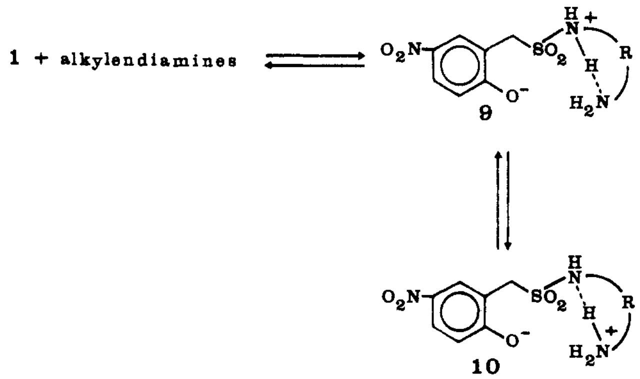
(33) The closest studied example is the limited dimerization of diethylamine in cyclohexane.[34]

(34) Hudson, R. F.; Stelzer, I. *J. Chem. Soc. B* **1966**, 775.

(35) Khan, M. A.; Wasif, S.; Salama, S. B. *J. Chem. Soc., Dalton Trans.* **1978**, 915.

time a hydrogen bond acceptor and donor.

Scheme II



Analogous correlations of the rate of reaction with the hydrogen bonding parameter have been used by Watson[2a] and Taft[6] in the aminolysis of *p*-nitrophenyl acetate. In the latter case the suggested product-forming step is diffusion out of the solvent cage of the protonated catalyst hydrogen bonded with the leaving group. In the aminolysis of sultone 1, the leaving group can hydrogen bond with the nucleophile or with the catalyzing base only after rotation about the C–S bond. Again, rotation and intramolecular catalysis by the phenolic oxygen seem the most likely processes leading to products, the alternative being protonation of the catalyst and formation of BH^+, which then diffuses out of the solvent cage.

Intramolecular Catalysis. In toluene the reactivity of polyoxyethylenediamines is much higher than those of *n*-butylamine and alkylenediamines. 1,8-Diamino-3,6-dioxaoctane (2) reacts 48 times faster than 1,8-diaminooctane, an amine with the same number of atoms between the two amino groups. Polyoxyethylenediamines 3 and 4 with four and six oxygen atoms, respectively, are even more reactive, the larger number of atoms between the two amino groups notwithstanding. In our opinion this can only be ascribed to intramolecular stabilization performed by the oxygen atoms as will be described below.

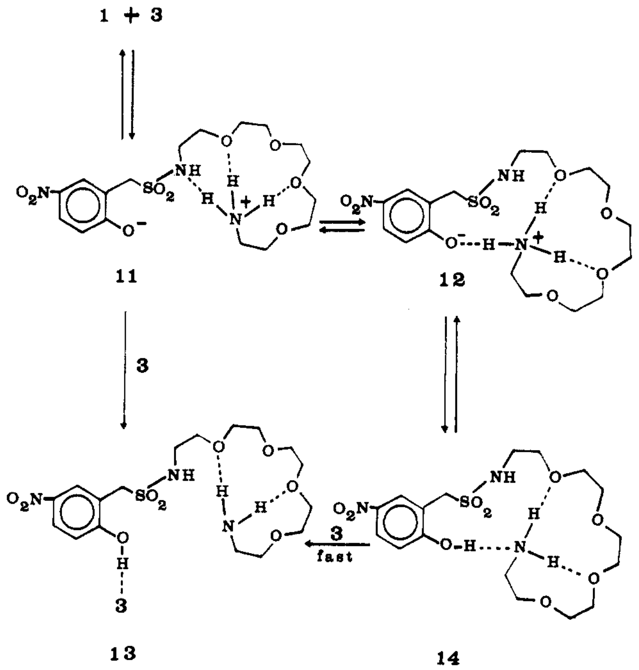
A reactivity ratio independent of the amine concentration cannot be given because the rates depend on various combinations of terms which are first, second, and third order in amine (eq 7). Thus, in Table III are reported the reactivity ratios calculated with eq 7 at 0.1 M amine concentration.

$$k_{\text{obsd}} = k_1[\text{amine}] + k_2[\text{amine}]^2 + k_3[\text{amine}]^3 \quad (7)$$

1,2-Diaminoethane, 1,3-diaminopropane, and 1,8-diaminooctane react with sultone 1 much faster than *n*-butylamine, and their reactivities are in an order which suggests intramolecular interaction between the two amino groups as shown in 9 (Scheme II). Thus, this intermediate is much more stable than the analogous intermediate, 7, formed with *n*-butylamine.

