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Halogens in γ-position enhance the acidity of alkyl aryl sulfones and alkane nitriles

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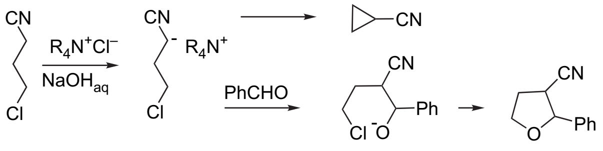
Abstract—On the basis of measuring the rates of base-catalyzed deuterium exchange the pK_a values of a series of 3-halopropyl aryl sulfones and 4-halobutyronitriles were estimated. It was shown that halogen substituents, although separated from the carbanionic site, exert a substantial carbanion stabilizing effect. These effects were rationalized by DFT calculations.

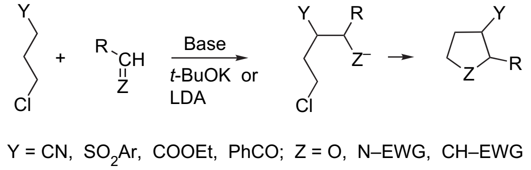
1. Introduction

4-Chlorobutyronitrile undergoes rapid conversion into cyanocyclopropane when treated with aqueous NaOH and a tetraalkylammonium salt catalyst—phase transfer catalysis, PTC conditions.[1] The reaction proceeds via formation of the α-cyanocarbanion which then intramolecularly substitutes the chloride. Since under identical conditions butyronitrile cannot be alkylated, even with such active haloalkanes as benzyl chloride or bromide, we have supposed that the Cl substituent, albeit located in γ-position in relation to the methylenic group, facilitates deprotonation, increasing the acidity of 4-chlorobutyronitrile as compared to butyronitrile. Indeed, the carbanion of the former nitrile can be readily generated under the PTC conditions, and moreover, in spite of very fast intramolecular substitution, it can be trapped by aromatic aldehydes to form aldol type anions that undergo intramolecular 1,5 substitution producing substituted tetrahydrofurans (Scheme 1).[2]



Scheme 1.

This observation opened a new route for the synthesis of tetrahydrofurans,[2,3] pyrrolidines,[4] and cyclopentanes[5] via reaction of γ-halocarbanions with aldehydes and ketones, imines and Michael acceptors (Scheme 2).



Scheme 2.

On the other hand, the qualitative observation that a halogen in γ-position facilitates formation of carbanions needs more rigid confirmation and rationalization. To this end we should collect at least semiquantitative data concerning effect of halogens in γ-position on CH acidity of aliphatic nitriles, esters, alkyl aryl sulfones, etc., namely comparing the pK_a values of 4-halobutyronitrile, alkyl 4-halobutyrates, and 3-halopropyl aryl sulfones with that of butyronitrile, alkyl butyrates, and propyl aryl sulfones. Unfortunately, the short lifetime of γ-halocarbanions, that enter fast intramolecular substitution reactions producing cyclopropanes, excludes direct measurements of pK_a by conventional methods, such as determination of acid−base equilibrium with standard indicators.

2. Results and discussion

In such cases the only possible and simple experimental evaluation of acidity of these compounds was measurement of the rates of deprotonation, that, when carried out under identical conditions, can be used for comparison and as a measure of acidities. The simplest way of determining the rates of deprotonation is measurement of the rates of

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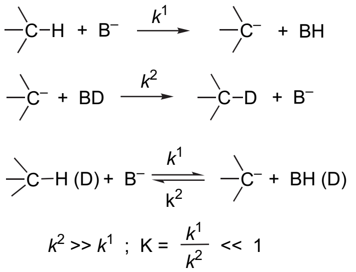
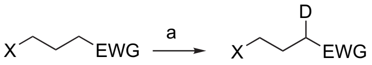
deuterium exchange under conditions that assure much higher rates of deuteration (protonation) of the carbanions than the rates of deprotonation producing the carbanions as shown in Scheme 3.



Scheme 3.

