MODERN SYNTHETIC METHODS 1976

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Seebach · S- und Se-organische Chemie

Salle + Sauerländer

MODERN SYNTHETIC METHODS

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Editor:
Prof. Dr. Rolf Scheffold
Institut für organische Chemie
der Universität Bern
Freiestraße 3
CH-3012 Bern

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Vorwort

Das geistige Verarbeiten der wichtigen neuen Literatur ist eine
Aufgabe, die der Chemiker in der ganzen Zeit seiner Aktivität
zu bewältigen hat. Auf dem Gebiet der organischen Synthese ist
dies besonders zeitraubend und schwierig, da die Entwicklung
stürmisch voranschreitet und neue Resultate in einem breiten
Spektrum chemischer Zeitschriften verstreut sind.

Mit dem "Workshop 1976" will der Schweizerische Chemiker-Verband
eine aktuelle Uebersicht über drei ausgewählte Stoffgebiete der
modernen Synthesemethoden bieten, denen allgemeine Bedeutung zu-
kommt. Als Referenten konnten Wissenschafter gewonnen werden,
welche die Entwicklung ihres Fachgebiets massgeblich mitgestaltet
haben und heute an vorderster Front stehen.

Das vorliegende Skript enthält die drei Autoreferate. Sie ver-
mitteln nicht nur den Ueberblick des kompetenten Fachmanns,
sondern enthalten daneben viele experimentelle Hinweise, die
dem Praktiker nützlich und willkommen sind. Als zusätzliche
Information sind auf den blauen Seiten die von den genannten
Firmen zusammengestellten Chemikalienlisten angefügt. Die Aus-
stattung und der Druck sind bewusst einfach gehalten, da ein
Kompromiss zwischen schneller Publikation, Uebersichtlichkeit
und Preis angestrebt wurde.

Wir hoffen, dass diese schriftlichen Unterlagen die Mitarbeit
am "Workshop" erleichtern und die persönliche Kreativität anregen.

R. Scheffold

Naked Anions - Phase Transfer

Prof. Dr. Mieczyslaw Mąkosza

Institute of Organic Chemistry, Polish Academy of Sciences,
01-224 Warszawa, Poland

1. Introduction

Reactions of organic and inorganic anions with organic comp-
ounds are of immense value in organic synthesis. Without exagge-
ration, one can say that at least one half of the synthetically
useful methods involve interaction of an anion with an organic
molecule at one or another step. Among the many types of such in-
teractions the most important and frequently encountered are:

1. Nucleophilic substitution of the S_N2, S_N1 or S_{NAr} type.
2. Addition to the polar double bounds followed by transforma-
   tions of the intermediate adducts.
3. Reduction, oxidation etc.
4. Attack on a C-H or Y-H bond resulting in abstraction of the
   proton and then subsequent reactions of the produced anion as
   in points 1-3.

In almost all these processes the reaction rate or position
of the equilibrium (in the case of reversible processes) depends
on the activity of the anions.

The major factors which determine the activity of anions
are:

1. Intrinsic factors - nature of anions.
2. External factors: anion-cation interaction, anion-solvent in-
   teraction, aggregation, external macroscopic conditions (tem-
   perature, pressure etc.) and others.

In order to discuss the problems, which form the subject of
my lectures, I have to repeat some basic principles. Let us for
example consider a S_N2 type process with one transition state in

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an imagined situation where there are no interactions of reactants (an anion and a substrate) with a third party. In this case the rate of the reaction determined by free energy of activation $\Delta G_o^{\ddagger}$ and the reaction profile is a function of sole intrinsic properties of the reactants (see scheme).

The problem – structure of the reactants – activation energy will not be discussed here. Passing to a real system in a condensed phase we observe a great decrease of free energy of the initial state due to anion-cation, anion-solvent and other interactions amounting to δG_i. Similar interactions occur in the transition state decreasing its free energy by $\delta G_i^{\ddagger}$.
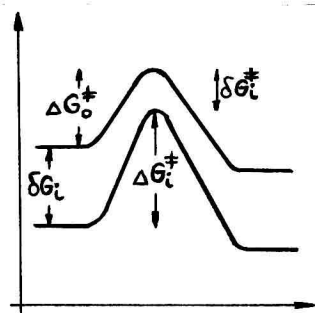
Thus considering that δG_i and $\delta G_i^{\ddagger}$ have always negative value the final result is $\Delta G_i^{\ddagger} = \Delta G_o^{\ddagger} - (\delta G_i - \delta G_i^{\ddagger})$, the last term $\delta G_i - \delta G_i^{\ddagger} = \delta\delta G_i$ represents the difference between all interactions in the initial and transition states. In the initial state these interactions are usually stronger than in the transition state, and therefore $\delta\delta G_i$ has a high negative value. This results in a considerable decrease in the rate of the reaction; obviously the stronger these interactions are, the less active are the anions and consequently the reaction is slower. Therefore any measure leading to a decrease in the energy of these interactions should enhance the activity of the anions. Under conditions where such interactions are completely eliminated, the activity of anions should be very high, corresponding to the imaginary situ-