Intermediate 9 is in rapid equilibrium with intermediate 10. This does not yield the products directly. In fact, the k_2 term (Table III) is prevalent, so that the intervention of at least a second molecule of amine is necessary. Clearly the hydrogen bonded ammonium group of 10 acts as an efficient intramolecular acid catalyst for cyclization. A similar situation can be suggested for the reaction of sultone 1 with 2 where the kinetics are cleanly second order in amine. For 3 and 4 on the other hand, a term which is first order in amine also appears in the kinetic expression. For these two amines it can be suggested that acid catalysis of the cyclization process is sufficiently reduced because of oxygen atom participation that the reaction can in part go to products without the participation of a second molecule of amine in a rate-determining step.

Scheme III



This is exemplified for the reaction of 3 with sultone 1 in Scheme III. Intermediate 11 can either react with a second molecule of amine, thus justifying the kinetic term which is second order in amine, or go directly to products as required by the term which is first order in amine. Since loss of a proton to the solvent toluene cannot be suggested as a product-forming step, intramolecular participation by the phenolic oxygen is the most likely explanation for the term which is first order in amine. It is suggested that 13 is the structure of the final product, but 14 or even 12 cannot be excluded at this stage as possible structures of the product. Many more intermediates than those of Scheme III could of course be written, but this would not change the main picture. Due to the complexity of the intermediates, space-filling models do not indicate with certainty the structure of the more stable intermediates, but those of Scheme III seem the more likely. Moreover, inter- and intramolecular acid–base equilibria of ion-pair or hydrogen-bonded pair formation concur to complicate the picture, so that Scheme III visualizes only some aspects of the mechanism.

Hydrogen bonding may not be the only catalyzing effect induced by the proximity of oxygen atoms to the reaction center. Electrostatic effects may also be in part responsible for the catalysis as was suggested, for example, for the catalysis of crown ethers on the aminolysis of *p*-nitrophenyl acetate.[36] The importance of polarity in the aminolysis of sultones can be perceived by comparing the absolute and the relative rates of the reactions of 1,3-diaminopropane and 3 in toluene and chlorobenzene. In the latter more polar solvent, the rates are higher while the relative reactivities of the two amines are smaller (Table III).

Experimental Section

Materials. Acetonitrile,[23] chlorobenzene,[37] toluene,[38] dimethyl sulfoxide,[2a] and *N*,*N*-dimethylacetamide[2a] were purified as previously described. Hexamethylphosphorotriamide and benzo-

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[36] Gandour, R. D.; Walker, D. A.; Nayak, A., Newkome, G. R. *J. Am. Chem. Soc.* **1977**, *100*, 3608.

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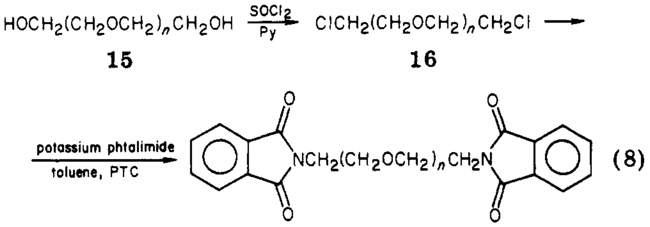
nitrile were kept over molecular sieves for several days and then fractionally distilled at reduced pressure. Triphenylphosphine oxide was recrystallized three times from a benzene–hexane mixture and dried in vacuo at 100 °C for 24 h, mp 155 °C (lit.[2a] mp 154–156 °C). *n*-Butylamine, 1,2-diaminoethane, 1,3-diaminopropane, 1,4-diaminobutane, and 1,8-diaminooctane were refluxed over and distilled from potassium hydroxide and then from sodium at atmospheric pressure except for 1,8-diaminooctane which was distilled at reduced pressure; bp 82 °C (0.4 torr). All distillations were performed under dry nitrogen, and boiling points were in good agreement with literature data.

2-Hydroxy-5-nitro-α-toluenesulfonic acid sultone was prepared as previously described.[23]

***N*-*n*-Butyl-2-hydroxy-5-nitro-α-toluenesulfonamide.** A 0.280-g (3.83 mmol) sample of anhydrous *n*-butylamine in acetonitrile were added to an acetonitrile solution of 0.466 g (2.17 mmol) of sultone 1 at room temperature. After neutralization with a hydrogen chloride solution in acetonitrile, the solvent was evaporated. Chloroform was added to the residue, and the *n*-butylamine hydrochloride was filtered off. Petroleum ether (30–50 °C) was added to the filtrate. The precipitated sulfonamide was recrystallized three times from a chloroform–petroleum ether (30–50 °C) mixture and dried in vacuo at room temperature: white needles; mp 162 °C; yield 80%.

