Effect of Chain Length on the Rate of Quaternization of Alkyl Amines

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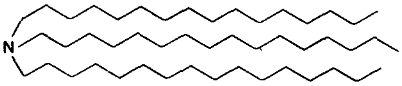
Trialkyl amines from triethyl to tristearylamine were quaternized with benzyl chloride and compared for the effect of chain length on the rate of quaternization. Triethylamine reacted about twice as fast as tripropylamine with virtually no chain-length effect from propyl to stearyl. Results are compared to previous rate studies on steric hindrance and chain-length dependence.

In the course of studying process improvements on alkylation of tertiary amines to quaternary ammonium salts, the reaction properties of trialkyl amines (Structure 1) were examined.

R_3N

STRUCTURE 1

Industrially, amines from trimethylamine (R = Me) to tristearylamine (R = $C_{18}H_{37}$) are readily available. Molecular models of the long-chain analogs (Structure 2) give the distinct impression of an aquatic organism.

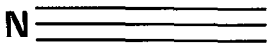


a 3-legged octopus.

STRUCTURE 2

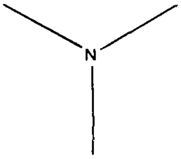
The flexibility and possible conformations are almost limitless. Depending on the conformations most favorable under a particular condition or solvent system, it is possible to theorize either equal quaternization rates for the short- and long-chain homologs of the tertiary amine series, or vastly differing rates. Three basic types of conformations seem possible in solution:

(i) parallel (Structure 3): where the hydrophobic tails cling together with no solvent molecules separating them:



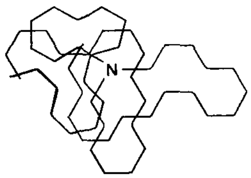
STRUCTURE 3

(ii) separated (Structure 4): where the hydrocarbon chains are widely separated by solvent molecules:



STRUCTURE 4

(iii) ball (Structure 5): where the chains are coiled and twisted around the nitrogen:



STRUCTURE 5

Structures 3 and 4 should offer no particular steric hindrance to quaternization, while Structure 5 should be very slow to quaternize due to steric problems. It is known that quaternizations occur best in solvents with high dipole moments and dielectric constants (1). Acetonitrile, ethanol, or tetrahydroforan are much better reaction media than hexane or toluene. The coiled conformation should create a non-polar hydrocarbon environment around the reactive nitrogen, disfavoring formation of polar transition states typical in SN2 displacements. The effect could further slow the rate of reaction of Structure 5.

While long-chain trialkyl amines do have appreciable solubility (at temperatures above their melting points) in polar organic solvents, it seems likely that they are not totally compatible on a molecular level. This conjecture is the basis for the three suggested conformation types. Rapid conversion between the types likely occurs with the important feature being the equilibrium ratio of the conformers. NMR evidence on the conformations of the amines in solution cannot be determined with certainty. The techniques are very difficult and not fully developed at this time (2).

The literature shows that the effect of steric hindrance on rates of various quaternizations has been studied. Pyridine derivatives (3-11), aromatic systems (12-14), thiazoles (15,16), polymers (17), and miscellaneous nitrogen and phosphorous systems (18-22) all exhibit a rate change with general steric crowding.

Berg *et al.* (23) discussed the empirical and theoretical parameters that describe steric and solvent effects on aromatic systems. In one of his examples, a methyl derivative was 2.5 times faster than an ethyl compound. Becket and Dwuma-Badu (24) noted that under certain circumstances and structures, pka relates to quaternization rate. He was reacting complex alkaloid amines where severe steric hindrance seems to determine pka and reaction rate, but this trend is not always the case for general amines.

H. C. Brown and group studied the methyl iodide quaternization of endo and exo dimethylaminonorboranes —the endo isomer was 50 times slower to react than the exo isomer, apparently due to steric strain developed in the intermediate as opposed to steric crowding around the nitrogen that would hinder initial attacks by the alkylating agent (25). Simchem quaternized several highly branched aliphatic amines noting that isopropyl analogs gave conversions of 5–17% at the same time ethyl versions reacted almost to completion (63–100%) (26). Fairchild studied the effects of chain branching on the quaternization of tertiary amines (27).

References documenting the effect of increasing chain length on various types of reactions are, however, very limited. The reaction of alkoxide ions with benzyl chloride to form ethers has been shown to have a chain-length effect. The rate constants decrease about 20% per carbon atom between n-propoxide and n-hexoxide (28). For methyl iodide quaternization of thiazole, relative rate constants found were methyl—11.8, ethyl—9.2, and n-propyl—9.1 (29). Bialik *et al.* (30) examined the synthesis of sulfobetaines from reaction of dimethylalkylamine with 1-chloro-2-hydroxypropane. A noticeable effect of the chain length was in evidence here, also (Table 1).

In contrast, the hydrolysis rate of 2-alkylimidazolines, however, is not chain-length dependent (31).

From earlier work (Frank, P.J., private communication, Sherex Chemical Company, 1987) in our lab, monoalkyldimethyl amines have shown no decrease in rate with increasing chain length (from C-6 to C-16). For the current study, it was anticipated that possibly the dialkyl methyl amines would, and certainly the trialkyl amines should, exhibit a noticeable chain-length effect.

