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

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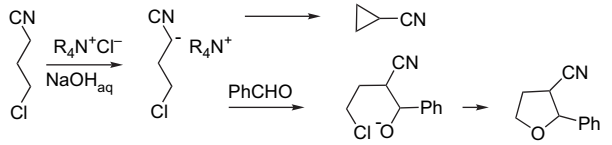
Abstract—On the basis of measuring the rates of base-catalyzed deuterium exchange the pK_a values of a series of 3-halopropyl aryl sulfones and 4-halobutyronitriles were estimated. It was shown that halogen substituents, although separated from the carbanionic site, exert a substantial carbanion stabilizing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

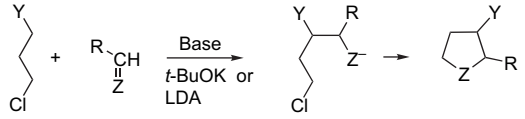
1. Introduction

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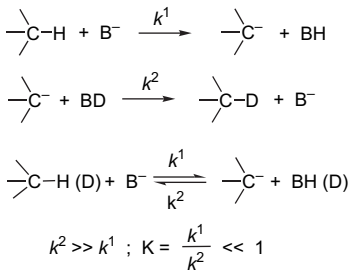
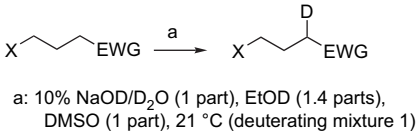
deuterium exchange under conditions that assure much higher rates of deuteration (protonation) of the carbanions than the rates of deprotonation producing the carbanions as shown in Scheme 3.



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.



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.

$$\log k = \alpha \log K_a + C \qquad (1)$$

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 $\alpha=0.82$ determined for the series of sulfones.[8] pK_a values for the γ-halosulfones and other sulfones of interest were recalculated using $\alpha=0.82$ 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 $\alpha=0.91$ 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.

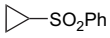
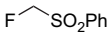
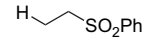
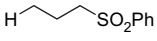
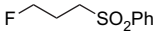
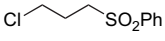
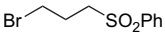
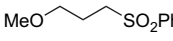
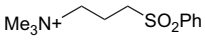
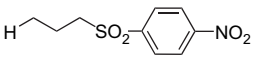
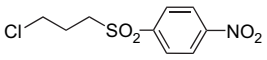
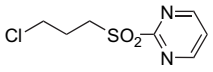
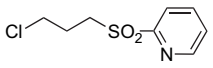
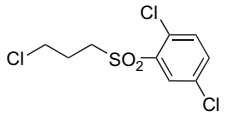
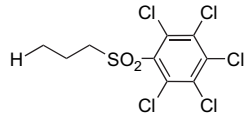
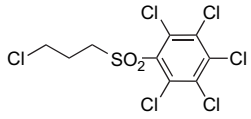
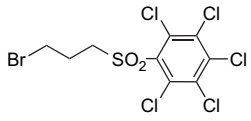
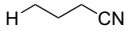
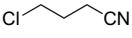
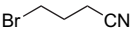
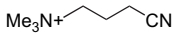
Since the electronic effects of substituents affect ^{13}C chemical shifts in ^{13}C NMR spectra, the ^{13}C chemical shifts of the α-methylenic carbon atom are also given in Table 1.

Values of $\Delta pK_a(X)$ for $X–CH_2–CH_2–CH_2–EWG$, $\Delta pK_a(X)=pK_a(X=H)-pK_a(X)$, 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

Table 1. CH-acidities of sulfones and nitriles determined by deuterium exchange and recalculated for pK_a values