Anal. Calcd for $C_{11}H_{16}N_2O_5S$: C, 45.82; H, 5.59; N, 9.72; S, 11.12. Found: C, 45.49; H, 5.49; N, 9.42; S, 10.87.

Polyoxyethylenediamines 2–4 were prepared according to the method of Lehn[39] except for the synthesis of the diphthalimido derivatives **17a–c** (eq 8) which was improved by using phase-transfer-catalysis[40] conditions and starting from the dichlorides.



15 **16** (8)

17

a, *n* = 2; **b**, *n* = 4; **c**, *n* = 6

1,8-Diphthalimido-3,6-dioxaoctane (17a). A 15.7-mL (0.1 mol) sample of 1,8-dichloro-3,6-dioxaoctane (Fluka) was added to 46 g (0.25 mol) of potassium phthalimide (C. Erba) and 5 g (0.01 mol) of hexadecyltri-*n*-butylphosphonium bromide[41] in toluene. The mixture was kept at 100 °C for 10 h under vigorous stirring. The solid formed was filtered and the mother liquor evaporated. The combined solids were washed with small portions of distilled water, crystallized from a great volume of ethanol, and dried at atmospheric pressure for several hours at 100 °C: yield 30.1 g (74%); mp 183–185 °C (lit.[39] mp 185–186). The NMR spectrum of the product was identical with that reported.[39]

1,14-Diphthalimido-3,6,9,12-tetraoxatetradecane (17b) was prepared by the same route as the analogous compound **17a**. The product, recrystallized several times from a benzene–petroleum ether (30–50 °C) mixture, melted at 99–101 °C: yield 88%; NMR ($CDCl_3$, Me_4Si) δ 3.47 (s, 4 H), 3.52 (s, 8 H), 3.37–3.62 (m, 8 H), 7.47–7.82 (m, 8 H).

1,20-Diphthalimido-3,6,9,12,15,18-hexaoxaeicosane (17c) was prepared by the same route as the homologue **17a**. The product, recrystallized from ethanol–petroleum ether (40–70 °C), melted at 73–75 °C: yield 70%; NMR ($CDCl_3$, Me_4Si) δ 3.58 (d, 20 H), 3.58–4.00 (m, 8 H), 7.50–7.90 (m, 8 H).

Anal. Calcd for $C_{30}H_{36}N_2O_{10}$: C, 61.63; H, 6.21; N, 4.79. Found: C, 62.05; H, 6.33; N, 4.91.

1,8-Diamino-3,6-dioxaoctane (2). A 45-g (0.11 mol) sample of **17a** was suspended in 200 mL of ethanol. After the mixture was warmed to the reflux of ethanol, 12.8 mL (0.25 mol) of hydrazine monohydrate (85%, Baker) was added. The mixture was refluxed for 1 h, and then, after it cooled, hydrochloric acid 6 N was added to slight acidity. The mixture was refluxed for 0.5 h more and, after it cooled, the phthalhydrazide was filtered and washed with ethanol. The solvent was removed from the filtrate by gently warming the mixture in a rotary evaporator. A successful modification was apported to the Lehn method of extraction.[39] A solution of 14 g (0.25 mol) of potassium hydroxide in ethanol was added to the residue, and potassium chloride was filtered off and washed with absolute ethanol. After the solvent was evaporated from the filtrate, chloroform was added to the oily residue. Potassium chloride and phthalhydrazide precipitated and could be removed by filtration. Finally, after evaporation of chloroform, distillation of the residue gave the diamine: 14.4 g (88.8% yield) (lit.[39] 70%); bp 95 °C (1 mm) [lit.[39] bp 77–78 °C (0.2 mm)]; n^{18}_{D} 1.4623. The NMR spectrum corresponds to that reported.[5] GLC analysis (5% XE-60 on Anakrom ABS, 100–110 mesh) gave only a single peak.

1,14-Diamino-3,6,9,12-tetraoxatetradecane (3) was obtained in 87% yield by the same route as that for the homologue diamine **2**: bp 138–139 °C (0.15 torr); n^{26}_{D} 1.4625; NMR ($CDCl_3$, Me_4Si) δ 1.40 (s, 4 H), 2.80 (t, 4 H), 3.47 (t, 4 H), 3.61 (s, 12 H). GLC analysis (5% XE-60 on Anakrom ABS, 100–110 mesh) gave only a single peak.