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ation presented earlier. Conditions in which anions are complete-
ly or almost completely free from any interactions can be created
only in the gaseous phase[1]. Measurement of the rates of the reac-
tions of anions in the gaseous phase reveals their very high ac-
tivity. For instance the rate of the reaction of many inorganic
anions with methyl chloride is collisionally controlled[2]. However,
the mentioned conditions cannot be applied in laboratory practice
therefore we should return to the liquid phase and reactions in
solutions.

In order to have an ionic compound dissolved, the free ener-
gy of the solution should be lower than that of the separate com-
ponents. This requires relatively high energy of solvation of
both the anion and cation, comparable to the energy of the crys-
talline lattice.

Thus searching for practically feasible conditions assuring
high activity of anions we are in a difficult situation: use of
solvents with a high solvation power to dissolve an ionic comp-
ound results in decrease of the activity of the anions, on the
other hand, in poorly solvating media the compound is insoluble,
and even if it is soluble, the cation-anion interaction and aggre-
gation becomes a problem. Fortunately the total solvation energy
requirement does not necessarily have to be shared equally by
cation and anion; one of them can supply the major part, leaving
the second relatively free. Thus the first solution of the above
mentioned difficulties is the use of solvents having high ability
to solvate cations.

The second answer to this problem is to decrease the anion-
-cation interaction by changing the nature of the cation or its

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properties, thereby decreasing the energy requirements for dissolving the compound. Both of the above mentioned approaches are mutually connected.

One of the most efficient applications of the former principle in practice is use of dipolar aprotic solvents for reactions of inorganic anions. Due to very strong cation-solvent and moderate non-specific anion-solvent interactions, the activity of anions become high. This results in dramatic increase of the rate of reactions of anions with a variety of substrates often amounting many powers of ten.

However there are considerable practical disadvantages connected with the use of these solvents. They are rather expensive, should be used in large amounts and their regeneration is often troublesome. In addition, there are often difficulties in separation of products from the solvents. The application of dipolar aprotic solvents in organic chemistry has been thoroughly reviewed[3] and will not be discussed here.

Application of the second principle is based on the introduction of anions into nonpolar media in form of their salts with some proper organic cations. Indeed with organic cations of sufficient size and lipophilicity even inorganic anions form salts which are soluble in nonpolar solvents. In such solutions anions are feebly solvated, the anion-cation interaction is pure ionic and the distance between ions is of substantial value, therefore they exhibit a high activity. Any organic cations of sufficient lipophilicity (tetraalkylammonium, tetraalkylphosphonium, trialkylsulfonium) can be used for this purpose unless they do not react with anions. For obvious reasons, tetraalkylammonium cat-

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ions are the most convenient.

Also sodium and potassium salts of various anions can enter
nonpolar media, when the cations gain organic properties by com-
plexing with some organic compounds. The most efficient complex-
ing agents for alkaline metal cations are crown ethers and cryp-
tants represented by typical structures 1 and 2.
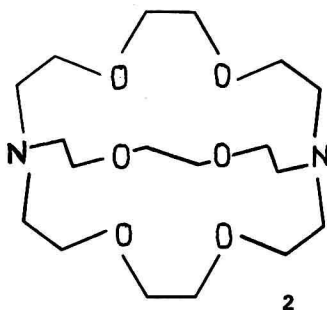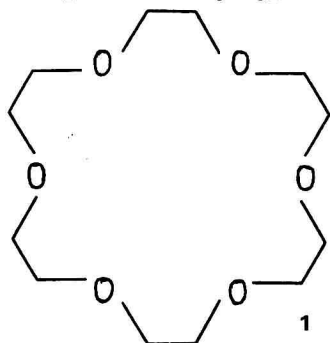
These compounds form highly stable complexes with sodium or
potassium cations and convert them into pseudoorganic cations
being able to enter nonpolar solvents together with accompanying
anions.
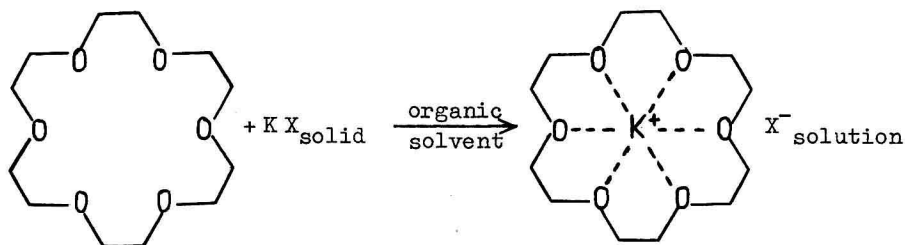
In the forthcoming text inorganic cations complexed with
crown ethers or cryptants will be represented as $(Na)^+$ or $(K)^+$.