No.	Compound	Deuterating mixtures	$\tau_{1/2}$[a] [s]	k[b] [s^{-1}]	^{13}C NMR, δ	p$K_{a\ DMSO}$	p$K_{a\ DMSO}$ (lit.)
1		2	3200	2.17×10^{-4}		31.9	32[12]
2	$H_3C–SO_2Ph$	3	15	4.62×10^{-2}	44.47	29.1	29.0[12]
3		3	11	6.30×10^{-2}	91.92	28.9	28.5[13]
4		3	840	8.25×10^{-4}	50.55	31.2	31.0[13]
5		1	900	7.70×10^{-4}	57.90	31.2	
6		1	43	1.61×10^{-2}	52.99	29.6	
7		1	22	3.15×10^{-2}	54.06	29.3	
8		1	17	4.08×10^{-2}	54.46	29.1	
9		3	200	3.47×10^{-3}	58.43	30.4	
10		2	1.2	5.78×10^{-1}	52.75	27.7	
11		4	8	8.66×10^{-2}	57.83	28.7	
12		4	0.11	6.30	53.45	26.5	
13		4	1.5	4.62×10^{-1}	48.64	27.8	
14		4	0.78	8.88×10^{-1}	49.31	27.5	
15		4	0.094	7.37	51.49	26.4	
16		4, 5	0.061	11.4	57.63	26.2	
17		4, 5	7.1×10^{-3}	97.6	53.77	25.0	
18		5	6×10^{-3}	116	54.25	24.9	
19		1	6500	1.07×10^{-4}	18.76	32.7	
20		1	320	2.17×10^{-3}	28.04	31.3	
21		1	250	2.77×10^{-3}	15.86	31.2	
22		2	13	5.33×10^{-2}	10.77	29.8	

[a] Recalculated for the conditions specified in Scheme 4.
[b] Calculated as $0.693/\tau_{1/2}$.

methylenic groups of alkyl phenyl sulfones were compared (Table 3).

$$\Delta\Delta pK_a(X) = \Delta pK_a(X_\alpha) - \Delta pK_a(X_\gamma) \quad (2)$$

Negative value of $\Delta\Delta pK_a(X)$ formally indicates that substituents X stabilize carbanions more efficiently when located in γ-position than α. Of course the negative value of $\Delta\Delta pK_a(X)$ observed for the methoxy and fluoro compounds is an artifact, the result of two opposite effects of these substituents—a relatively weak inductive effect of the α-oxygen stabilizing carbanions is compensated by the stronger destabilization of carbanions by non-bonded *p*-electron pairs. A similar situation exists for fluorine, but in this case the former effect is somewhat stronger. Both of these substituents exert a weak stabilizing effect when located in the

Table 2. Effect of substituents in position γ on CH acidity of $XCH_2CH_2CH_2EWG$

EWG	X	$\Delta pK_a(X)$
SO_2Ph	F	1.6
SO_2Ph	Cl	1.9
SO_2Ph	Br	2.1
SO_2Ph	Me_3N^+	3.5
SO_2Ph	OMe	0.8
CN	Cl	2.5
CN	Br	2.6
CN	Me_3N^+	4.1
$SO_2C_6H_4NO_2$	Cl	2.2
$SO_2C_6Cl_5$	Cl	1.2

Table 3. Comparison of the effect of the substituents X in positions α and γ to the methylenic group on the acidity of alkyl phenyl sulfones

	$PhSO_2CH_2X$		$PhSO_2CH_2CH_2CH_2X$		$\Delta\Delta pK_a$
	pK_a	ΔpK_a	pK_a	ΔpK_a	
H	28.9		31.0		
OMe	30.7[a]	−1.8	30.2	0.8	−2.6
F	28.7	0.2	29.4	1.6	−1.4
Cl	23.8[a]	5.1	29.1	1.9	3.2
$^+NMe_3$	19.4[a]	9.5	27.5	3.5	6

[a] Taken from literature.[13]

γ-position. On the other hand, Cl in α-position exerts much stronger carbanion stabilizing effect than in γ-position, $\Delta\Delta pK_a$=3.2.

It was of substantial interest to clarify the nature of the carbanion stabilizing effects of substituents γ to the carbanion center. It does not seem to be of pure inductive nature, because in such case ΔpK_a(F) should be larger than ΔpK_a(Cl). Also values of ^{13}C chemical shifts do not correlate with such supposition. In order to gain better insight into the electronic effects of substituents X responsible for stabilization of γ-halocarbanions, a series of calculations have been performed for γ-substituted butyronitriles. We have selected nitriles as the model compounds because the respective sulfone molecules were too large to make advanced ab initio or DFT calculations practical. Ab initio calculations for the α-anions of γ-chloro- and γ-fluorobutyronitriles at the MP2/6-31+G(d,p)//MP2/6-31+G(d) level have been already performed by Gronert et al.[14] In their work these authors were interested in modeling the transition state of the intramolecular nucleophilic substitution reaction leading from the γ-halobutyronitrile α-carbanion to the cyanocyclopropane and the respective halide anion. They found that in the case of the chloro derivative the activation energy of this reaction is very low (5.1 kcal/mol) indicating early (substrate-like) transition state. For the γ-fluorobutyronitrile anion this barrier was substantially higher (14.1 kcal/mol). In their paper, Gronert et al. did not address, however, the problem of the acidity of the starting γ-substituted butyronitriles.