Anal. Calcd for $C_{10}H_{24}N_2O_4$: C, 50.08; H, 10.20. Found: C, 50.69; H, 10.08.

1,20-Diamino-3,6,9,12,15,18-hexaoxaeicosane (4) was prepared by the same procedure described as that for the homologue diamine **2**: 70% yield; bp 193–194 °C (8×10^{-4} torr); NMR ($CDCl_3$, Me_4Si) δ 1.57 (s, 4 H), 2.80 (t, 4 H), 3.48 (t, 4 H), 3.63 (s, 20 H). GLC analysis (5% XE-60 on Anakrom ABS, 100–110 mesh) gave only a single peak.

Anal. Calcd for $C_{14}H_{32}N_2O_6$: C, 51.83; H, 9.94. Found: C, 51.64; H, 9.76.

pK_A Determinations. In water pK_A values were obtained by potentiometric titration performed with a Metrohm E 512 pH meter. Titrations of the diamines were conducted according to the method described by Albert and Serjeant[42] in a water-jacketed cell compartment thermostated at 25 ± 0.1 °C. Calculations were performed by using a computer program written in Fortran IV.[42]

In toluene the pK values for ion-pair formation between the bases and dinitrophenol were performed according to the method of Pearson.[14]

Kinetics. Reaction kinetics were spectrophotometrically monitored by following the change in absorbance due to the formation of products in the 380–420-nm region with respect to changes in the solvent, nucleophile, and base used. A suitable choice was made in each case after comparison of the reagents and products spectra.

A stoppered cuvette containing 3 mL of a freshly made solution of the amine or of amine and catalyzing base was equilibrated at 25 ± 0.1 °C for 20 min in the thermostated cell compartment of a UV–vis Varian 635 D spectrophotometer. A small amount (30 μL) of the sultone solution was then added, and the increase in absorbance was traced as a function of time until the reaction was complete (9–10 half-lives). The fastest reactions were carried out with a UV–vis, stopped-flow, Durrum D-110 spectrophotometer. Care was used in order to avoid as much as possible water and carbon dioxide contamination.

The sultone concentration was about 3×10^{-5} M. All other reagents were in large excess in all runs so that good first-order kinetics were observed. Pseudo-first-order rate constants (k_{obsd}) were determined from plots of log $(A_\infty - A_t)/(A_\infty - A_0)$ vs. time. The specific rate constants of the uncatalyzed reactions in acetonitrile and toluene were obtained from the intercept and slope of plots of $k_{obsd}/[BuNH_2]$ or $k_{obsd}/[BuNH_2]^2$, respectively, vs. $[BuNH_2]$. The catalytic constants of added bases and the form of eq 5 were derived from two sets of experiments. k_{obsd} was plotted vs. the concentration of base at constant amine concentration. In each case a linear relation was found, indicating a first-order dependence on added base. The order in amine and the catalytic constants were determined by plotting $(k_{obsd} - k_2[BuNH_2]^2 - k_3[BuNH_2]^3)/[BuNH_2][base]$ vs. $[BuNH_2]$ at constant base concentration. In each case a linear plot was obtained which

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suggested eq 5 as the correct expression for the rate of reaction. The k_B value was given by the intercept and the k_B' value from the slope. Various checks have been made at different amine and base concentrations, and in each case the observed rate constants agreed well with those calculated from the reported specific rates.

Acknowledgment. This work was supported by CNR, Rome.

Registry No. 1, 14618-10-1; 2, 929-59-9; 3, 68960-97-4; 4, 76927-70-3; **17a**, 31255-11-5; **17b**, 70110-27-9; **17c**, 76927-71-4; *n*-butylamine, 109-73-9; 1,2-diaminoethane, 107-15-3; 1,3-diaminopropane, 109-76-2; 1,4-diaminobutane, 110-60-1; 1,8-diaminooctane, 373-44-4; *N*-*n*-butyl-2-hydroxy-5-nitro-α-toluenesulfonamide, 76927-72-5; 1,8-dichloro-3,6-dioxaoctane, 112-26-5; 1,14-dichloro-3,6,9,12-tetraoxatetradecane, 5197-65-9; 1,20-dichloro-3,6,9,12,15,18-hexaoxaeicosane, 56930-39-3; potassium phthalimide, 1074-82-4; benzonitrile, 100-47-0; *N*,*N*-dimethylacetamide, 127-19-5; dimethyl sulfoxide, 67-68-5; triphenylphosphine oxide, 791-28-6; hexamethylphosphortriamide, 680-31-9.

