Unimetal Super Bases

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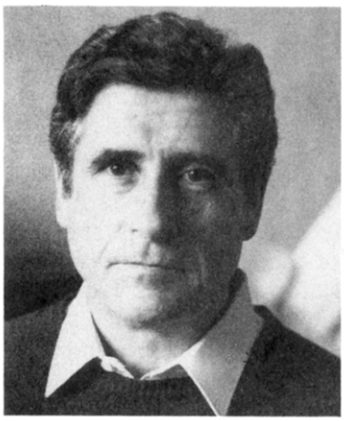

Paul Caubère was born in Paris, France, in 1937. He graduated from Sorbonne (Paris) with a Ph.D. in 1963 under the direction of H. Normant in Sorbonne. He became an assistant professor in 1965 at the University of Clermont-Ferrand (France) and a full professor (chair of organic chemistry) in 1970 at the University of Nancy. The French Chemical Society awarded him the Adrian Prize in 1964 and the Le Bel prize in 1983. The French Academy of Sciences awarded him the La Caze prize in 1989. His current interests are aggregative activation in bases and reducing agents, synthesis of strained rings and of polycyclic aromatic or alicyclic derivatives, and synthesis in medicinal chemistry.

I. Introduction

In order to place this review within a well-defined context a number of comments should first be made.

First of all it is necessary to define a base. Any nucleophile which is capable of abstracting a proton from an organic substrate will, for the purpose of this review, be considered a base. Thus, for example, enolates, which are known to participate in acid–base equilibria, will be considered bases. We will see later why such weak bases play a part in a review on super bases.

A chemist involved in organic synthesis routinely encounters the crucial problem of selecting the appropriate base for the reaction to be performed. Because the choice is so vast and varied, the solution is not always an easy one.

A vast number of covalent or ionic organic as well as inorganic bases have been described in the literature. Their properties are a function of both their structure and the solvent used in the reaction.

With ionic bases, the behavior of the anionic moiety depends on the countercation as well as on the solvent. In addition, the concentration of an ionic base and the related molecular associations are also significant. The simultaneous control of these parameters is not an easy task. Frequently the choice of base is decided by its so-called "strength", at best a vague concept.

In organic chemistry a base is defined as a reagent capable of abstracting a proton to form an anion, in many cases a carbanion. In a number of cases the anion is evidenced by reaction with an electrophile (Scheme 1) and the basicity is characterized by the yield of the product Σ-E.

For simplification the ionic species are considered to be monomers and the reaction performed under homogeneous conditions. In such reactions the experimental conditions must be chosen so that the equilibrium is "frozen" during reaction with the electrophile. If this requirement is not observed, the proton abstraction will continue during the formation of Σ-E. In this case, a base corresponding to a rapidly-reached "left-shifted" equilibrium may appear to be as strong as a base with a slowly-reached "right-shifted" equilibrium. However, from the thermodynamic point of view the second base is stronger than the first one.

Scheme 1

$$\Sigma\text{-H} + M^+B^- \rightleftharpoons \Sigma^-M^+ + BH \xrightarrow{E\text{-}X} \Sigma\text{-E} + M^+X^- + BH$$

Even if all the necessary precautionary measures are taken, a number of other difficulties exist in characterizing the strength of a given base. These are due to the inherent chemistry and not to the chemists defining the characterization. From our experience we venture to say that the situation is even much more confusing than would first appear and that enormous difficulties are encountered in even qualitatively interpreting the reactions observed. To illustrate this assertion, let us first consider the acid–base equilibrium in Scheme 1.

As soon as a few molecules of Σ^-M^+ have been formed, new species may appear, leading to new acid–base equilibria as symbolized in Scheme 2. In addition, the salt (M^+X^-) can also associate with the ionic species to give new, more or less reactive, reagents.

In addition, the second step (the nucleophilic condensation) is also subject to the same environmental influences. In other words, the nucleophilicity of Σ^-M^+

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Scheme 2

$$[M^+B^-] + [\Sigma^-M^+] \rightleftharpoons [B^-M^+M^+\Sigma^-] \quad (1)$$

$$\Sigma\text{-H} + [B^-M^+M^+\Sigma^-] \rightleftharpoons 2\ \Sigma^-M^+ + BH \quad (2)$$

Scheme 3

$$\left.\begin{array}{l}[\Sigma^-M^+]\\ [B^-M^+M^+\Sigma^-]\\ [\Sigma^-M^+M^+X^-]\\ [B^-M^+M^+\Sigma^-M^+X^-]\end{array}\right\} + EX \longrightarrow \Sigma\text{-E} + \text{"}M^+X^-\text{"} + \text{"}M^+B^-\text{"}$$

may be modified, not only by traditional solvent effects, but also by any other ionic species present at the beginning of the reaction or formed during it. Thus, the second step in Scheme I can actually mask the reactions shown in Scheme 3.

It should be noted that since the concentration of the various species varies, the apparent nucleophilicity of Σ^-M^+ must also vary throughout the reaction. In order to simplify the situation, BH is assumed not to associate with the species present in the reaction medium. In many reactions this hypothesis is yet to be verified.

Finally, if the equilibrium in Scheme 1 is completely shifted toward the formation of Σ^-M^+, the composition of the reaction medium becomes somewhat simpler since there is no M^+B^- left. Even so, the quantitative aspect of this chemistry is very difficult to master.

Added complications are the fact that ionic bases are not always monomeric and the ratio of the different possible associated species depends on both concentration and solvent. So it may be concluded that an accurate description of such apparently simple reactions as presented in Scheme I is far from being easy. Needless to say the situation with heterogeneous systems is even worse!

Another kind of difficulty arises when bases are studied in aprotic solvents which are not quite aprotonic enough (DMSO for example). Some of the supposed "solvent effects" may in fact be actually due to the presence of the conjugate base of the solvent.

Finally it should be noted that electron-rich species are not only potential nucleophiles and bases but also potential reducing agents (NBR properties) and that their single electron transfer (SET) capability, although far from being unlikely[1] is, unfortunately, often neglected. Which of the NBR properties actually dominates for a given reagent is related to the intrinsic properties of the anions and the countercations, as well as to the physical state of the reagent, the structure of the substrate it reacts with, and the experimental conditions.

In this general context the meaning of expressions such as "strong" or "very strong" bases depends on the organic chemist who in fact uses them. Moreover, even when simple acid–base reactions are being considered, these expressions are sometimes unfortunately applied indiscriminately to thermodynamic as well as to kinetic basicities. In fact, over the years, they have become synonymous with base efficiency, giving a feeling of basicity rather than actual well-defined position scales relative to well-defined acids.

Scheme 4

$$\text{Base 1} + \text{Base 2} + \cdots \rightleftharpoons [\text{Super Base}]$$

Scheme 5

$$A^-M^+ + B^-M^+ \longrightarrow [\text{Unimetal Super Bases}]$$

Scheme 6

$$A^-M^+ + B^-M_1^+ \longrightarrow [\text{Multimetal Super Bases}]$$

Finally, organic chemists have introduced the magic expression "super bases" often used without any regard to the fact that an unambiguous definition does not even exist. The term "super bases" should only be applied to bases resulting from a mixing of two (or more) bases leading to new basic species (Scheme 4) possessing inherent new properties.

In this review the term super base does not mean a base is thermodynamically and/or kinetically stronger than another. Instead it means that a basic reagent is created by combining the characteristics of several different bases. A super base may be more efficient than its component bases in the case of some reactions and less efficient in others. In other words, such a definition assumes that if it is of paramount interest to substantially increase the basic power of a particular base it is of no less interest to modify its properties in order to fit the reagent to the desired reaction.

As will be mentioned later in more detail, the existence of the so-called super bases has been long suspected.[2] In 1966 investigations on the reactivity and synthetic applications of super bases prepared according to the general principle given in Scheme 5 were initiated by our group.

The reagents presented in Scheme 5 contain only one kind of cation and will therefore be called unimetal super bases (USB).

At the same time Schlosser et al. initiated an independent investigation with the important difference that they studied super bases formed from bases with different cations (Scheme 6). Such bases will therefore be called multimetal super bases (MSB) and are finding many applications.[3]

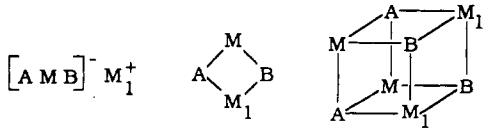
We carried out an empirical investigation of the reactivity of a number of USB's and the synthetic consequences of such base associations. Thus, step by step, we established a means of fitting a base to a given reaction.

Meanwhile, during recent years numerous relevant publications have appeared. Most of them involve physicochemical studies. The results obtained are very useful, and it is interesting to note that they support the hypothesis and conclusions arrived at from synthetic studies.

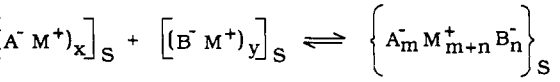
The present review will be devoted to USB's and will describe work where reagents of this kind are involved as well as cases where such base associations can be supposed to intervene.

Before developing this topic it might be useful to give some consideration to the behavior of USB's as well as a few arguments supporting their existence.

Scheme 7 (Adapted from Ref 4 with Permission)



Scheme 8 (From Ref 5 with Permission)



II. Basic Principles of Aggregative Activation

First of all and in order to avoid any misinterpretation, it is necessary to define the word "aggregate" for the purpose of this review. Seebach in one of his excellent articles[4] mentions the difference which may be made between ate complexes, dimers, and higher aggregates respectively as symbolized in Scheme 7.

No discrimination between these species, which overall will be called aggregates, will be made here for the following reasons.

According to its usual definition, the word aggregate means the sum or association of different substances or elements. It can thus be attributed to any association of bases including those given in Scheme 7 without generating any misunderstanding.

It is not unreasonable to reason that the association of given reagents may continuously evolve from one kind of species to another as experimental conditions are continuously varied. We shall see later that observations confirming such continua have been carried out.

Moreover it is not unreasonable to reason that even ate complexes could give rise to reactive oligomeric species (which ought therefore to be called aggregates) where some of the characteristics of the triplet anion $[AM^1B]^-$ would be preserved.

Finally, as we shall see, the actual nature of the reactive moiety of super bases are generally inaccurately known or completely unknown. Thus a general term such as aggregate which covers a broad variety of species appears well-suited to the present situation.

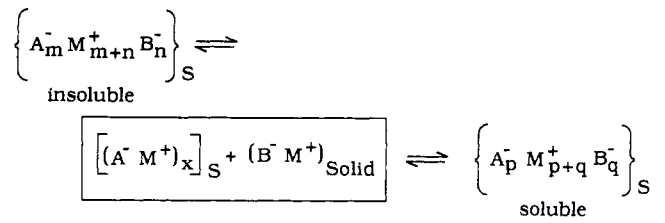
With this understanding in mind we can now come to the heart of the matter. Super bases can be related to the concept of aggregative activation (AA). An extensive review has recently been devoted to AA,[5] so we will confine ourselves to a brief summary of the corresponding basic principles.

Let us first consider homogeneous systems. It is generally accepted that the mixing of two ionic reagents with a common cation and appropriate structures may lead to the formation of mixed aggregates as symbolized in Scheme 8 where "S" represents the solvation.

The mixed aggregates $\{A^-_m M^+_{m+n} B^-_n\}_S$ may exist as an equilibrium of different kinds of mixed aggregates.