For our calculations we selected the DFT method utilizing the most commonly used B3LYP hybrid functional. Details of the calculations are described in Section 3. In the first series of calculations gas-phase acidities (GPA) of γ-methoxy-, γ-fluoro-, γ-chloro-, and γ-bromobutyronitriles have been determined (Table 4).

The results presented in Table 4 follow the same pattern as observed for pK_a values measured experimentally (Table 2). The gas-phase acidity of all γ-substituted butyronitriles is larger than that of unsubstituted compound and the order of substituents, concerning their carbanion stabilizing effect, is exactly the same as experimental. Much larger differences between values of the calculated gas-phase acidities in the series of γ-substituted butyronitriles in comparison to the experimental values, measured in liquid phase, are typical and reasonably rationalized as a consequence of lack of a solvation in the gas phase.

The results of the calculations can also give some clues to the rationalization of the carbanion stabilizing effects by the γ-substituents. The first important parameter that can serve as a measure of the stabilizing effect of substituent is the difference in the C–X bond lengths in the carbanion and the neutral molecule. As can be seen in Table 4, there is a dramatic change in the C–X bond length when moving from a neutral molecule to its carbanion for γ-chloro and γ-bromo substituted butyronitriles. This effect is much less pronounced in the case of MeO– and F–substituents. These results show that the carbanions of γ-Cl– and γ-Br–butyronitriles are 'ready' for intramolecular nucleophilic substitution reaction leading to cyanocyclopropane and the respective halide anion and their structures are close to the expected transition state of this reaction. This supposition is confirmed by the calculated structures of the most stable conformers of carbanions of γ-substituted butyronitriles (Fig. 1). Our results are also in full agreement with those obtained by Gronert (vide supra).[14]

In addition to lengthening of the C–X bond, the distance between carbon atoms C2 and C4 is shortened (2.55, 2.52, 2.32, and 2.26 Å for X=MeO–, F–, Cl–, and Br–, respectively). This effect also indicates that especially the carbanions with Cl– and Br–substituents have the structure, which favors the intramolecular substitution reaction.

The last information that was obtained from the calculations is the shapes of HOMO orbitals of the respective carbanions (Fig. 2).

Table 4. Gas-phase acidities (GPA) and C–X bond lengths of γ-substituted butyronitriles, $X–CH_2–CH_2–CH_2–CN$, calculated at the B3LYP/6-311+G(3df,2p)//B3LYP/6-31G(d) level

X	GPA [kcal/mol]	ΔGPA=GPA(X)−GPA(H)	ΔpK_a calcd	$l_{C-X(N)}$ (in neutral) [Å]	$l_{C-X(A)}$ (in anion) [Å]	$\Delta l_{C-X}=l_{C-X(A)}-l_{C-X(N)}$ [Å]
H	364.0	—	—	—	—	—
OCH_3	361.2	−2.8	−2.1	1.416	1.443	0.027
F	356.2	−7.7	−5.6	1.395	1.426	0.031
Cl	351.3	−12.7	−9.3	1.820	2.075	0.255
Br	346.9	−17.0	−12.5	1.985	2.295	0.310

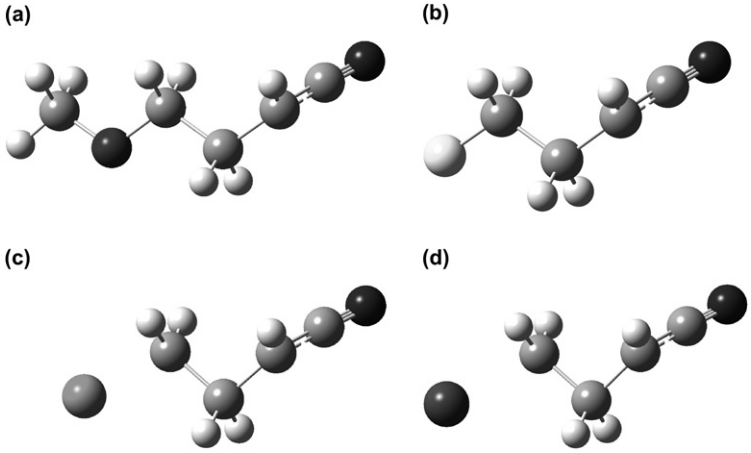


Figure 1. Calculated minimum energy structures (using B3LYP/6-31G(d) method) of α-carbanions of γ-substituted butyronitriles: (a) MeO–, (b) F–, (c) Cl–, (d) Br–.