RESULTS AND DISCUSSION

Eight trialkyl amines from triethyl to tristearylamine were quaternized with benzyl chloride in isopropanol. Several dialkylmethyl amines were also studied. It was important to insure that no perceptible change occurred in the polarity of the solvent/reaction system when testing the various members of the tertiary amine series. Because the molecular weights varied tremendously (triethyl = 101, tristearyl = 773), the reactions were done in dilute solutions (5 mole %) so the effective dipole moment was that of isopropanol. Due to the dilute technique used, experimental error in the rate data is estimated at ±7%.

As Table 2 reveals, the rate constants do **not** vary from tripropylamine to tristearyl amine. This finding is quite amazing when considering the extreme bulk of the long-chain trialkyl amines compared to tripropyl and tributyl amines. Triethylamine, however, does react almost twice as fast. The dialkylmethyl amines quaternize much quicker, and no chain-length effect was seen from C-8 to C-18. All reactions cleanly fit second-order kinetics.

TABLE 1

Effect of Chain Length on the Reaction of Dimethylalkyl Amines with 1-Chloro-2-Hydroxypropane in Isopropanol

% Conversion after 12 hr		Number of carbons in alkyl chain
81°C	60°C	
91	70	4
89	63	8
87	60	12
85	55	18

TABLE 2

Effect of Chain Length on the Quaternization Reaction of Alkyl Tertiary Amines with Benzyl Chloride[a]

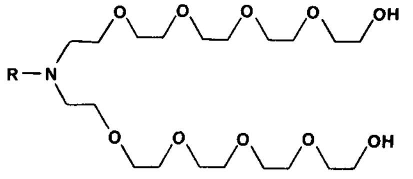
Number of carbons in alkyl chain	Rate constants (kg-solution/mole-hr)	
	Trialkyl amine	Dialkyl methyl
2	.77, .83	
3	.44	
4	.40, .43	
8	.41	2.28
10	.45	
12	.41	2.26
16	.46	
18	.40	2.19

[a]At 71°C in isopropanol.

For studies like ours that saw no chain-length effect, it seems likely, that with the conditions used, the molecule existed primarily in a favorable conformation. For those that documented a chain-length effect, an unfavorable conformation may have dominated. It is interesting that Bialik saw a significant effect at 60°C and a much less pronounced one at 81°C.

Our data and others (28) show the biggest steric effect when going from an ethyl to a propyl group which can bend back and seriously block attack on the nitrogen (32).

Another tertiary amine was quaternized that possesses a similar steric structure. Ethoxylation of a long-chain primary amine gives a tertiary amine with the general structural (Structure 6) shape of a trialkyl amine.



STRUCTURE 6

The amine used was hydrogenated tallow (about 33% C-16 and 66% C-18) primary amine ethoxylated with 10 moles of ethylene oxide. Exactly 10 moles of ethylene oxide (EO) do not add to the amine, instead a Gaussian distribution results, giving a complex mixture of similar amines containing 5 to 15 moles of EO.

Quaternization of Structure 6 resulted in somewhat inconsistent data (.26 to .34 kg-solution/mole-hr), but generally a slower rate constant than the pure trialkyl amines (.43 kg-solution/mole-hr). The reason for this is not at all obvious since this ethoxylated amine should be very compatible with the isopropanol system and exist in Structure 2. A faster rate had been expected.

EXPERIMENTAL PROCEDURES

Amines. Triethyl, tripropyl, and tributylamine were obtained from Eastman Kodak and their purity confirmed to be greater than 99% by gas chromatography. Triethylamine was freshly distilled prior to use.

The C-8, C-10, C-12, C-16, C-18 trialkyl amines and the C-8, C-12, C-18 dialkylmethyl amines were prepared from the corresponding alcohol or nitrile and ammonia using known methods (33). If necessary, the amines were distilled under high vacuum, or molecularly distilled until the chain-length purity was 95% minimum and the tertiary amine purity was 97% minimum. The tri C-18 amine was recrystallized from IPA until it gave one spot by thin-layer chromatography and its amine value titrations (34) matched theory. The ethoxylated amine studied is a standard product (Varonic U210) of Sherex Chemical Company and was used as is. The sample used had an average molecular weight of 721.

Kinetic procedure. Tertiary amine (.01 mole, for tributylamine 1.85 g) was dissolved in enough anhydrous isopropanol to give a total weight of 200 g of solution. This solution was charged to a 500 mL 3-neck RB flask fitted with a condenser and a magnetic stirrer, and heated to 71°C. Benzyl chloride (1.26 g, 1.15 mL, .01 mole) was added quickly via syringe.

At appropriate intervals over 10 hr, small aliquots were withdrawn and the unreacted amine determined by titration (32) with alcoholic .5N HCl to a bromocresol green endpoint. Conversions were limited to 40% to obtain good initial rate data.

ACKNOWLEDGMENTS

In addition to the Reference listings Corresponding sources may be consulted: CA *107*:39090S; CA *82*:171648a; CA *91*(23):192388f; CA *95*:41787s; CA *93*:48509v; CA *90*:167838z; CA *91*:4771d; CA *86*:88905h; and CA *105*:23745x are listed with References 3, 7, 11, 12, 13, 15, 19, 20, and 30, respectively.

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