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Quaternary Ammonium Compounds: Simple in Structure, Complex in Application

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Abstract

Quaternary ammonium compounds, referred to as QACs, are cationic substances with a structure on the edge of organic and inorganic chemistry and unique physico-chemical properties. The purpose of the present work is to introduce QACs and their wide application potential. Fundamental properties, methods of preparation, and utilization in organic synthesis are reviewed. Modern applications and the use of QACs as reactive substrates, reagents, phase-transfer catalysts, ionic liquids, electrolytes, frameworks, surfactants, herbicides, and antimicrobials are further covered. A brief discussion of the health and environmental impact of QACs is also provided. The emphasis is largely on tetraalkylammonium compounds bearing linear alkyl chains.

Keywords Quaternary ammonium compounds · QAC · Synthesis · Surfactant · Herbicide · Antimicrobial

1 Introduction

From their early appearance at the beginning of life on earth, to their first use in organic synthesis by Hofmann [1], organic amines constitute an important group of natural and reactive substances. In general, four groups can be distinguished: primary (RNH_2), secondary (R_2NH), and tertiary (R_3N) amines, and quaternary ammonium compounds (R_4N^+ , QACs or quats). While the first three classes possess similar properties including Lewis nucleophilicity and basicity, due to the presence of a lone electron pair on the nitrogen atom, the latter group is cationic and cannot be considered as a base/nucleophile or electrophile. Despite eight electrons in the broad vicinity of the nitrogen atom, QACs possess completely different electron distribution, as shown in Fig. 1. The nitrogen atom in alkylamines is negatively charged, whereas it becomes positive in tetraethylammonium ion.

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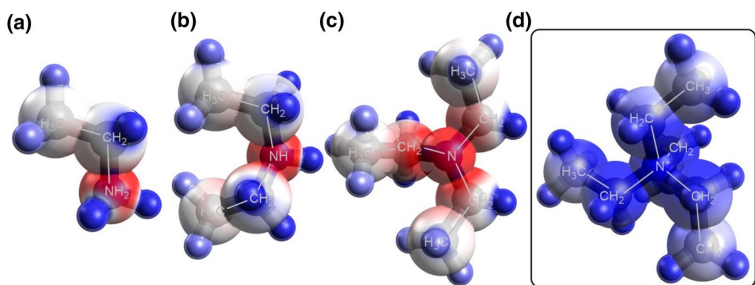


Fig. 1 Optimized molecular structure and charge distribution (electrostatic potential) along ethylamine (a), diethylamine (b), trimethylamine (c), and tetraethylammonium (d). Negative potential is shown in red, positive in blue

Taking ammonia (NH_3) and ammonium (NH_4^+), respectively, as parent inorganic structures, organic amines are derived by a gradual hydrogen substitution with organic residues (R). R generally stands for alkyl chain, benzyl, aryl, or heteroaryl, which however may be further functionalized [2]. The replacement of the original hydrogen atoms has a significant effect on the properties of the resulting amino and quaternary ammonium compounds. Compared to the ammonium cation, QACs are generally much bulkier (e.g. COSMO volume of NH_4^+ and Et_4N^+ is 34 and 160 \AA^3 , respectively). Four alkyl/aryl substituents in QACs also account for significant separation of R_4N^+ from its counter anion, especially in solution. It is believed that R_4N^+ , often referred to as synthetic alkali metal, is completely dissociated in water solutions. As ionic substances, QACs are generally highly soluble in polar and protic solvents such as water and alcohols. However, their solubility decreases dramatically with increasing chain length, and QACs with R exceeding C14 have low solubility, or further are practically insoluble, in water. On the contrary, the solubility of QACs bearing long chains in nonpolar solvents is substantially improved. QACs are generally solids, but their thermal properties can be modulated to a wide extent by the structure and length of the appended R-residues. Another notable feature of QACs is their ionic conductivity; their solutions are very good electrolytes. Because of their structure comprising both polar (N^+) and nonpolar (R) terminuses, QACs are able to absorb on a surface or an interface, thus reducing their tension. This feature makes them a very popular group of surfactants. QACs exhibit a very wide range of biological and antimicrobial activity, which also determines their current application as bioactive agents. The aforementioned unique physicochemical properties of QACs have resulted in their wide and diverse applications and their large industrial production. With production exceeding 500,000 tons/year worldwide, QACs have been included on the list of high-production-volume chemicals by the Organisation for Economic Co-operation and Development (OECD) [3].

The subsequent sections will focus on recent progress in the chemistry of QACs and their prospective uses in various fields. The main purpose of this review is not to cover all recent contributions, but rather to demonstrate the wide application

potential of QACs as shown in selected examples. The emphasis will be mostly on the QACs bearing alkyl chains.