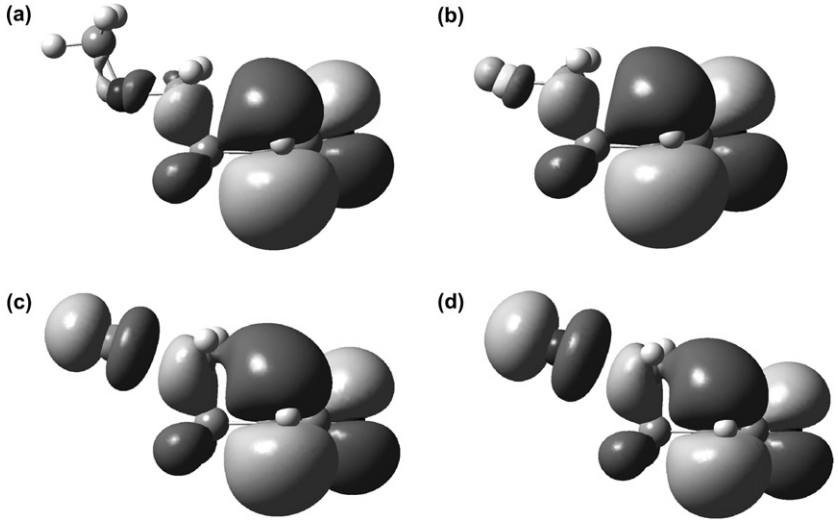


Figure 2. HOMO orbitals of α-carbanions of γ-substituted butyronitriles: (a) MeO–, (b) F–, (c) Cl–, (d) Br–.

Comparing the results obtained for X=MeO and F with results for Cl and Br substituents it can be seen that in the latter case the σ-bond between C2 and C4 is starting to be formed. This effect is probably the most 'visual' presentation of the carbanion stabilizing effect of Cl and Br atoms in γ-position.

It should be however stressed that, in spite of the effects disclosed by calculations, γ-halocarbanions are kinetically free entities and can be efficiently trapped by active external electrophilic reagents.

3. Conclusions

On the basis of measurement of rates of the deuterium exchange of a series of sulfones and nitriles that were recalculated for values of pK_a we have shown that halogenation in γ-position to aryl sulfonyl and cyano groups exerts a significant effect, stabilizing their respective carbanions. DFT calculations performed on a moderately advanced level of theory are in good agreement with experimental data and gave insight to the fact that the carbanion stabilizing effects of the γ-halosubstituents are of dual character. Substituents like methoxy and fluorine exert only an inductive effect, whereas chlorine and bromine atoms can stabilize γ-carbanions also by a special conformational effect that makes possible preformation of C2–C4 bonds accompanied by lengthening of the C–X bond.

Strong carbanion stabilizing action of Cl and Br substituents in γ-position, that is connected with a special conformational effect promoting C_α–C_γ bond formation explains satisfactorily numerous observations that alkylation of methylenic carbanions with 1,2-dihaloethanes cannot be arrested on introduction of β-haloethyl substituents and, as a rule, leads to cyclopropane derivatives.[15]

4. Experimental

4.1. Calculations

Density functional theory (DFT) calculations with a hybrid B3LYP functional were performed using Gaussian 03W

software package.[16] Geometries, zero point energy (ZPE) corrections and thermal corrections to Gibbs free energy were calculated using 6-31G(d) basis set. Despite that the calculations were performed for carbanions, we found that there was no reason for utilizing 6-31+G(d) basis set with diffuse functions for these purposes. For both basis sets the results were quite similar and, additionally, there is no reliable ZPE scale factor published for B3LYP/6-31+G(d) type of calculations. The geometries of both neutral molecules and their respective anions were optimized taking as the starting points all staggered conformations resulting from the rotation of C2–C3 and C3–C4 bonds of the γ-substituted butyronitriles. Final energies were calculated for the most stable conformers using 6-311+G(3df,2p) basis set as suggested by Smith and Radom.[17] ZPE values were scaled using a standard scale factor SF=0.9804.[18]