It had been proposed[6] that the properties of the new species should be due in part to the presence of two different anions A^- and B^-. Consequently, a dissymmetrical repartition of cations M^+ among the anionic framework results. Relative to the starting materials, the interionic distances and formal oxidation states of the ionic species must differ thus causing changes in the NBR behavior.

Scheme 9 (Adapted from Ref 5 with Permission)



Solvation effects have to be expected of course with mixed aggregates as with every chemical reagent. Solvent molecules can interact with the ionic species in aggregates and cause structure modification. The extreme limit may be complete disaggregation accompanied by reorganization and/or dissociation of the ionic species.

It is assumed[5] that, as a consequence of aggregation, the anionic electron availability is modulated (increased or decreased) with respect to the electron availability of the starting reagents.

It is also accepted that the formation of mixed aggregates increases the SET ability of the reagents thanks to a so-called "cluster effect" according to which a single electron generated by SET from the electron-rich parts of an aggregate may be stabilized by delocalization over the whole aggregate. It follows therefore that aggregates should also be able to stabilize "external" radical due to electron transfer from the aggregates to a substrate through some kind of electron delocalization. Consequences such as these of aggregation on the SET ability are also to be expected for homoaggregates formed by self-association of a given reagent. The proposed increase in the SET ability of aggregates has already found some experimental support.[7] In addition hypotheses such as these led to the discovery of new reducing agents called complex reducing agents (CRA).[5,6c,8]

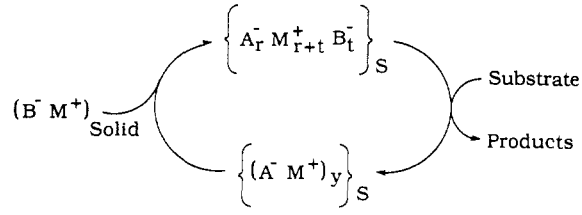
Finally, the term aggregates also means ion associations limited by ionic surfaces where interionic distances strongly depend on the nature of the constituent species. Such surfaces may be used for the syn attack of substrates in syn eliminations (*vide infra*).

Let us now consider heterogeneous systems resulting when one of the reagents, let us say B^-M^+, is poorly soluble in the reaction solvent while the coreagent A^-M^+ is more soluble. Under these conditions the equilibrium in Scheme 8 must be written as in Scheme 9.

Within a mixed aggregate, B^- has a greater probability of being more reactive than in the solid starting reagent. Indeed within the aggregates the ionic dissociation is expected to be more significant than in the solid state. Moreover, the ionic dissymetry due to the presence of two different kinds of anions (A^- and B^-) must have as a consequence an increase in the local polarizations. With appropriate solvents some kind of solvation may also take place during aggregate formation resulting in a weakening of ionic interactions.

In addition, when the poorly-soluble reagent is not completely transformed into aggregates it is also assumed that during a given reaction the overall reactivity of such mixed aggregates will depend not only on the amount of B^-M^+ extracted and included in the new reagent but also on the rate of formation of the mixed species. In other words, if B^- is the active part of the reagent, any reaction between a substrate and

Scheme 10 (Adapted from Ref 5 with Permission)



Scheme 11

$$(A^- M_1^+)_x + (B^- M_2^+)_y \rightleftharpoons \left\{(A^-)_p(M_1^+)_q(M_2^+)_r(B^-)_s\right\} \rightleftharpoons (A^- M_2^+)_m + (B^- M_1^+)_n$$

the mixed aggregates will release A^-M^+ which will go back to extract some B^-M^+ at the surface of the solid reagent (Scheme 10). Such a catalytic cycle strongly resembles phase-transfer catalysis (PTC) where A^-M^+ plays the part of the catalyst.

Finally, it is clear that all of the above statements may also apply to multimetal super bases. The dissymmetry of ionic distribution in the corresponding mixed aggregates should be even more accentuated than in USB's. With certain ions under appropriate conditions such dissymmetry may cause cation exchanges between anions, as symbolized in Scheme 11. Such situations have already been described in the literature.[3]

III. Unimetal Super Bases: Their Reality and Applications to Organic Synthesis

A. Existence of Unimetal Mixed Aggregates

From the literature it appears that, up until now, with only a few exceptions, the family of USB essentially consisted of alkali metal reagents which are generally restricted to lithium or sodium derivatives.

On the other hand, plenty of investigations show that alkali metal derivatives possess a strong propensity to give homoaggregates through self-association. A large amount of the reported literature is devoted to lithium derivatives and deals with the aggregation of organoalkali derivatives,[9] alkali amides[10] as well as alkali alkoxides, phenolates or enolates.[11] Much useful information on alkalimetal homoaggregates can also be obtained from a number of reviews[4,12] as well as from a recent publication by Jackman and Rakiewicz.[13] Since alkali derivatives easily form homoaggregates it must be concluded that they are also able to form mixed aggregates and that such species play an important role in the chemistry of USB's.

It is not by chance alone that lithium derivatives have been studied in more detail than any other group alkali compounds. Generally easily prepared and handled, they allow structure studies in solution as well as in the solid state. However, it is noteworthy that in spite of the enormous wealth of knowledge acquired, little mechanistic detail of their reaction pathways is known.

Little is known about the structure of alkali USB's and even less about their reaction mechanisms in spite of the fact that numerous reactions have been performed thanks to these reagents. In many cases it is an accumulation of experimental and synthetic results which indirectly leads to the conclusion that the formation of mixed aggregate USB's is in fact involved.

Interestingly enough, during the past few years, physical chemistry, in particular spectroscopic methods, has brought to light some very interesting data for some of these reagents. The fact that the results thus obtained very often agree with the suggestions formulated from synthetic experiments is very encouraging.

We will now consider some synthetic studies in which the so-called mixed aggregates USB's were first suggested. Many years ago the efficiency of amylsodium in proton abstraction metalations as well as in butadiene polymerizations was found to be increased by the presence of sodium alkoxides.[14]

These results were interpreted as being due to the formation of mixed aggregates. It emerged that the amylsodium activation depended on the structure of the alkoxide. Thus secondary[14a] and tertiary sodium alkoxides[14b] led to the most marked change in the amylsodium behavior. The ratio AmNa/RONa had also to be considered. Thus it was found that a 2:1 ratio was necessary with some alkoxides in order to reach optimum activity.[14a]

Alkoxides were also found to accelerate the condensation of alkylsodium with alkyl halides.[15] This result indicates that any increase in the basicity of an anionic species is accompanied by an increase in its nucleophilicity, according to the inseparable NBR properties mentioned before.

The formation of mixed aggregates between AmNa and sodium alkoxides during the metalation of aromatic hydrocarbons was later questioned.[16] These authors found that in nonane the completely insoluble AmNa led, in the presence of *t*-BuONa, to a brown solution containing definite quantities of AmNa and *t*-BuONa. This brown solution was capable of metalating aromatic hydrocarbons. The role of the *t*-BuONa was interpreted as being dispersing or peptizing one on the AmNa aggregates, causing them to disintegrate into much finer particles. This interpretation is really a semantic one because any dispersing or peptizing action of the *t*-BuONa involves molecular interactions with the AmNa on the solid surface as well as in solution. In other words it means the formation of mixed aggregates.

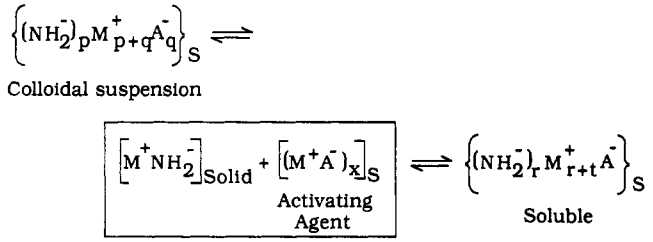
During a study of arynic condensations,[17] the activation of $NaNH_2$ by ionic nucleophiles was suggested. This observation was confirmed and it was established that numerous *in situ* generated sodium alkoxides, enolates or thiolates combine with $NaNH_2$ to give super bases called sodamide containing complex bases.[6a,18] It should be noted that the term complex bases is sometimes misused.[19] According to our definition[6a-c] when these reagents were first discovered, they belong to the USB family and have nothing to do with MSB's.

The properties of sodamide (or other alkali amide) containing complex bases (MNH_2–CB) were explained by the formation of mixed aggregates as shown in Scheme 12.

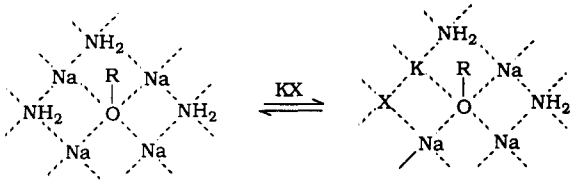
Although a huge variety of activating agents can be used, it was also found that a number of alkali derivatives proved completely inefficient. In other words, and according to the AA principle, the actual nature of the anionic part A^- plays an important role.

Briefly (the topic will be developed further) it can be said that very efficient activating agents are found

Scheme 12 (Adapted from Ref 5 with Permission)



Scheme 13 (From Ref 22 with Permission)



among the alkali salts of diethylene glycol monoalkyl ethers, of tertiary alcohols, as well as of secondary and primary alcohols with some chain branching. The corresponding USB's are called nonnucleophilic complex bases.[5,6c] Nucleophilic complex bases are also obtained with activating agents such as enolates, thiolates, and so on.

It was also found that in aprotic solvents, inorganic alkali salts could also combine with alkali amides and modulate their properties.[20] A similar effect has been observed in dimethylamine.[21]

Interestingly, it was observed that, with very few exceptions, the highest efficiency of these reagents corresponded to a ratio of MNH_2/activating agent of 2:1. However no clear information can be obtained from this observation since the reagents are heterogeneous.

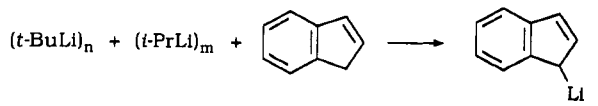
The solvent, which of course must be aprotic, plays an important part in the reactivity of MNH_2–CB's. Thus, the more polar the solvent, the more reactive the base. This result may be interpreted as due to an insertion of solvent molecules into the mixed aggregates thus increasing the ion separation and the anionic reactivity. Later we shall see that recent results obtained with lithium derivatives support this solvent effect.

Another argument supporting a mixed aggregate structure for complex bases is the appreciable rate increase in carbanion formation–electrophilic condensation (*vide infra*) when potassium halide is added to $NaNH_2$–CB.[22] This result is interpreted as partially due to the formation of a MSB as symbolized in Scheme 13.

Sodium hydride was also found to be activated by sodium alkoxides.[5,8,23] In dipolar aprotic solvent such as hexamethylphosphoramide (HMPA) the efficiency of proton abstraction was considerably increased. Interestingly enough and according to AA principles, in less polar aprotic solvents such as tetrahydrofuran (THF) the reducing properties of NaH compete with its basicity. Reduction was the only observed reaction with a number of substrates.

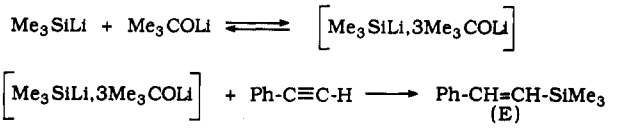
In a work dealing with the study of reactions between *i*-Pr_2NLi and *t*-BuOK in toluene, Lochmann and Trokeval[24] reported the formation of the aggregates, $\{(PhCH_2K)_m(t\text{-BuOK})_n\}$ the composition of which depended on the amount of *t*-BuOK.