The synthesis, study of complexing properties and numerous other aspects of crown ethers and cryptants chemistry have been thoroughly reviewed[4].

Apart from the above mentioned cyclic complexing agents many di- and polyamines, derivatives of ethylenediamine exhibit similar, but weaker, complexing properties. The most typical representatives of these compounds are tetramethylethylenediamine (TMEDA) and diazabicyclooctane (DABCO)
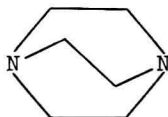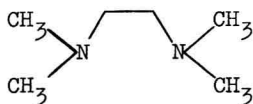
The agents complexing alcaline cations are used not only for solubilization of ionic compounds in nonpolar media, but also for changing reactivity of partially ionic compounds (like lithium or magnesium organic compounds) soluble in nonpolar solvents.

The use of tetraalkylammonium salts or crown ether complexed sodium or potassium salts of various anions, although very effective, has many practical disadvantages. Usually only tetraalkylammonium halides are commercially available, thus the salts of required anions have to be prepared from the corresponding sodium or potassium salts. The preparation of these tetraalkylammonium salts is often troublesome and laborious. These salts are obviously much more expensive as compared with sodium or potassium ones, therefore the tetraalkylammonium cations should be recovered after the reaction. Moreover separation of products from tetraalkylammonium salts is sometimes difficult.

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The problems connected with the preparation of tetraalkyl-ammonium salts of required anions was recently solved by Brändström who has shown, that ion exchange between two liquid phases (water – an organic solvent) allows one to prepare many tetraalkyl-ammonium salts of inorganic and particularly organic anions[5]. This method is presently known as the "ion-pair extraction" procedure. When combined with a simultaneous reaction of the extracted anions in the organic phase with an alkyl halide it is referred to as the "extractive alkylation" for example.

Similar but even more serious disadvantages are connected with the use of Na^+ or K^+ salts. First of all crown ethers are very expensive, and due to their high molecular weight they have to be used in large quantities. Then the complexed salts should be prepared before the use, and, after the reaction, complexing agents should be separated from the products and recovered.

Most of these disadvantages are eliminated by application of two-phase systems in which tetraalkylammonium salts or complexing agents are used only in small amounts – 1-5 % with respect to the reactant.

Typically in these two-phase systems organic reactants, neat or in nonpolar solvents, form an organic phase whereas inorganic salts are used in solid state or in form of aqueous solution. Tetraalkylammonium salts and crown ethers allow that some amounts of anions continuously enter the organic phase where they react with an organic reactant. The former approach, the use of solid--liquid two-phase systems, was introduced by Sam and Simmons[6] and Liotta[7] employing crown ethers in order to solublize partially some inorganic salts in nonpolar solvents.

In these solutions both anion-solvent and anion-cation inter-actions are very weak, the latter being such due to considerable shielding effect of the large complexing molecule. In this situation the activity of anions is very high, thus they react with many substrates at a high rate.

Liotta[7] termed these anions as "naked" on the basis of apparent similarity to the situation in the gaseous phase. There, however, still considerable interactions between anions and the components of the solution thus the anions are not really "naked", they are "bikini" or "top-less" at the best. But the term "naked anions" is nice and very promising, so I am not going to propose to replace this term with "topless anions" for example.

The second approach – the liquid-liquid two-phase systems was introduced for reactions of organic anions mainly by us[8] and for inorganic anions by Starks[9]. In these systems tetraalkylammo-nium salts are originally employed as catalysts introducing orga-nic or inorganic anions to the nonpolar organic phase. It was shown recently that crown ethers and cryptants are equally effi-cient catalysts in these systems[10-12]. The reactions carried out in these two-phase systems are usually referred to as "phase--transfer catalyzed" according to the term introduced by Starks[9]. As it will be shown later the term "phase-transfer" catalysis is adequate only in the case of reactions of inorganic anions and anions of strong organic acids. In the case of reactions of carb-anions or halocarbenes carried out in two-phase systems in the presence of tetraalkylammonium catalysts, the "phase-transfer" phenomena do not take place[13]. Applications of the liquid-liquid catalytic two-phase systems in organic chemistry has been re-