Gas-phase acidities (GPA) were calculated at 298.15 K as the Gibbs free energy of the reaction:

$$AH \rightleftarrows A^- + H^+$$

using the equation:

$$GPA_{AH} = \Delta G_r^{298} = \left(G_{A^-}^{298} + G_{H^+}^{298}\right) - G_{AH}^{298}$$

The Gibbs free energy of the proton at 298.15 K was taken as −6.27 kcal/mol. All G^{298} values were calculated using the following equation: $G^{298} = E^0 + G_{therm}^{298} - ZPE + SF \cdot ZPE$.

The procedure described above has been widely tested in our lab[19] on the large set of CH acids and it was found to give reliable gas-phase acidities (usually within ±2 kcal/mol range from the experimental values) for many different types of these species.

HOMO orbitals were rendered using GaussView 3.0 program[20] from the results obtained using single point calculations on the B3LYP/6-311+G(3df,2p) level performed for the most stable conformers, whose geometries were calculated as described above.

4.2. Isotope-exchange experiments

A series of deuterating mixtures of various basicity were prepared in the following way. A stock solution of 10% NaOD in D_2O was prepared by dissolving Na_2O (1.5 g) in D_2O (18.4 g), to give solution A. This solution A was used for preparation of deuterating mixtures 1–5.

1. Solution A (10 g), EtOD (14 g), DMSO (10 g);
2. Solution A (10 g), EtOD (14 g);
3. Solution A (5 g), D_2O (5 g), EtOD (14 g);
4. Solution 3 (1 g), D_2O (6 g), EtOD (6 g);
5. Solution 4 (2 g), D_2O (6 g), EtOD (6 g).

In the preliminary experiments deuterated solutions of proper basicity were selected to keep rate of the exchange of CH acids of various acidity in the range convenient for measurements. Time of half-exchange of the studied CH acids was determined following the standard procedure exemplified for 3-chloropropylphenyl sulfone. The sulfone (109 mg, 0.5 mmol) dissolved in THF (0.5 ml) was mixed with the deuterating mixture no. 2 (1.3 ml) and the mixture stirred at 20 °C for a given time. The mixture was quenched with diluted HCl; the sufone was isolated and ^1H NMR spectrum was measured. Degree of isotope exchange was determined on the basis of disappearance of the signal of α-protons in relation to β- and γ-protons. The experiments were repeated few times and the half-exchange time calculated assuming that the exchange progress is proportional to the reaction time. There were no significant discrepancies between times of half-exchange determined in a few experiments by this way. These values were averaged. In the exemplified experiment after 15 min there was 16% of exchange so the half-time of exchange was $t = 15 \text{ min} \times (50/16) = 46.9 \text{ min} = 2814$ s. Under the same condition half-time of exchange of 3-chloropropyl-2,5-dichlorophenyl sufone was 12 s. Similarly determined time of half-exchange of 3-chloropropylphenyl sulfone in the standard deuterating mixture no. 1 was 22 s, thus one can calculate time of the exchange of 3-chloropropyl-2,5-dichlorophenyl sufone in mixture no. 1 as $t_{1/2} = (12 \times 22)/(2814) = 0.094$ s. All other values of $t_{1/2}$ were determined and calculated in a similar manner.

Sulfones and nitriles studied were commercial and synthesized according to literature or prepared as described.

Phenyl sulfones: fluoromethyl,[21] 3-fluoropropyl,[3] 3-chloropropyl,[3] 3-bromopropyl,[3] 3-methoxypropyl,[22] 3-trimethylammonio propyl,[3,23] propyl *p*-nitrophenyl sulfone,[24] 3-chloropropyl *p*-nitrophenyl sulfone,[25] 3-chloropropyl and 3-bromopropyl pentachlorophenyl sulfones,[4,5] and 3-cyanopropyl trimethyl ammonium chloride.[3]

4.3. General procedure for synthesis of sulfides

To a solution of thiol (50 mmol) in ethanol (100 ml) KOH (3.4 g, 60 mmol) was added. After 5 min 1,3-bromochloropropane or propyl bromide (in case of propyl pentachlorophenyl sulfide) (150 mmol) was added and mixture was refluxed for 2 h (in case of 3-chloropropyl-(2-pyridyl)sulfide reaction was carried out at room temperature). The majority of ethanol was evaporated, the residue was treated with water, the product was extracted with methylene chloride, the solvent was evaporated, and the residue was purified by passing through short layer of silica gel (hexane/ethyl acetate) giving sulfide.