Scheme 14



Time	$k_{i\text{-PrLi}}/k_{t\text{-BuLi}}$
0.3 h	15 ± 4
93 h	1.3 ± 0.2

Scheme 15



During the same study it was also found that the bases formed from *i*-Pr_2NNa and *t*-BuONa had properties different (*vide infra*) from those of the isolated starting reagents. This observation was interpreted as due to the formation of mixed aggregates of the type $NaNH_2$–CB.

Lithium reagents are easily prepared and handled and are in themselves very efficient bases. Thus, it is not surprising that, except in the field of polymerizations,[12d] much fewer works have been devoted to their activation as USB's for synthetic purposes. However, there is indirect evidence for the formation of mixed aggregates.

For example,[25] a study of the competitive metalation of indene by *t*-BuLi and *i*-PrLi in pentane has shown that the relative reactivities of the two alkyllithium reagents was a function of the time after mixing prior to addition of the indene. Such a result strongly supports the formation of mixed aggregates. Indeed *t*-BuLi which is particularly unreactive toward proton abstraction in pentane became nearly as reactive as *i*-PrLi after the two organolithium compounds were allowed to stand long enough to form a statistical aggregate mixture (Scheme 14).

More recently,[26] the formation of the mixed aggregates $(Me_3SiLi)(Me_3CLi)_3$ and $[Me_3SiLi,3Me_3COLi]$ was invoked for the addition of organolithium derivatives to phenylacetylene (Scheme 15).

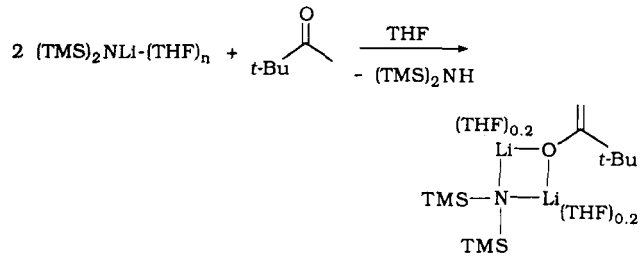
The participation of the aggregates $(BuLi\text{–}ROLi)_x$ was proposed[27] to explain that under appropriate conditions, the rate of addition of BuLi to 1,1-diphenylethylene was appreciably increased on addition of lithium alkoxides. Aggregate formation was also suggested to explain the modulation of the basic as well as nucleophilic behavior of organolithium reagents in the presence of lithium alkoxides.[28]

During a study of the heat of deprotonation (ΔH_{dep}) of a series of substrates[29] it was found that ΔH_{dep} changed during the incremental addition of acids to lithium bis(trimethylsilyl)amide (LiHMDS) in THF.

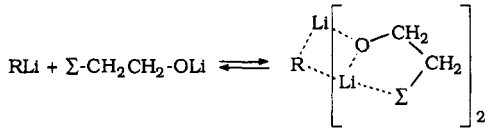
This observation was made with acids such as *o*-*tert*-butylphenol, pinacolone, or *tert*-butyl alcohol and to a lesser extent with neopentyl and isopropyl alcohols. The ΔH_{dep} changes were interpreted as being due to the formation of mixed aggregates as shown in Scheme 16 for pinacolone.

Through the use of deuterium exchange experiments the formation of mixed aggregates between lithium diisopropylamide (LDA) and keto acid enolates has been

Scheme 16



Scheme 17



shown.[30] The reactions observed between the enolates and the electrophiles were attributed to such aggregates. However, it is not unreasonable to suggest that in such associations, the basic properties of the LDA must also be altered. In fact such mixed aggregates may be considered as USB's resembling nucleophilic complex bases (*vide supra*).

The formation of mixed aggregates between organolithium derivatives and lithium alkoxides during the polymerization of vinyl monomers has also been suggested.[12d,31]

Let us now consider some more direct evidence for the existence of mixed aggregates. Lithium-containing reagents are of course more prone to study using physical methods and works described in the literature are essentially performed with these reagents.

IR spectroscopy cannot give the exact structure of aggregates. However it does allow the observance of such associations. Thus, for example, 1:1 mixed aggregates between *t*-BuOLi and RLi (R = Bu, *i*-Pr, *t*-Bu) were detected.[32] Mixed aggregates between lithium ester enolates and lithium alkoxides were also detected using IR and UV spectroscopy.[33]

By using appropriate reagents, electronic spectra not only permit the detection of mixed aggregates but also give some electronic structural information. Thus,[31b] from results obtained during the copolymerization of styrene and butadiene with BuLi or $PhCH_2Li$, associated with $Me_2NCH_2CH_2OLi$ or $MeOCH_2CH_2OLi$, it was concluded that active species consisting of 1 equiv of lithium reagent and 2 equiv of lithium alkoxides were involved (Scheme 17). The electronic spectra of reagents prepared from the above-mentioned alkoxides with 1,1-diphenyl-*n*-hexyllithium showed the formation of similar mixed aggregates.

From spectroscopic data it was proposed that local polar conditions in the vicinity of the organolithium species in such aggregates could be responsible for the unique behavior of these catalysts.

In fact, anionic polymerization led chemists in this field, to examine the interactions between alkali derivatives used as initiators. A number of mixed aggregates were either suspected or proven as being involved.[12d]

Lithium, nitrogen, and carbon NMR spectroscopy are being used more and more to study the behavior of organolithium reagents as well as lithium amides. The judicious use of these physical techniques provides interesting evidence on the structure as well as the reactivity of the reagents.

NMR[34] showed that, besides $(t\text{-BuLi})_4$, mixed aggregates such as $[(t\text{-BuLi})_3,Me_3SiCH_2Li]$ and $[(t\text{-BuLi})_2,(Me_3SiCH_2Li)_2]$ also exist on mixing *t*-BuLi and Me_3SiCH_2Li. Intra- as well as intermolecular exchanges operated, and it was established that the solvent played a part in exchange rates. Similar observations were made with EtLi and *t*-BuLi.

Of course, as expected, the nature of the aggregates depended on the time the reagents were allowed to stand together. It should be noted that the existence of mixed aggregates in the gas phase was confirmed by mass spectrometry. During this work, the formation of mixed aggregates between *t*-BuLi and *t*-BuOLi was also established using mass spectrometry.

The formation of mixed aggregates between BuLi and BuOLi has also been shown by NMR.[9d,35] The incorporation of alkoxy groups into BuLi aggregates apparently increased the polarization of the C–Li bonds with, as a consequence, an increase in carbon nucleophilicity. Interestingly enough it was observed that BuLi in a mixed Li_4 aggregate with three BuOLi ligands or in a mixed Li_2 aggregate with one BuOLi ligand, behaved kinetically as a monomer.

Aggregates formed from lithium amides, mainly LDA and lithium 2,2,6,6-tetramethylpiperidide (LiTMP), were studied intensively for some years.

We shall now digress somewhat in order to report some interesting studies[36] dealing with solvent effects on aggregates.

Thanks to NMR spectroscopy, it was shown, among other things, that dipolar aprotic solvents with strong solvating powers such as HMPA were not able to disaggregate organolithium derivatives. For example, with LDA or LiTMP, HMPA did not dramatically shift the monomer–dimer equilibria. However, it appeared to readily causes ionization of the dimers to form ion triplets $[R_2NLiNR_2]^-//Li^+S_n$ bearing three or four HMPA ligands on the Li^+ counterion.

This interesting result supports the hypothesis according to which the solvent effects observed for mixed aggregates ought to be due to insertion of solvent molecules into the aggregates without complete disaggregation. Moreover, it indicates that the formation of ion triplets must be considered as possible reactive species of super bases. It should be remembered that such an observation confirms the idea of a continuous transformation of the ionic associations with continuous change in the nature of the reaction medium.

Returning to mixed aggregates we will now mention two NMR papers reporting the formation of aggregates between lithium amides and keto enolates.[37] It was shown that LDA combines with lithium pinacolate to give 1:1 mixed aggregates, whereas with lithium cyclohexenolates there is no evidence of such associations.[37a] On the contrary, mixing LiTMP and lithium cyclohexenolate led to the formation of 2:1, 1:1, and 2:2 mixed aggregates.[37b] In other words, the actual formation of mixed aggregates depended on the structure of the starting reagents. Moreover, it was also established that the concentration of the solvent had a strong influence not only on the nature but particularly on the ratio of the coexisting aggregates.

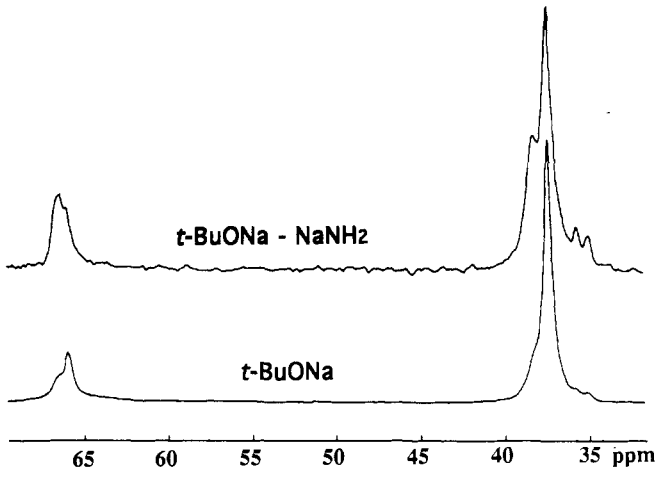


Figure 1. ^{13}C CP/MAS spectra of *t*-BuONa and $NaNH_2$–*t*-BuONa.

These results agree completely with those obtained for nucleophilic sodamide-containing complex bases with keto enolates as the activating agents. In fact they appear to confirm the possible formation of mixed aggregates between $NaNH_2$ and keto enolates and that a number of keto enolates are inefficient in promoting sodamide reactivity (*vide infra*). The qualitative observation that with complex bases results sometimes depend on the amount of solvent used could be related to the concentration effects observed in lithium amide aggregations.

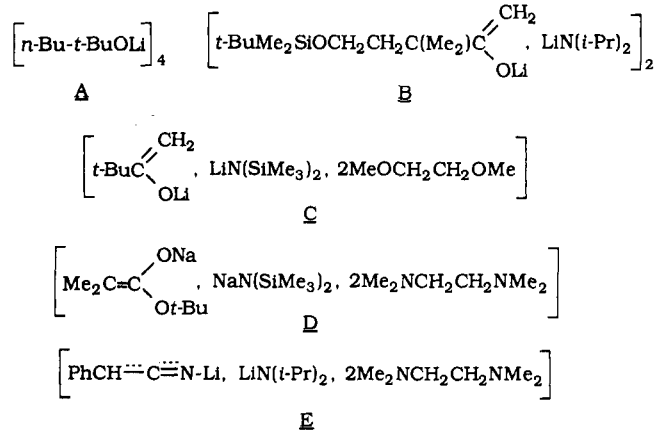
With regard to Na^+-containing USB's it should be mentioned that recent preliminary results obtained using solid-state NMR spectroscopy of $NaNH_2$–*t*-BuONa.[38] In Figure 1 are shown the ^{13}C cross polarization/magic-angle spinning (CP/MAS) spectra of *t*-BuONa and the corresponding complex base.