2 Preparation and Chemical Reactivity of QACs

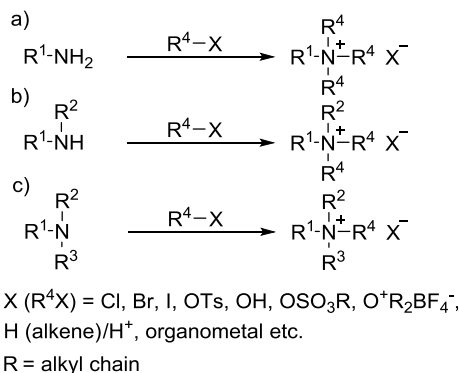
In most cases, the synthesis of QACs is carried out from an amino compound, a nucleophile, and its exhaustive alkylation with a variety of electrophilic agents (Scheme 1).

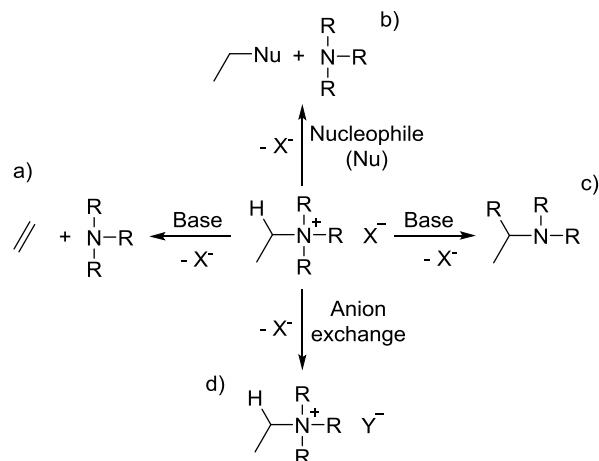
In principle, primary, secondary and tertiary amines can be used; however, the latter is the most common and convenient starting material. Quaternization of tertiary amines is also referred to as Menshutkin reaction. From the history, *N*-alkylation of amines involves Hofmann's reaction utilizing halogen alkanes (both S_N1 and S_N2 reactions are possible, depending on the haloalkane used). The structure of the resulting QAC (R^{1-4} substituents) can easily be modulated by using appropriate starting amine and halogen derivative. There are several known methods for preparing primary, secondary, and tertiary amines, for instance, reduction of nitrogen-containing compounds, reductive amination, Gabriel synthesis, and Hofmann degradation [4]. Symmetrical QACs can be produced analogously directly from ammonia. The alkylating agent R^4X represents haloalkane in most cases, but (tosylated) alcohols, dialkyl sulfates, oxonium salts, alkenes in acid media, and organometallic reagents can also be used [5]. The alkylating agent also determines the counter ion X^- in the resulting QAC, which however may be further replaced by ion exchange.

In general, QACs undergo four type of reactions: (a) elimination, (b) substitution, (c) rearrangement, and (d) ion exchange reactions, as depicted on Scheme 2.

The negative inductive effect of the ammonium group results in pronounced acidification of the hydrogen atoms present at the α -carbon adjacent to the R_3N^+ residue. This feature generally determines QAC reactivity, in which a reaction with a base/nucleophile results in Hofmann elimination or alkyl displacement. In contrast to amines, the R_3N^+ residue can serve as a good leaving group as well as an alkyl

Scheme 1 General synthetic route towards QAC starting from primary (a), secondary (b), and tertiary amines (c)





Scheme 2 General reactivity of quaternary ammonium salts

source. The Stevens 1,2-migration may take place upon α -deprotonation as a competing reaction. This rearrangement has also proved to be a useful strategy in preparing unsymmetrical tertiary amines. Similar Sommelet–Hauser 1,2-migration has also been observed on benzyl substituted QACs. Anion exchange has generally been accomplished by passing the QAC solution through various membranes, resins, and polymeric membranes [6] such as commercially available Amberlite or Dowex [7].

3 QACs in Organic Synthesis

In organic synthesis and routine laboratory practice, four general functions of QACs can be distinguished; the QAC may act as a (1) starting material, (2) reagent, (3) catalyst, and/or (4) solvent. Application of QACs in organic synthesis was last reviewed by Dockx [8]. Since then, the organic synthesis has undergone significant development and QACs have also found various new applications. Hence, the subsequent text will focus on selected recent examples and utilization of readily or commercially available QACs (Fig. 2).

Utilization of QACs as starting materials is demonstrated in Scheme 2. In particular, QACs have found useful application in Hofmann elimination reactions producing alkenes. However, this reaction is generally limited to tetraalkylammonium hydroxides. Therefore, most of the ammonium halides are converted to hydroxides by reacting them with silver oxide prior to thermal elimination. Another useful feature of this reaction is its possible extension to amines, which may be converted in situ into corresponding QACs by exhaustive alkylation with reactive methyl iodide. The methyl group has no β -hydrogens and thus cannot compete in the subsequent elimination reaction. The three-step reaction sequence is depicted

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