4.3.1. 3-Chloropropyl-(2-pyrimidyl)sulfide. Yield 9.4 g, 92%; oil; ^1H NMR (200 MHz, $CDCl_3$): δ=2.18–2.31 (m, 2H), 3.32 (t, ^3J(H,H)=7.0 Hz, 2H), 3.72 (t, ^3J(H,H)=6.4 Hz, 1H), 6.99 (t, ^3J(H,H)=4.8 Hz, 1H), 8.52 (d, ^3J(H,H)=4.8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=27.95, 31.94, 43.54, 116.48, 157.17, 171.90; IR (film CH_2Cl_2, ν_{max}/cm^{-1}): 3032, 2959, 1565, 1548, 1382, 1310, 1273, 1204, 1193, 982, 953, 856, 800, 773, 748, 629; MS (EI 70 eV) *m/z* (%): 188 (M^+, 17), 155 (32), 139 (74), 126 (100), 112 (51), 98 (17), 80 (43), 68 (14), 57 (10), 53 (29), 41 (29); HRMS (EI) calculated for $C_7H_9ClN_2S$ 188.0175, found 188.0181. Anal. Calcd for $C_7H_9ClN_2S$: C 44.56, H 4.81, Cl 18.79, N 14.85, S 16.99. Found: C 44.61, H 4.90, Cl 18.62, N 15.05, S 16.95.

4.3.2. 3-Chloropropyl-(2-pyridyl)sulfide. Yield 36%; oil; ^1H NMR (500 MHz, $CDCl_3$): δ=2.15–2.22 (m, 2H), 3.32

(t, ^3J(H,H)=6.9 Hz, 2H), 3.68 (t, ^3J(H,H)=6.4 Hz, 2H), 6.95–6.99 (m, 1H), 7.15–7.19 (m, 1H), 7.44–7.49 (m, 1H), 8.40–8.44 (m, 1H); ^{13}C NMR (125 MHz, $CHCl_3$): δ=27.01, 32.21, 43.58, 119.41, 122.33, 135.87, 149.41, 158.38; IR (film CH_2Cl_2, ν_{max}/cm^{-1}): 3046, 2996, 2958, 1579, 1556, 1454, 1415, 1283, 1268, 1147, 1124, 1043, 985, 758, 724, 648; MS (EI 70 eV) *m*/*z* (%): 187 (M^+, 19), 138 (81), 125 (100), 111 (37), 78 (47), 67 (30), 51 (18), 39 (19); HRMS (EI) calculated for $C_8H_{10}ClNS$ 187.0223, found 187.0229.

4.3.3. 3-Chloropropyl-(2,5-dichloro)phenyl sulfide. Yield 55%; oil; ^{1}H NMR (200 Hz, $CDCl_3$): δ=2.10–2.17 (m, 2H), 3.10 (t, ^3J(H,H)=7.0 Hz, 2H), 3.69 (t, ^3J(H,H)=6.2 Hz, 2H), 7.08 (dd, ^3J(H,H)=2.4, 8.5 Hz, 1H), 7.24 (d, ^3J(H,H)= 2.4 Hz, 1H), 7.28 (d, ^3J(H,H)=8.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=29.38, 31.06, 43.17, 126.42, 127.42, 130.53, 131.46, 133.06, 137.48; IR (film CH_2Cl_2, ν_{max}/cm^{-1}): 3090, 3067, 2959, 2854, 1873, 1614, 1568, 1553, 1448, 1371, 1308, 1270, 1244, 1139, 1094, 1034, 955, 853, 806, 668, 652, 573, 551, 434; MS (EI 70 eV) *m*/*z* (%): 254 (M^+, 43), 191 (47), 178 (100), 142 (31), 107 (13), 63 (12), 41 (38), 39 (15); HRMS (EI) calculated for $C_9H_9Cl_3S$ 253.9491, found 253.9499. Anal. Calcd for $C_9H_9Cl_3S$: C 42.29, H 3.55, Cl 41.61, S 12.54. Found: C 42.13, H 3.63, Cl 41.55, S 12.53.