In each spectrum the two lines are broadened and exhibit a fine structure due to the dipolar interaction of the relevant ^{13}C with the quadrupolar nucleus ^{23}Na. One striking feature is the dramatic change on going from *t*-BuONa to $NaNH_2$–*t*-BuONa. These changes, although not yet quantitatively interpreted, clearly indicate the formation of new molecular associations. On the other hand the ^{23}Na spectra of the same species support the above conclusion and ought to provide complementary information concerning the exact structure of the complex base.

X-ray diffraction studies have recently confirmed the reality of mixed aggregates. Thus, as shown in Scheme 18 the structure of a tetrameric mixed aggregate A obtained from hexane solution was elucidated.[39] It appeared that, as suggested during the study of complex bases,[6] there was a dissymetrical repartition of the cations relative to the anionic sites. The crystalline structure of the mixed aggregates B[40] and C[41] has been completely established. Of interest also is the fact that the sodium-mixed aggregate D has also been obtained and characterized.[41]

These data support the hypothesis that the formation of mixed aggregates must in fact be a very general phenomenon to be expected whenever two ion–pair species are mixed. Moreover, the above result also shows a similarity of behavior between lithium- and sodium-containing species. Such a similarity had already been outlined.[12f-h] In other words, results obtained for lithium-containing reagents (more easily studied than sodium ones) may be taken as a starting point and guide to explore the field of sodium-containing reagents. That the formation of mixed aggregates between amides and enolates is a general phenomenon was exemplified by the isolation and crystalline structure determination of E[42] (Scheme 18).

Scheme 18



The goal of the present section was to give a short overview of works dealing with aggregation. Additional information can be obtained from the articles quoted as well as the references cited therein.

In conclusion there is little doubt as to the actual formation of mixed aggregates when appropriate reagents are mixed under either homogeneous or heterogeneous conditions.

Since the formation of USB's is in fact due to such mixing it is highly probable that the particular properties displayed by these reagents are due to mixed aggregates.

The structures established by X-ray diffraction spectroscopy may be used as a guide to interpreting the observed results. However, we must remember that in solution the structure of the aggregates may be different and that new species may appear as would appear to be the case from a number of spectroscopic studies. Finally, correlated to this statement and as briefly mentioned above, both solvent insertion and solvation must also be taken into account.

A knowledge of the actual structure of a base or USB is in itself insufficient to accurately explain the reactions observed. Indeed, when the reagent reacts with a substrate, its structure changes and new, more or less reactive spcies, may be formed. This is particularly true in cases where the reaction between the basic reagent and the substrate results in the formation of ionic species.

Thus, the reaction medium continuously evolves and the mechanisms taking place at the very beginning of the reaction may be different from the ones at the end of the same apparent reaction.

In other words, information acquired from physical chemistry are of considerable help for synthetic applications of USB's. However, it is not less unquestionable that in addition to these studies, plenty of "trial and error" investigations have to be carried out.

B. Proton Abstractions

Proton abstraction from organic substrates is generally performed using either lithium- or sodium-containing reagents.

By taking into account the large variety of organolithium compounds and lithium amides with very powerful basic properties, it is not surprising that lithium-containing USB's were not studied with the simple goal of increasing the efficiency of a lithium base in proton abstraction. Nevertheless, much interesting work remains to be done in this particular field as illustrated by the following two examples.

First, the study of the enthalpies of the deprotonation (ΔH_{dep}) of isopropyl alcohol in hexane–ether where the bases used were lithium amides and organolithium reagents both with and without *t*-BuOLi.[43] It was concluded that as far as soluble reagents were concerned, and within experimental error, no changes in the ΔH_{dep} [$\Delta(\Delta H_{dep}) = 0$] were observed as the result of the addition of *t*-BuOLi. On the contrary, dramatic effects were observed for the solubilities of lithium cyclohexylamide and lithium isopropylamide. On its own neither salt is soluble in the 90:10 hexane–diethyl ether solvent but both are completely soluble if 1 equiv of *t*-BuOLi is added to the solution prior to introducing the lithium amide.

This second observation is in complete agreement with the observation made in section II about the increase of efficiency of an insoluble base through association with a more soluble one.

The first observation is also very interesting in so far as at first sight it appears to question the actual intervention of USB's, at least in the cases considered. A number of questions are raised. What about ΔH_{dep} when other organic acids are used? Are these results independent of the time the basic reagents were allowed to stand together? Are the same results obtained if *t*-BuOLi was generated *in situ*? Are these results independent of both the ratio of organolithium reagent–*t*-BuOLi (1:1 in this study) and the nature of the solvent? Does $\Delta(\Delta H_{dep}) = 0$ indicate that no USB of synthetic interest was formed?

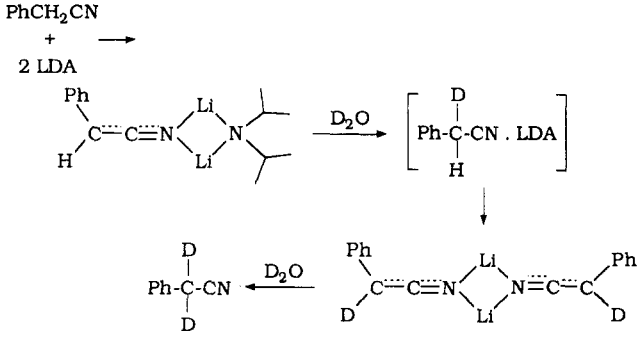
It would appear that an estimation of $\Delta(\Delta H_{dep})$ ought to be an excellent method for screening potential USB's as well as for obtaining information concerning the behavior of a given base when its composition is changed. In addition, it should be of great synthetic interest to establish correlations between $\Delta(\Delta H_{dep})$ values and the reactivity of USB's in a number of test reactions.

A second report[42] deals with the curious behavior of a mixed aggregate toward the electrophilic reagent D_2O. It was shown that dideuteriation of phenylacetonitrile by successive reaction with LDA and D_2O takes place according to the mechanism reported in Scheme 19.

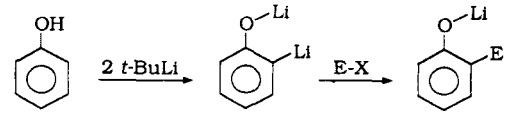
This result illustrates how the formation of a USB can modify the behavior of anionic species toward electrophilic substrates. It would be very interesting to know the exact structure of the nonisolable intermediate in order to explain that deprotonation was the only reaction observed during the third step.

Lithium-containing USB's ought to find application in regio- and/or stereoselective proton abstractions. This is clearly illustrated in the study of the enolization of 3-pentanone with LiTMP in THF.[44] Under kinetic

Scheme 19 (Adapted from Ref 42 with Permission)



Scheme 20



E-X = Electrophile

conditions it was found that at 5% conversion the *E*/*Z* selectivity was 30:1 while at >80% conversion the *E*/*Z* selectivity was <10:1. A number of control experiments as well as a spectroscopic study attributed this result to the formation of mixed aggregates between LiTMP and the lithium enolate.

In the same report the influence of the formation of mixed aggregates LiTMP–LiX (X = Br, Cl), on the stereochemistry of enolization, was also described. The positive as well as negative influence of lithium halides on the reactivity of organolithium compounds and lithium amides has been frequently mentioned.[10f,45]

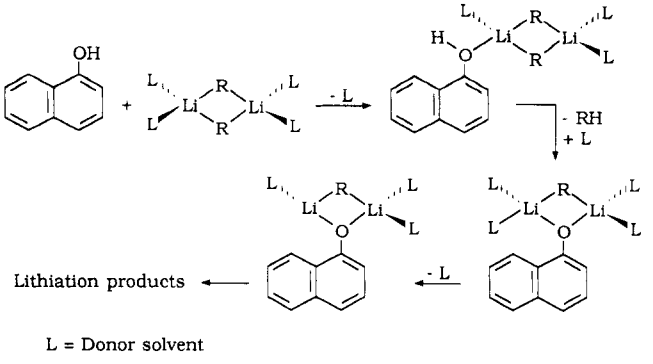
Proton abstraction lithiations which are intramolecularly directed by lithium alkoxides have been known for several years.[28d,46] Examination of the literature dealing with these so-called complex-induced proximity effect (CIPE) processes[28d] strongly suggest that some kind of USB's must be formed during the metalations. To illustrate we will briefly report phenol lithiations.

In their pioneering work Posner et al.[46b] showed that under suitable conditions organolithium reagents abstracted the protons of lithium phenoxide only from the ortho position (Scheme 20).

This result was interpreted as being due to a coordination of the organolithium reagent with lithium phenoxide and to a particular stability of the intermediate dianion which may be considered as belonging to the very stable triplet ion class.[47]

Saa et al. also studied the directed lithiation of polycyclic aromatic phenoxides.[48] The directing effect was found to depend on the structure of the starting phenoxide. Thus the lithium salt of 2-naphthol led only to the 3-substituted derivative, whereas the 1-naphthol salt led to a mixture of compounds substituted at the 2- and 8-positions. Even more interesting was the finding that the experimental conditions such as rate, temperature of addition of the organolithium reagent, its concentration, as well as the concentration of the substrate played an important part in the efficiency of the proton abstraction. These observations are not unusual where USB's are concerned and are a good argument in support of the formation of such reagents.

Scheme 21



L = Donor solvent

Finally, in agreement with theoretical considerations Saa et al.[28c] proposed the formation of aggregates such as the ones exemplified on Scheme 21 with 1-naphthol to account for their observations.

Similar ortho-directed lithiations were performed with lithium thiophenoxides.[49] It is of interest that as in the case of phenoxide lithiations, the efficiency of the metalation depends on the ability of the solvent used to favor the formation of aggregates.[49a]

To continue with anionic chemistry, it is clear that sodium salts of very weakly acidic organic substrates should be useful in synthesis. Their behavior would be expected to differ somewhat from the behavior of the corresponding lithium salts.

However, the situation for sodium- and lithium-containing bases is far from being identical. Indeed organosodium reagents are much less easily prepared than their corresponding lithium derivatives, and their poor stability in most current solvents[12d] cannot be neglected. Thus, the low interest devoted to these reagents as bases in organic synthesis is not surprising. Even worse is the importance accorded to organopotassium reagents.

In contrast, among the few well-known sodamides, $NaNH_2$ is commercially available, inexpensive, and could be of interest for small- as well as large-scale applications. However, the efficiency of this rather insoluble strong base in most organic solvents, is not enough in the case of a number of reactions.

These observations justified investigation of sodium-containing USB's with a view to simple proton abstraction, either with organosodium reagents in solvents where they are stable but of low reactivity or with sodium amide.

Although USB's obtained from organosodium reagents have so far not found application in organic synthesis, we will first talk about the activation of one of them: AmNa.[14b,16] Indeed, it is a good illustration of the effect of an activating agent on the reactivity of an organosodium derivative, as well as of the difficulties encountered in interpreting the results obtained.

The reaction studied was the metalation of *tert*-butylbenzene in saturated hydrocarbons. It was first discovered[14b] that the behavior of AmNa was modified in the presence of sodium alkoxides and several of these activating agents were studied. Broadly speaking, it appeared that tertiary alkoxides increased the metalation ability of AmNa and favored dimetalations. It was also found that the meta–para isomer ratio of the monometalated derivatives depended on the presence and nature of the activating agent.