Fragmentation of Aryl Alkyl Sulfides. A Simple, One-Pot Synthesis of Polymercaptobenzenes from Polychlorobenzenes

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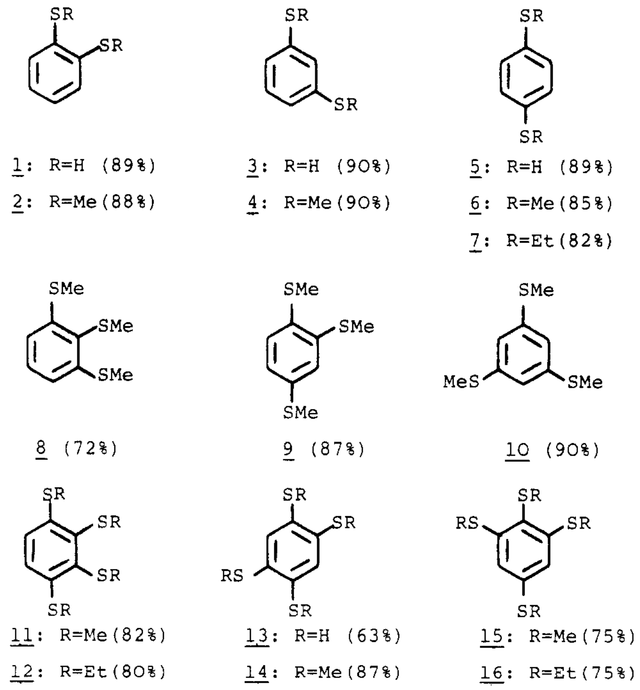
A simple procedure is described which allows one to prepare polymercaptobenzenes starting from chlorobenzenes. The reactions of all the possible chlorobenzenes with Me_2CHSNa in HMPA give the corresponding (isopropylthio)benzenes which can be cleaved by adding sodium to the reaction mixtures to give the arenethiolates in good yields. In some cases the polymercaptobenzenes were isolated after treatment with acid; in other cases methyl iodide was added to the reaction mixture and poly(methylthio)benzenes were obtained. It is suggested that the (isopropylthio)benzenes react with sodium to give the corresponding radical anions which fragment at the sulfur–alkyl bond to give the arenethiolates.

(Alkylthio)benzenes can be easily obtained from the reaction of alkanethiolate anions with polynitro-[1] or halogenonitrobenzenes.[1,2] More conveniently, the same compounds can be prepared from polychlorobenzenes. We have recently reported that the reactions of Me_2CHSNa with di-,[3] tri-, tetra-, penta-, and hexachlorobenzene, in hexamethylphosphoramide, give rise to the complete replacement of chlorine, leading to the corresponding (isopropylthio)benzenes.[4] Similar reactions can be also effected by EtSNa and MeSNa. These reactions, however, require careful control of the reaction conditions because the initially formed (ethylthio)- and (methylthio)benzenes further react with the thiolates to give the products of monodealkylation.[4,5] These dealkylation reactions can find useful applications. We have recently reported a convenient synthesis of aromatic thiols from unactivated aryl halides by reaction with excess sodium methanethiolates; in this case the initially formed methyl aryl sulfides are dealkylated by the excess of MeSNa to give good yields of the aromatic thiols.[6]

It is reported in the literature that (alkylthio)benzenes can be cleaved by alkali metals in liquid ammonia,[7] in methylamine[8] or in ether[9] to give aromatic thiols. We report in this paper a very simple and efficient one-pot synthesis of mercaptobenzenes starting from the readily available corresponding chlorobenzenes and using the (isopropylthio)benzenes as intermediate products.

Chart I



1: R=H (89%)
2: R=Me (88%)
3: R=H (90%)
4: R=Me (90%)
5: R=H (89%)
6: R=Me (85%)
7: R=Et (82%)
8 (72%)
9 (87%)
10 (90%)
11: R=Me (82%)
12: R=Et (80%)
13: R=H (63%)
14: R=Me (87%)
15: R=Me (75%)
16: R=Et (75%)

$C_6H(SR)_5$
17: R=Me (87%)
18: R=Et (80%)

$C_6(SMe)_6$
19 (60%)

Results

The general procedure employed consists of the reaction of chlorobenzenes with Me_2CHSNa in HMPA; the reaction mixtures, containing the (isopropylthio)benzenes,[3,4] are then directly treated, at 100 °C, with excess sodium.

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