4.3.4. Propyl pentachlorophenyl sulfide. Yield 60%; mp 54–55 °C (EtOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.01 (t, ^3J(H,H)=7.3 Hz, 3H), 1.58 (sextet, ^3J(H,H)=7.3 Hz, 2H), 2.91 (t, ^3J(H,H)=7.3 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=13.35, 23.14, 37.89, 132.00, 134.03, 135.17, 138.75; IR (film CH_2Cl_2, ν_{max}/cm^{-1}): 2963, 2931, 2871, 1512, 1461, 1454, 1418, 1378, 1334, 1307, 1239, 1099, 1061, 875, 785, 737, 689, 602; MS (EI 70 eV) *m*/*z* (%): 322 (M^+, 28), 282 (100), 246 (30), 212 (13), 139 (12), 103 (9), 79 (7), 43 (99); HRMS (EI) calculated for $C_9H_7Cl_5S$ 321.8711, found 321.8718. Anal. Calcd for $C_9H_7Cl_5S$: C 33.31, H 2.17, Cl 54.63, S 9.88. Found: C 33.21, H 2.32, Cl 54.40, S 10.15.

4.3.5. 3-Chloropropyl-(2-pyrimidyl)sulfone. To a solution of sulfide (7.76 g, 41.2 mmol) in methylene chloride (150 ml) was added *m*-chloroperbenzoic acid (85%, 17.5 g, 86 mmol). The mixture was refluxed for 24 h and after cooling *m*-chlorobenzoic acid was filtered off. The solution was washed with aqueous $KHCO_3$, brine and dried with $MgSO_4$. The solvent was evaporated and the product purified by column chromatography (hexane/ethyl acetate). Yield 2.9 g, 33%; mp 47–48 °C (EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.35–2.42 (m, 2H), 3.70–3.76 (m, 4H), 7.64 (t, ^3J(H,H)=4.9 Hz, 1H), 8.99 (d, ^3J(H,H)=4.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=25.37, 42.68, 48.66, 123.97, 158.68, 165.44; IR (KBr, ν_{max}/cm^{-1}): 3047, 2954, 2942, 2927, 2351, 1566, 1552, 1439, 1385, 1322, 1309, 1260, 1211, 1187, 1122, 1091, 1024, 990, 960, 820, 791, 772, 760, 741, 644, 625, 609, 526, 499; MS (EI 70 eV) *m*/*z* (%): 171 (9), 128 (34), 121 (24), 80 (100), 53 (47), 41 (55); HRMS (ESI) calculated for $C_7H_9ClN_2O_2SNa$ 242.9966, found 242.9958. Anal. Calcd for $C_7H_9ClN_2O_2S$: C 38.10, H 4.11, Cl 16.07, N 12.69, S 14.53. Found: C 37.95, H 4.10, Cl 15.84, N 12.54, S 14.36.

4.3.6. 3-Chloropropyl-(2-pyridyl)sulfone. 3-Chloropropyl-(2-pyridyl)sulfide was oxidized with *m*-chloroperbenzoic acid as above giving the sulfone. Overall yield 22%; oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.20–2.35 (m, 2H), 3.53–3.61 (m, 2H), 3.66 (t, ^3J(H,H)=6.3 Hz, 2H), 7.57 (ddd, ^3J(H,H)=1.3, 4.7, 6.0 Hz, 1H), 7.98–8.13 (m, 2H), 8.75 (ddd, ^3J(H,H)=0.9, 1.7, 5.6 Hz 1H); ^{13}C NMR (50 MHz, $CHCl_3$): δ=25.41, 42.67, 49.31, 121.94, 127.48, 138.21, 150.17, 156.56; IR (film CH_2Cl_2, ν_{max}/cm^{-1}): 3057, 2967, 2927, 1579, 1453, 1428, 1307, 1258, 1165, 1111, 1083, 992, 776, 749, 695, 655, 617, 598, 564, 532; MS (EI 70 eV) *m*/*z* (%): 170 (12), 127 (17), 79 (100), 67 (8), 51 (40), 41 (30); HRMS (ESI) calculated for $C_8H_{10}ClNO_2SNa$ 242.0013, found 242.0002. Anal. Calcd for $C_8H_{10}ClNO_2S$: C 43.74, H 4.59, Cl 16.14, N 6.38, S 14.60. Found: C 43.89, H 4.64, Cl 16.05, N 6.39, S 14.68.