It was assumed that mixed aggregates between AmNa and the activating agents were formed. Moreover the proton abstraction with organosodium reagents was believed to proceed via a radical mechanism. It was then proposed that the mixed aggregates had more RNa bonds per R than AmNa itself, different bond distances, and, therefore, a greater chance of forming the radicals that initiate the reaction. The interpretation of the monometalation orientations was not very clear.

The metalation of *tert*-butylbenzene with AmNa–*t*-BuONa was reinvestigated[16] and further information was obtained. Thus according to the preceding work it was found that the yield of metalations in the presence of alkoxides was much higher than in their absence. However, it was found that dimetalation took place principally at the expense of the meta isomer and thus affected the isomer distribution.

Interestingly enough in the presence of alkoxide, the meta isomer (initially rapidly formed) equilibrated with an excess of *tert*-butylbenzene via a transmetalation and was converted to the more thermodynamically favored para derivative. In the absence of alkoxide such a transmetalation took place only very slowly. The para isomer isomerized to the meta isomer very slowly even in the presence of alkoxide.

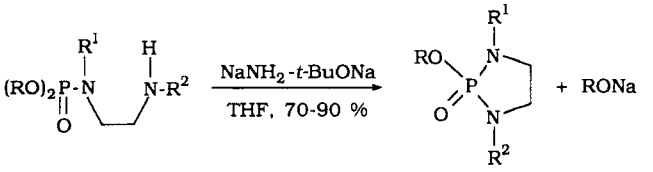
Although, as reported in section III.A, the formation of mixed aggregates was questioned,[16] it seems very likely that not only were the USB's AmNa–RONa responsible for the observed metalation but that some kind of mixed aggregates between the meta isomer and sodium *tert*-butoxide is also involved.

Let us now consider $NaNH_2$ and the corresponding nonnucleophilic sodamide-containing complex bases. These USB's, easily prepared from $NaNH_2$ and an alcohol in such a way that $NaNH_2/RONa = 2$, were found to be very efficient in proton abstraction–electrophilic condensations for a number of organic substrates.[6,18]

Thus, in solvents such as THF, DME, benzene, or cyclohexane, $NaNH_2$ abstracted protons very poorly or not at all from Ph_3CH and Ph_2CH_2. As expected sodium alkoxides were completely inefficient. In contrast, under comparable conditions, numerous nonnucleophilic $NaNH_2$–CB's nicely transformed the hydrocarbons into the colored corresponding anions. If condensations of alkyl or benzyl halides were then performed as colored titrations, condensation products were obtained in yields of 85–95%.

Of course the activation (measured as the condensation reaction time) depended on the nature of the alkoxide. The best activating agents were found among tertiary alkoxides such as *t*-BuONa and the sodium salt of diethylene glycol monoalkyl ethers such as Et-$(OCH_2CH_2)_2ONa$.[50] The latter led to the most powerful complex base and might be used in nonpolar solvents. However, the carbanions were only partially formed as confirmed by carboxylation experiments. Thus it was found that under the same conditions, acid yields depended on the nature of the alkoxide and varied from 15 to 70%. No relation was found between the yields of carboxylation and of alkylations. In other words a low carboxylation yield could correspond to an excellent alkylation yield. An excess of alkyl halides was not needed in order to obtain good results.

Scheme 22



Interestingly enough it was observed that a number of nucleophilic complex bases, with for example keto enolates as activating agents, were found efficient in the alkylation as well as in the carboxylation of polyphenyl methanes.

With the AA basic principles as a starting point we undertook a study in an attempt to increase the efficiency of such USB's in proton abstraction–electrophilic condensation reactions.[22] It was found that the simple addition of potassium halides to $NaNH_2$–*t*-BuONa led to an appreciable (2–3 times, depending on the nature of the salt) increase in the reaction rate. A weak thermodynamic effect was also observed. Indeed carboxylation of Ph_3CNa at −60 °C was increased by about 15% in the presence of KX.

$NaNH_2$–CB's failed to abstract a proton from toluene. However later[24] it transpired that whereas *i*-Pr_2NNa also failed to react with toluene, the complex base *i*-Pr_2-NNa-*t*-BuONa metalated at the benzylic position. It was also observed that the promoting effect of *t*-BuONa increased with its concentration. This effect has been interpreted as due to the formation of mixed aggregates between $PhCH_2Na$ and *t*-BuONa.

Preliminary studies[51] showed that $NaNH_2$–*t*-BuONa might be used for the α-alkylation of aldehydes and imines, but these reactions need to be more accurately studied. Interestingly enough these complex bases appear to be very efficient in the monoalkylation of imines.

$NaNH_2$–$Et(OCH_2CH_2)_2ONa$ was also found[51a] to be very efficient in the methylsulfenylation of ketones using dimethyl disulfide as well as the alkylation of dithioketals or 1,3-dithiane. The results obtained compared favorably with those described using more sophisticated bases. A more recent systematic study[52] indicates that the excess of complex bases used in the alkylation of dithioketals[51a] may be considerably decreased without affecting the outcome of the reaction.

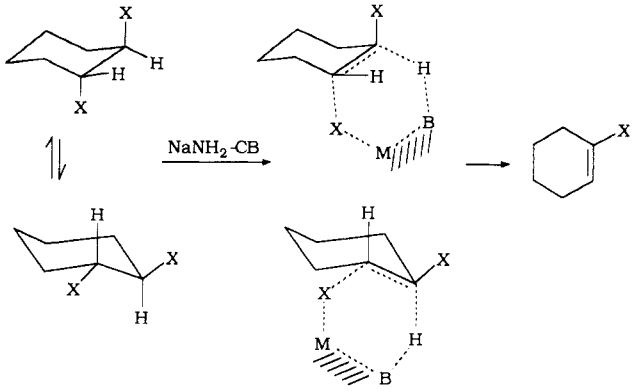
The easy preparation of $NaNH_2$–CB's and their strong propensity to favor monoalkylation of activated methylenes as well as their favorable cost, makes them well suited to industrial monoalkylation of carboxylic acid derivatives.[53] The very important pharmaceutical intermediate di-*n*-propylacetonitrile can be thus prepared on a large scale from valeronitrile.

As far as yields are concerned, $NaNH_2$–*t*-BuONa was found to be just as efficient as BuLi or Et_2NLi in the synthesis of diazaphospholanes as shown in Scheme 22.[54]

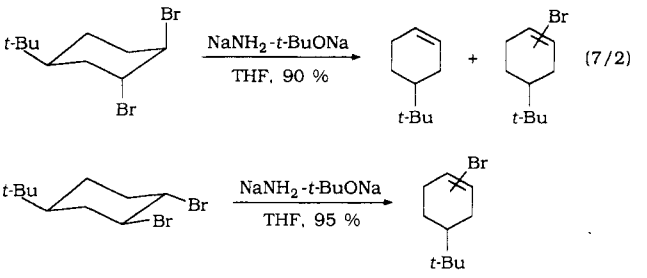
It should be noted, however, that with $NaNH_2$–CB the reaction temperature must be higher than with the lithium-containing bases.

Interestingly enough it was observed that the yield of the cyclization product reached 70–90% with $NaNH_2$/*t*-BuONa = 2. When $NaNH_2$/*t*-BuONa = 1, a 50:50 equilibrium between the open and cyclized products was obtained. This illustrates the important part played by the ratio of the constituting reagents of a USB. The complex base NaH–*t*-BuONa was found to be much less efficient. Finally, $NaNH_2$, NaH, and *t*-BuONa when used separately were found to be completely ineffective.

Scheme 23



Scheme 24



Complex bases such as MNH_2–*t*-BuOM (M = Li, Na, K) were also found to be efficient in the preparation of alkali phosphinites from $R_2P(O)H$.[55] In these condensations, the USB advantageously replaced the alkali metals currently used to prepare the alkali salts.

C. Eliminations

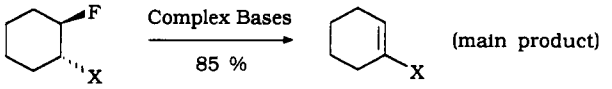
It is mainly in the field of syn eliminations that the efficiency of $NaNH_2$–RONa USB's has been investigated. The studies were undertaken in order to test the hypothesis, mentioned in the AA theory, dealing with the expected properties of the ionic surfaces of mixed aggregates. At that time it was well known[56] that syn eliminations of HX from *trans*-1,2-dihalocyclohexanes could not be performed efficiently with classical bases.

A solution to this problem, as well as an argument in support of the theory, was to perform these eliminations using a $NaNH_2$–CB through a transition state (Scheme 23) of the type proposed by Sicher.[57]

The first experiments using $NaNH_2$–*t*-BuONa (2:1) and *trans*-1,2-dibromocyclohexane were successful. The desired elimination was easily achieved in 60% yield.[58] Control experiments confirmed the complete inefficiency of $NaNH_2$ or *t*-BuONa when used separately.

Subsequently it was shown, with the conformationally blocked 4-*tert*-butyl-1,2-dibromocyclohexanes, that the diequatorial isomer was completely transformed into the *tert*-butylbromocyclohexenes while an important anti elimination of "Br_2" was observed with the trans diaxial isomer (Scheme 24).[59]

Scheme 25



X = Cl, Br

We presently think that the competitive antielimination of "Br_2", observed in the trans diaxial substrate, could be due to the propensity of aggregates to single electron transfer.

Supporting a syn elimination through a Sicher-type transition state were the following observations: (i) replacing Br by a tosyl group led to no syn elimination;[59] (ii) the nature of the activating agent, which controls the USB structure, played an important part.[60] Thus it was found that the most efficient activating alkoxides were those with lightly branched chains behind the oxygen atom. As expected there was no relation between the efficiency of a complex base in syn eliminations and its proton abstraction ability. For example syn elimination using the powerful $NaNH_2$–$Et(OCH_2CH_2)_2ONa$ was unsuccessful.

Before further discussion of syn eliminations an important point should be made to illustrate the confusing situation which can arise when the role played by the ratio of the USB constituents is forgotten.

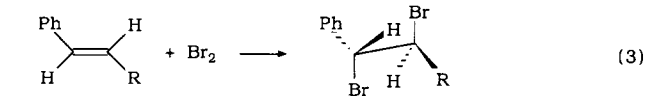
Lee and Bartsch[61] extended our syn elimination studies to *trans*-1-chloro-2-fluoro- and 1-bromo-2-fluorocyclohexanes. They observed that $NaNH_2$–*t*-BuONa preferentially eliminated the poorer leaving group (Scheme 25). This exceptional property of the complex bases was related to their tendency to favor syn eliminations.

However, these authors used a complex base $NaNH_2$–*t*-BuONa (1:1) and not a 2:1 one. We had found that the latter was in fact essential to perform the eliminations under the best conditions. The unusual properties of the 1:1 complex base were later confirmed[62] and attributed to the fact that "*t*-BuONa serves only to activate the effective base species $NaNH_2$". Hudlicky[63] refuted the above results by showing that $NaNH_2$ was just as effective as $NaNH_2$–*t*-BuONa (1:1) in the selective elimination of "HF" from *trans*-1-bromo-2-fluorocyclohexane!