Such requirements were fulfilled when the deuterium exchange experiments were carried out in a solution of NaOD in a mixture of D_2O, EtOD, and DMSO. Thus we have used these base-solvent systems for determination of the rate of deuterium exchange in a series of sulfones and nitriles of interest. Progress of the deuterium exchange was monitored by ^1H NMR. For convenience reasons the time of the half-exchange was determined, which can be easily recalculated for the first order rate constants (see Table 1). The assumption of first order kinetics is justified because the deuterating mixture was used in a large excess. The rate constants of the isotope exchange of compounds of interest varied in a relatively broad range; hence measurements of the exchange rates for all compounds studied could not be done with proper precision under identical conditions. In order to eliminate these difficulties we have prepared a few standard exchange 'cocktails' of various basicity by changing the concentration of NaOD and ratio of solvents in such a way as to keep the time of the half-exchange of all measured compounds in the range convenient for measurement. Determination of the exchange rate of a given compound and a compound used as a standard in two different standard deuterating systems allowed the recalculation of all results for one standard set of conditions as presented in Scheme 4.



a: 10% NaOD/D_2O (1 part), EtOD (1.4 parts), DMSO (1 part), 21 °C (deuterating mixture 1)

Scheme 4.

In order to estimate effects of a halogen on the acidity of the γ-halocarbanion precursors, and locate them on the commonly used acidity scale we have converted results of the kinetic measurements into pK_a values that represent a thermodynamic scale. For this conversion we have used the Brönsted equation that correlates rates and equilibria; in this particular case rate of the isotope exchange with equilibrium acidity expressed as pK_a value.

$$\log k = \alpha \log K_a + C \tag{1}$$

Direct conversion of the kinetic into thermodynamic acidity data is connected with error due to phenomena such as variation of charge distribution in carbanions, the internal return, ion-pairing, etc. Thus an empirical Bronsted coefficient α ($0<\alpha<1$) characteristic for compounds of similar structure and functionality is used to compensate such phenomena.[6]

For conversion of the rates of deprotonation of γ-halopropyl phenyl sulfones into pK_a values we have measured rate of deprotonation, under our standard conditions, of ethyl phenyl sulfone for which the pK_a is known,[7] and used value of the rate constant for determination of C in the Brönsted equation, accepting α=0.82 determined for the series of sulfones.[8] pK_a values for the γ-halosulfones and other sulfones of interest were recalculated using α=0.82 and C=22.5 as determined for ethyl phenyl sulfone. In the same way, we have also determined rate constants for the isotope exchange and on this basis the pK_a of a series of 3-halopropyl aryl sulfones containing electron-withdrawing substituents in the phenyl ring or when the aryl group was a 2-pyridyl or 2-pyrimidyl substituent. Similarly, using the known pK_a value of propionitrile,[9] which should be very close to butyronitrile and α=0.91 as was determined by Pearson,[10] the value of C=25.8, and subsequently the pK_a values of γ-halonitriles and other related nitriles were calculated. Of course, the values of pK_a presented in Table 1 are the result of a rather coarse estimation obtained by recalculation of the kinetic measurements in protic media for thermodynamic (equilibria) measurements in aprotic media (DMSO). Nevertheless, since these calculations were based on kinetic measurements of the exchange rates under identical conditions and also that they were made on the basis of measurements for sulfones and nitriles of similar structures with known pK_a values, and taking into account that in the carbanions stabilized by cyano and sulfonyl groups there is only small charge delocalization[11] the results presented in Table 1 are rather reliable. All data—time of half-conversion, rate constants, and calculated pK_a values are collected in Table 1.

Since the electronic effects of substituents affect ^{13}C chemical shifts in ^{13}C NMR spectra, the ^{13}C chemical shifts of the α-methylenic carbon atom are also given in Table 1.

Values of ΔpK_a(X) for X–CH_2–CH_2–CH_2–EWG, ΔpK_a(X)=pK_a(X=H)−pK_a(X), collected in Table 2 show that although X are in remote positions to the carbanion centers, they nevertheless exert a substantial effect on CH acidity of sulfones and nitriles.

Replacing a hydrogen by a fluorine atom in position 3 of propyl phenyl sulfone results in change of acidity by 1.6 pK_a unit, the effect of chlorine and bromine is somewhat larger, whereas trimethyl ammonium group exerts a much stronger effect. Similar regularities are observed for nitriles. It is noteworthy that the effect of chlorine in γ-position of 3-chloropropyl pentachlorophenyl sulfone was smaller than in other precursors of γ-chlorocarbanions, this observation can be explained by the saturation effect. Pentachlorophenyl sulfonyl group is very effective in stabilization of the carbanion, therefore replacement of the hydrogen by the chlorine in γ-position increases the acidity of the 3-chloropropyl pentachlorophenyl sulfone only 1.2 units of pK_a.

An interesting observation is made when effects of halogens and other substituents X located in α- and γ-positions to the