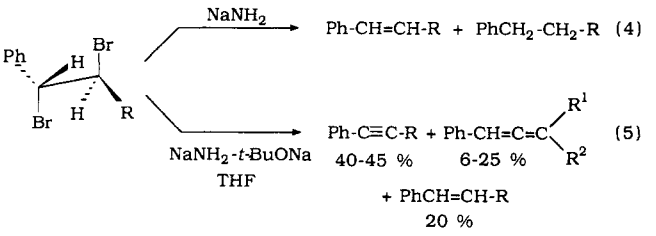
Last, but not least, Lee et al.[64] demonstrated that a Sicher-type transition state was involved during reactions performed between *trans*-1,2-dichloro- or dibromocyclohexanes and $NaNH_2$–*t*-BuONa (1:1). This result means that even under the least favorable conditions, the reagent is partially formed of aggregates suited to syn eliminations. Such a result is to be expected if we admit the hypothesis formulated at the beginning of this review and according to which USB's must be seen as made up of aggregates under dynamic equilibration.

Finally, the only conclusion which may be drawn at this time is that as far as *trans*-1,2-dibromocyclohexanes are concerned neither $NaNH_2$ or *t*-BuONa were individually capable of the syn elimination promoted by the corresponding complex bases. Concerning the selective elimination of the less nucleofugal halide this question needs to be reconsidered in light of the above observations. A study of the influence of the ratio of the constituents of the USB's would certainly be of interest.

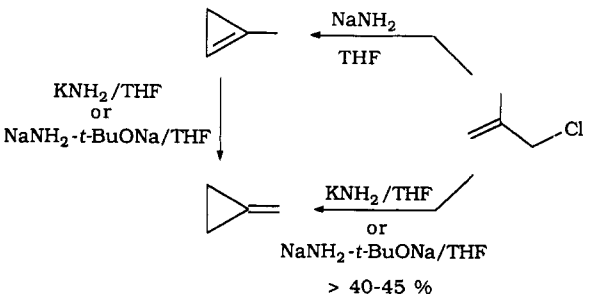
Scheme 26



(R = *t*-Pr, Me(Et)CH)



Scheme 27



That $NaNH_2$–CB's are particularly well suited to syn elimination is also supported by the reactions reported in Scheme 26.

When $NaNH_2$ is used alone (reaction 4) anti elimination of "Br_2" accompanied by a side reduction occurred. No acetylenic compound was isolated.[65]

On the contrary, with the $NaNH_2$–CB (reaction 5)[66] the main products formed were the acetylenic derivatives accompanied by their corresponding allenes. However a small amount of "Br_2" anti elimination was also observed.

These results were later extended to the formation of some cyclic acetylenes.[67] In fact it seems that their isomerizing power is the only limitation of complex bases in the preparation of acetylenic compounds proceeding from reactions where at least one syn elimination step is needed. A systematic study with activating agents other than *t*-BuONa should clarify this problem.

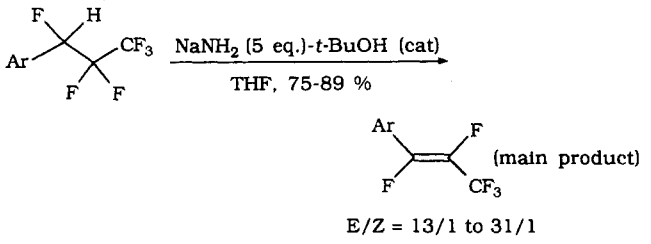
Finally, it is well known that a huge variety of bases can promote eliminations other than syn. The use of USB's in such cases has not been thoroughly investigated. In fact, in many cases, the use of elaborated USB's is inappropriate since simpler bases are sufficient. However, USB's may be of help in solving a number of problems such is given by the reactions reported in Scheme 27.

Starting from metallyl chloride, $NaNH_2$ on its own eliminated "HCl" leading to methylcyclopropene, whereas KNH_2 led to methylene cyclopropane.[68] Only KNH_2 was able to efficiently isomerize methylcyclopropene to methylenecyclopropane.

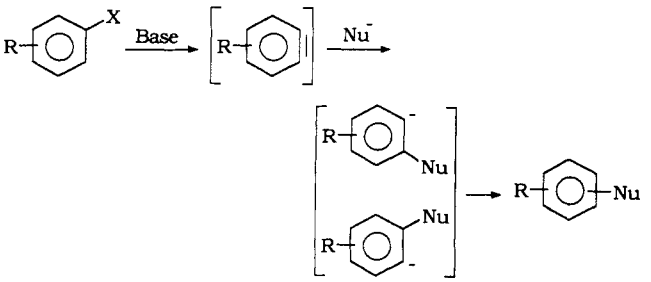
Later it was shown[18c] that $NaNH_2$–*t*-BuONa gave the same reactions as KNH_2 which it could then advantageously replace supporting the expected increased basicity of $NaNH_2$ when incorporated into a USB.

Another example is the case of $NaNH_2$ associated with a catalytic amount of *t*-BuOH which was recently

Scheme 28



Scheme 29



found able to give the reaction in Scheme 28 with excellent *E* selectivity. A number of classical bases proved incapable of giving this reaction.[69]

Although complex bases were not suggested and the catalytic amount of *t*-BuOH added was not specified, it may be supposed that some kind of $NaNH_2$–*t*-BuONa association must intervene in such reactions. Further study of these eliminations as a function of the ratio $NaNH_2$/*t*-BuONa is needed in order to clarify the influence on the *E*/*Z* ratio and to optimize the large excess of $NaNH_2$ used.

D. Aromatic Elimination–Additions

Aromatic elimination–additions[70] are a powerful method for substituting aromatic rings.

These two-step reactions are often performed by the reaction of nucleophiles with aryl halides in the presence of a base through the intermediate formation of didehydrobenzenes or arynes (Scheme 29).

A close examination of the literature[70] shows that the most widespread experimental procedures consist of performing the condensations in liquid NH_3 in the presence of $NaNH_2$ or preferentially KNH_2 generally prepared *in situ*.

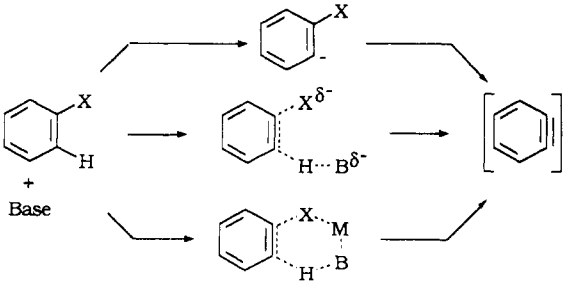
Such processes, although very useful, suffer from a number of drawbacks such as the use of liquid NH_3 and KNH_2.

Even more annoying is the fact that a number of aryl halides are unreactive or destroyed under these conditions. In the same way a number of nucleophiles do not react in liquid NH_3 and the protic behavior of this solvent limits the possibility of condensing the aryl anionic intermediates. It is not surprising, therefore, that investigations were undertaken in order to use the inexpensive, easily handled, and commercially available $NaNH_2$ in aprotic solvents.

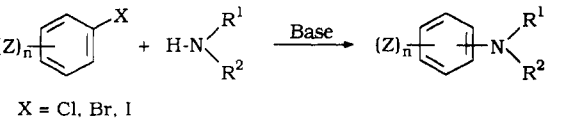
With few exceptions[70a] sodamide was found to be completely inefficient in arynic condensations in ethereal solvents. The use of THF–HMPA mixtures has been proposed as a first solution.[71]

In spite of some improvement, these reactions were still not optimized. The main drawback being the use of expensive carcinogenic HMPA.

Scheme 30 (From Ref 5 with Permission)



Scheme 31



The discovery of $NaNH_2$ activation using a number of nucleophiles in arynic condensations[17] led to the suggested use[18b] of the complex base $NaNH_2$–*t*-BuONa in condensations in THF.

If we consider the properties of these USB's (*vide supra*) and the possible mechanisms of aryne generation reported in Scheme 30, it is not surprising that such reagents were found to be very efficient in arynic condensations in THF, DME, as well as benzene or cyclohexane.[6b,c]

It should be noted that the last mechanism, although generally not evoked,[70a] cannot be dismissed with certain bases.

Arynic condensations using $NaNH_2$-containing complex bases, nucleophilic aromatic substitutions, polycyclic aromatic synthesis, as well as uses in medicinal chemistry have been already reported elsewhere.[5,6b,c]

In this review we will use arynic condensations to illustrate the advantages of using USB's.

Let us first discuss the arynic condensations of amines (Scheme 31).

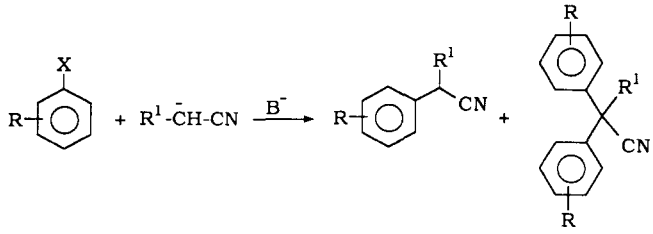
Broadly speaking it is well known[70a] that mono and dialkylamines do not condense with aryl halides in liquid NH_3 in the presence of $NaNH_2$ or KNH_2. With the latter bases a few successful condensations have been performed using a large excess of the amine to be condensed as the reaction solvent. Better results were obtained when the corresponding lithium amides were used.

These drawbacks could be avoided, at least in part, by using a base possessing the following characteristics: (i) it must work in ethereal solvents; (ii) it must be strong enough to attack the protons ortho to the halide; (iii) the tendancy to promote syn eliminations is an advantage; (iv) its nucleophilicity must be as weak as possible in order to avoid any competition with the amines during the nucleophilic condensation.

The nonnucleophilic complex base $NaNH_2$–*t*-BuONa satisfied the above conditions. It was found that in the presence of this USB, smooth arynic condensations of amines, used only in small excess, occurred with yields varying from 60 to 100%.[72]

Special mention must be made of aryl fluorides which are normally unreactive in arynic condensations.[70a,73] With $NaNH_2$–CB's in THF, however, they react to form arynes. Condensation of amines were easily performed in the presence of $NaNH_2$–*t*-AmONa with yields varying

Scheme 32



from 40 to 90%.[74] A nonnucleophilic complex base is obviously required for such a reaction. However, the choice between *t*-BuONa and *t*-AmONa necessitated a few exploratory experiments.

The large scope and efficiency of the above condensations is demonstrated by successful condensations of polychlorobenzenes[75] and polyfluorobenzenes.[76]

A new problem arises with anionic nucleophiles such as thiolates which do not react with aryl halides in the presence of $NaNH_2$ in liquid NH_3.[70a] Indeed some sodium thiolates were found to be capable of activating $NaNH_2$ (*vide supra*). Thus, the question arose as to whether or not the nucleophilic complex bases $NaNH_2$–RSNa could generate benzynes, thus permitting thiolate condensation. In fact these USB's were not efficient enough while $NaNH_2$–*t*-BuONa promoted the desired condensations[18b] even with aryl fluorides.[74]

Another good illustration of the usefulness of USB's is found in the arynic condensation of nitrile anions depicted on Scheme 32.

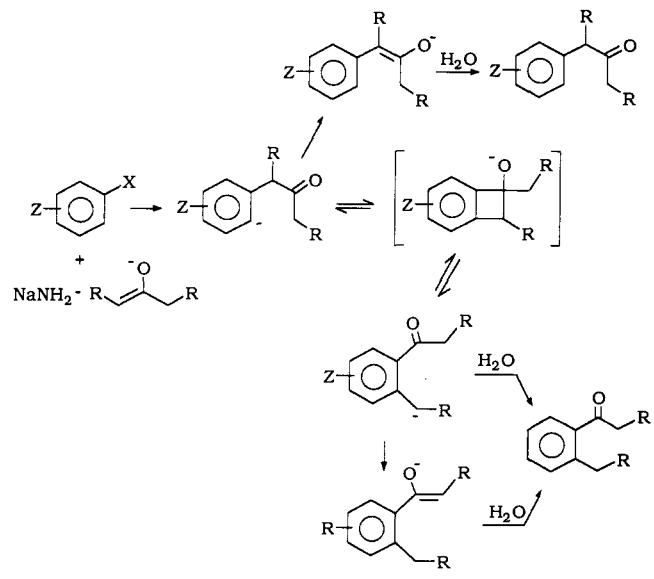
Of course the goal is generally to achieve monoarylation, while the nitriles, formed in the reaction medium after the first arylation, possess more acidic protons than the starting nitriles. Considering the high propensity of nitrile anions to autocondense, the problem to be solved may be put as follows: to find a base strong enough to enolize nitriles at sufficiently low temperature to avoid autocondensations of the starting material, which is also able to generate arynes and lead to selective monoarylation.

Recently[77] such monoarylations were examined using polyalkyl and polymethoxy aryl halides in liquid NH_3 in the presence of KNH_2. A number of these attempts were unsuccessful. A satisfying solution to the problem was found, however, thanks to complex bases. A few control experiments showed that $NaNH_2$–*t*-BuONa in THF was either not strong enough to generate the nitrile anions in good conditions, not efficient enough to generate the arynes from certain aryl halides, or not selective enough or a combination of all three!

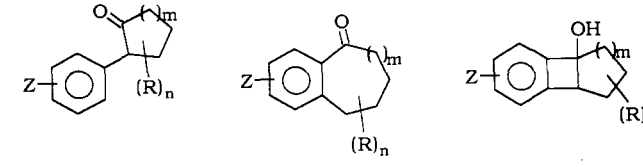
Finally the strongest nonnucleophilic USB $NaNH_2$–$Et(OCH_2CH_2)_2ONa$ in DME, which has always shown more "polar" behavior than THF, was tried. Under such conditions selective monoarylations were easily performed with isolated yields varying from 60 to 85%. Bisarylation remained between 0 and 20%.[78]

At this point it should be pointed out that in the above condensations, the USB's reacting with the aryl halides were in fact, at least at the beginning of the condensation, $NaNH_2$–$Et(OCH_2CH_2)_2ONa$–R^1-CHNaCN. Each of the three components of the super bases can be expected to modify the reactivity of the other two. As a consequence, the nucleophilicity of the nitrile anions must also be modified, not only by $NaNH_2$, but also by association with the alkoxides. Thus, in

Scheme 33 (Adapted from Ref 5 with Permission)



Scheme 34



such reagents we must expect some modification of the reactivity of a reagent possessing a high nucleophilicity/basicity ratio through varying the nature of the activating agent whose ratio basicity/nucleophilicity is high. A few results obtained in elimination–additions, currently under investigations in our laboratory, appear to support this hypothesis.

Let us now return to arynic condensation of enolates and look at the interesting case of ketones. Although somewhat limited, arynic condensations of keto enolates in liquid NH_3 was known to be feasible. However, the only products formed, generally in fair yields, were the corresponding monoaryl ketones.[70a,79] Indeed under the conditions used, the aryl carbanionic intermediate was rapidly protonated.

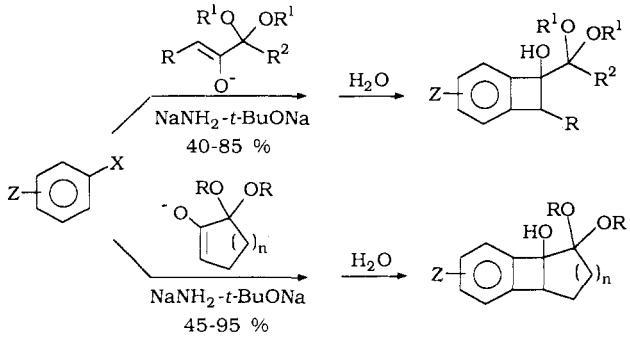
As mentioned in section III.B some keto enolates were found to be capable of combining with $NaNH_2$ to give USB's. Thus it was not surprising that a number of such nucleophilic complex bases were found to be efficient in arynic condensations of keto enolates.[80] The latter also play both the role of activating agents for $NaNH_2$ and of nucleophiles.

As we showed for the first time, the enormous difference with those reactions carried out in liquid NH_3 was that the anionic intermediate had the opportunity to be intramolecularly trapped as shown for aliphatic ketones in Scheme 33. Changing the experimental conditions permits selective control (the ratio of the formed ketones) of these condensations.

Another factor which played an important part in the nature of the products formed was the nature of the keto enolates. Thus, with alicyclic ketones the compounds shown in Scheme 34 were obtained.

Appropriate experimental conditions permit a convenient preparation in good to fair yields of numerous arylcyclanones (40–80%) and benzocyclenones (20–

Scheme 35



60%) as well as benzocyclobutenols (30–75%). Many of these compounds cannot be easily obtained by other ways.

These arynic condensations constitute the first steps in several syntheses conducted by other groups. For example, the easy preparation of benzocyclobutenols has found application in the synthesis of benzocyclobutacycloheptene derivatives[81] as well as in the synthesis of indole derivatives.[82] The preparation of benzocyclenones has also been used to obtain a number of hormone analogues.[83]

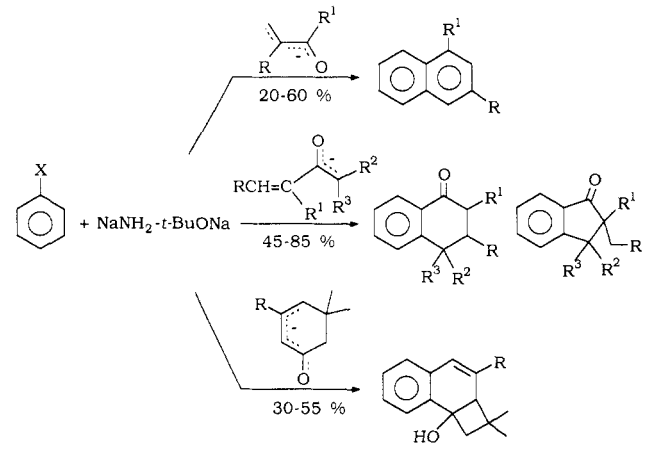
However, our access to the interesting benzocyclobutenols was limited to the condensations of five-, six-, and seven-membered keto enolates. On the other hand, it was of interest to obtain benzocyclobutenols functionalized on the α position of the hydroxyl group. Thus the arynic condensation of 1,2-diketo monoketal enolates was considered. Exploratory experiments showed the ineffectiveness of these enolates at activating $NaNH_2$.

This difficulty was easily overcome by using the nonnucleophilic complex base $NaNH_2$–*t*-BuONa. With such a USB the arynes were easily generated and the nucleophilic enolates condensed without competition from the base. In addition it was found that the presence of the ketal function considerably favored the formation of the benzocyclobutenols which were thus obtained in the case of linear ketones as well as with cyclic ones, whatever the ring size (Scheme 35). Numerous condensations and extensions were, therefore, performed.[84] α,β-Unsaturated keto enolates were also found incapable of activating $NaNH_2$ in order to perform arynic condensations and once more the USB $NaNH_2$–*t*-BuONa was used to generate the arynes. These investigations were simultaneously and independently initiated in two groups.[85]

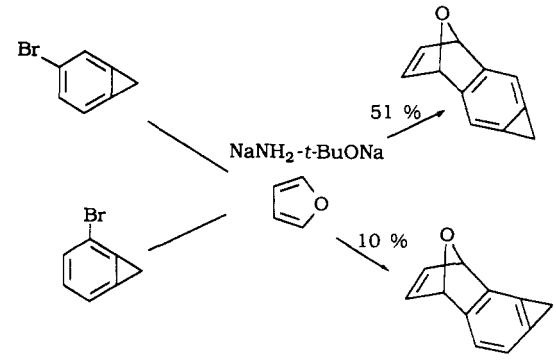
The structures and yields of the products formed depended on the starting ketone as well as on experimental conditions. These condensations were synthetically useful for preparing naphthalene derivatives,[86] tetralone and indanone derivatives,[86b,87] as well as a new class of cyclobutanols.[86b] The relation between the nature of the enolates and the structure of the products formed is given in Scheme 36. The mechanisms of these condensations are discussed in the references cited above and summarized in one of my reviews.[6c]

It should be noted that in the condensations reported in Schemes 35 and 36, the actual bases are tricomponent USB's and it could be of interest to study the possible influence of the nature of the activating alkoxides on these condensations.

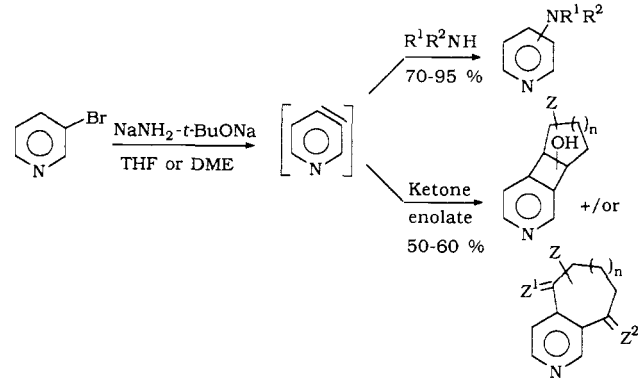
Scheme 36



Scheme 37



Scheme 38

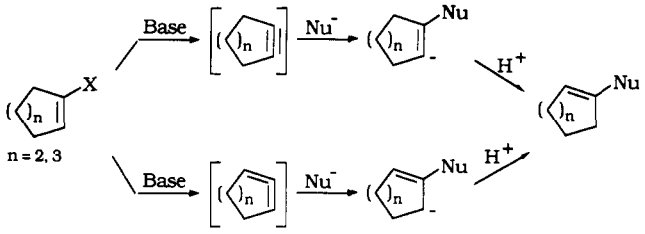


Sodamide-containing USB's also proved of interest in the preparation of cyclopropabenzynes. Tentative generation of such intermediates from the corresponding halides under classical conditions in liquid NH_3 were unsuccessful, whereas $NaNH_2$–*t*-BuONa in the presence of furan led to the condensations reported in Scheme 37.[88]

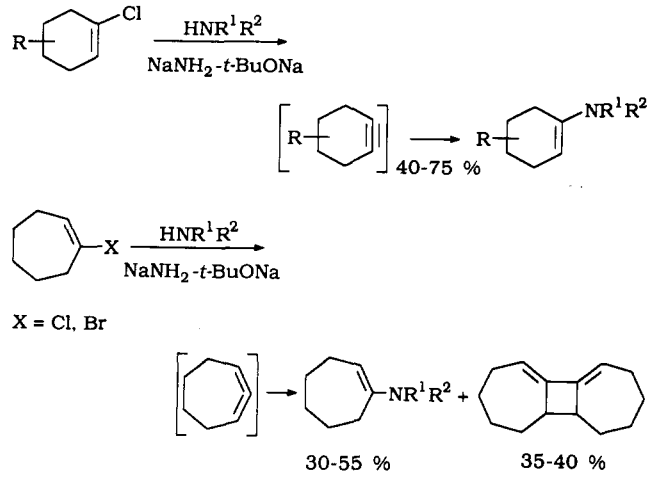
Finally, it was recently found[89] that $NaNH_2$–*t*-BuONa was much more efficient than classical reagents[70a] in the condensation of nucleophiles with pyrid-3-yne generated from 3-bromopyridine (Scheme 38). Current investigations point out that such reactions are very promising in the synthesis of heterocyclic derivatives.

Bases such as lithium dialkylamides have been used to perform a number of arynic condensations of anionic nucleophiles.[70c,90] Although USB's have never been invoked, the formation of mixed aggregates between the nucleophiles and the bases is to be expected in most

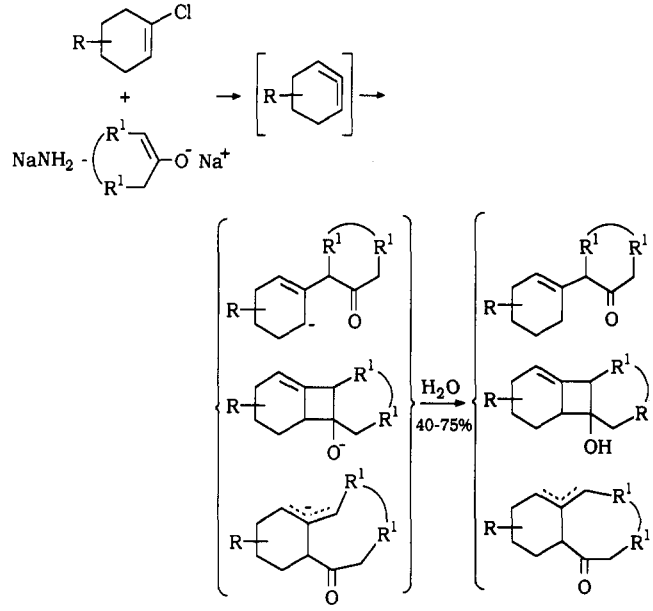
Scheme 39 (From Ref 5 with Permission)



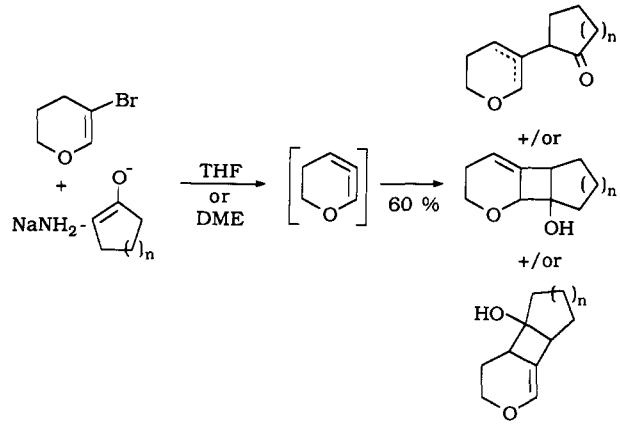
Scheme 40 (Adapted from Ref 5 with Permission)



Scheme 41 (Adapted from Ref 5 with Permission)



Scheme 42 (From Ref 5 with Permission)



of these reactions. It would certainly be of interest to reconsider these condensations from this point of view.

E. Cyclenic Elimination–Additions

Although the cyclenic elimination–additions symbolized on Scheme 39 have been known for a long time[70a] their synthetic usefulness was very limited.

Indeed all the bases known to be capable of generating the reactive didehydro intermediates did not allow the condensation of nucleophiles other than themselves.

Sodium amide-containing complex bases solved this problem and nucleophilic condensations on 1-chlorocyclohexene were reported for the first time.[91] Reactions performed with 1-chlorocycloheptene and 1-chlorocyclohexene derivatives[92] deserve some comment as an illustration of the use of USB's, their influence on the reaction mechanisms, as well as to underscore the complexity of the situation.

It was found[91,92a,b] that, contrary to what was generally observed, a small amount of *t*-BuONa ($NaNH_2$/*t*-BuONa = 1:0.08) was sufficient (but necessary) to condense the amines with 1-chlorocyclohexenes (Scheme 40). Under these conditions, cyclohexynes were the intermediates.

In contrast, $NaNH_2$ on its own as well as $NaNH_2$–*t*-BuONa gave cyclohepta-1,2-diene from 1-halocycloheptene.[92e] However, the presence of *t*-BuONa favored the formation of the enamines at the expense of the dimer.

With the nucleophilic complex bases "$NaNH_2$–sodium keto enolates", the condensation with 1-halocycloheptene took place through the cyclohepta-1,2-diene while the cyclohexa-1,2-dienes were the main or only intermediates formed from 1-halocyclohexenes.[92c,d,f] In other words, changing the nature of the reagent associated with $NaNH_2$ led to a change in the nature of the intermediates in the cyclohexenic series.

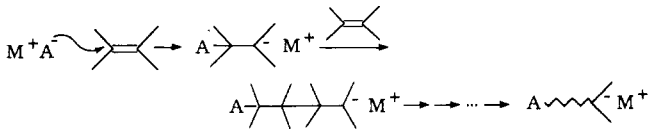
Once more, as with arynic condensations, it was observed that the nucleophiles, which are normally expected to intervene only in the condensation step on the transient species, took an important part in the elimination step. In other words, the nature of the bases changed when the structures of the nucleophiles were changed. Such an observation is another argument in favor of the formation of USB's through association of $NaNH_2$ with the nucleophiles.

These condensations were found to be of synthetic value as is briefly shown in Scheme 41.

The ratio of the products formed depended on the structure of the starting materials. However, as usual, the control of the experimental conditions allowed partial direction of the selectivity. Numerous interesting new methylene cyclobutanols were consequently synthesized. A number of extensions and applications of these reactions can be found in reviews[5,6c] as well as in more recent reports.[93]

Finally, in a new field of investigation in the heterocyclic chemistry, the same kind of nucleophilic complex bases were found capable of generating didehydrodihydropyran with keto enolates which condensed easily (Scheme 42).[94] Our current investigations are proving very promising in the synthesis of polycyclic oxygenated heterocycles.

Scheme 43



F. Anionic Polymerizations

The present review has been directed toward the role of USB's in organic synthesis and deals with basicity rather than with nucleophilicity. However, a few comments on the usefulness of USB's as initiators of anionic polymerizations are in order.

Indeed results in this very important field of organic chemistry illustrate the fact that basicity and nucleophilicity are so closely related that any investigation dealing with one of these properties must also consider the other.

Anionic polymerizations may be generally symbolized as in Scheme 43.

They are triggered by the nucleophilic addition of an initiator A^- whose counterion M^+ is generally an alkali or alkaline earth metal cation. The propagation takes place through a so-called "living" polymer.[12d,95]

Various initiators may be used. Among them organolithium reagents play an important part while other alkali derivatives as well as alkaline earth reagents are less useful.

The formation of mixed aggregates between the initiator reagents and the living polymers is usually observed.[12d] On the other hand, it has also been suggested that some polymerizations could be due to internal initiation of monomers complexed with aggregated lithium reagents.

From these observations it may be deduced that mixed aggregates ought to initiate anionic polymerizations.

In practice alkoxides have been used as additives to modify initiators such as organolithium reagents.[12d,95] It was found that such additives considerably modify the kinetics of the reactions as well as the structure of the polymers.

Of course the behavior of these systems is not easy to describe. The complexity appears to be due to the simultaneous presence in the reaction medium of different kinds of mixed aggregates.[12d]

What these results do show is that USB's may be used to initiate anionic polymerizations. The interesting point, with these reagents, is that their properties may be easily modified, thus offering a large choice of initiators. Moreover, reagents more reactive, as well as less sensitive to usual impurities, may be thus obtained from inexpensive weakly efficient reagents.

Examples of such initiators were given with MNH_2 (more specifically $NaNH_2$) containing complex bases which were found to be very efficient in initiating polymerizations of vinyl monomers in solution as well as in bulk polymerizations. It was also found that under these conditions block copolymers could be obtained.[6d]

As expected it was observed that the activating agents, used to prepare the USB's, modulated the nucleophilicity of NH_2^- which was the active component in the reagents.

Clearly the concept of USB's as initiators in anionic polymerizations should still find numerous interesting applications in spite of much work which remains to be done in order to master these reagents.

IV. Conclusion and Outlooks

The fundamental importance of super bases lies in the aggregation of the reagents, a general phenomenon whose implications go far beyond the notion of basicity and must be considered in anionic as well as in cationic chemistry. One of the consequences of the aggregation of species is an alteration of their inherent electronic properties. Thus, and as far as anionic chemistry is concerned, the reactivity perceived by the organic chemists, that is to say basicity, nucleophilicity, and reducing properties, are also modified.

Besides these electronic effects, steric effects cannot be neglected and it is clear that the stereochemistry of a given reaction can be changed through aggregate formations. Subsequent chiral changes can also be expected with changes in appropriate reagents.

Less obviously important but not to be neglected, is the resulting increase in solubility, dissolving rate, and reactivity of the insoluble reagents due to aggregation.

From a general point of view, in any reaction medium where aggregate formations are suspected, the question of whether aggregates are implicated in the results observed must kept in mind.

Thus this rich, exciting, and potentially important question of aggregation deserves to be accurately studied in order to gain information about the influence of the nature of the ions, the solvent, as well as the concentration and the ratio of the species present in the reaction medium.

Physical chemistry should prove useful in improving our knowledge of the static and dynamic structure of aggregates as well as of their structural evolution and reactivity during their reactions with organic substrates.

In parallel, investigations dealing with the role of aggregates in organic synthesis must be actively pursued in order to extend both knowledge and applications.

The balance between physical and synthetic results will, of course, be of paramount importance.

However, we must be aware that the problems associated with super bases which remain to be solved are complicated and will necessitate much work.

With unimetal super bases, although a number of results have been obtained, there are numerous alkali and alkaline earth reagents left which should prove of interest.

One goal is the generation of powerful bases from less efficient ones and control of the stereochemistry through choice of activating agents and additives. Interesting applications in chiral synthesis can also be expected.

The same is true for multimetal super bases which, as mentioned at the beginning of this review, have been the subject of important research leading to more elaborate powerful bases.

In closing this review it should be noted first that any result obtained during an investigation of super bases could have important consequences in both the nucleophilicity and reduction fields and be of help in finding new reagents and reactions.

And second, it should be noted that practical applications of such important research should not be

neglected; it is always rewarding to find industrial uses for academic research.

Acknowledgments. I would like to express all my thanks to Professors R. Noyori and J. Michl for having invited me to write this review. I express my wholehearted thanks to my co-workers, who are individually mentioned in the references, coming from our laboratory and particularly my present collaborators, B. Jamart-Grégoire and Y. Fort. I thank the reviewers and Professor Gladysz for their help in writing the manuscript. This research was supported by the CNRS, DGRST, MRT, SNPE, and CEC (SCI*-CT910657) to whom go my grateful thanks.

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