4.3.7. 3-Chloropropyl-(2,5-dichloro)phenyl sulfone. 3-Chloropropyl-(2,5-dichloro)phenyl sulfide (5.1 g, 20 mmol) was dissolved in acetic acid (60 ml) and to this solution hydrogen peroxide 30% (5 ml) was added. The mixture was gently refluxed for 2 h; acetic acid was evaporated under vacuo; the residue was treated with aqueous $NaHCO_3$ and extracted with methylene chloride. The solvent was evaporated and the residue recrystallized from hexane. Yield 3.2 g, 54%; mp 87 °C (hexane); ^{1}H NMR (500 Hz, $CDCl_3$): δ=2.20–2.28 (m, 2H), 3.57–3.63 (m, 2H), 3.66 (t, ^3J(H,H)=6.1 Hz, 2H), 7.51 (d, ^3J(H,H)=8.5 Hz, 1H), 7.56 (dd, ^3J(H,H)=2.5, 8.5 Hz, 1H), 8.11 (d ^3J(H,H)=2.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=25.48, 42.49, 51.49, 130.98, 131.39, 133.16, 133.91, 134.88, 137.79; IR (KBr, ν_{max}/cm^{-1}): 3098, 2953, 2916, 1453, 1440, 1375, 1295, 1246, 1193, 1142, 1100, 1038, 957, 886, 835, 781, 742, 695, 659, 582, 545, 505, 405; MS (EI 70 eV) *m*/*z* (%): 286 (M+, 7), 215 (10), 210 (11), 185 (15), 162 (24), 146 (35), 127 (13), 109 (31), 75 (23), 49 (11), 41 (100); HRMS (EI) calculated for $C_9H_9Cl_3O_2S$ 285.9388, found 285.9380.

4.3.8. Propyl pentachlorophenyl sulfone. Propyl pentachlorophenyl sulfide obtained from pentachlorophenol and propyl bromide was oxidized by H_2O_2 in acetic acid as above. Yield 50%; mp 143 °C (EtOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.12 (t, ^3J(H,H)=7.5 Hz, 3H), 1.83–2.10 (m, 2H), 3.45–3.53 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=12.90, 15.91, 57.47, 133.84, 134.83, 138.76, 147.54; IR (KBr, ν_{max}/cm^{-1}): 2967, 2932, 2875, 1513, 1460, 1401, 1342, 1305, 1249, 1212, 1154, 1093, 1062, 911, 877, 776, 736, 694, 672, 613, 561, 538, 522, 506; MS (EI 70 eV) *m*/*z* (%): 354 (M^+, 4), 250 (33), 214 (12), 179 (7), 142 (11), 43 (100); HRMS (EI) calculated for $C_9H_7Cl_5O_2S$ 353.8609, found 353.8623. Anal. Calcd for $C_9H_7O_2Cl_5S$ (356.48): C 30.32, H 1.98, S 8.99. Found: C 30.13, H 2.03, S 9.05.

References and notes

1. Cohen, S.; Zoran, A.; Sasson, Y. *Tetrahedron Lett.* **1998**, *39*, 9815.
2. Mąkosza, M.; Przyborowski, J.; Klajn, K.; Kwast, A. *Synlett* **2000**, 1773.
3. Mąkosza, M.; Judka, M. *Chem.—Eur. J.* **2002**, 4234; Barbasiewicz, M.; Judka, M. *Russ. Chem. Bull.* **2004**, *53*, 1771; Barbasiewicz, M.; Mąkosza, M. *Synthesis* **2006**, 1190.
4. Mąkosza, M.; Judka, M. *Helv. Chim. Acta* **2005**, *88*, 1676.
5. Mąkosza, M.; Judka, M. *Synlett* **2004**, 717.

6. Bordwell, F. G.; Matthews, W.; Vanier, N. *J. Am. Chem. Soc.* **1975**, *97*, 442.
7. Bordwell, F. G.; Van Der Puy, M.; Vanier, N. *J. Org. Chem.* **1976**, *41*, 1883.
8. Bordwell, F. G.; Boyle, W., Jr.; Hautala, J.; Yee, K. *J. Am. Chem. Soc.* **1969**, *91*, 4002.
9. Bordwell, F. G.; Van Der Puy, M.; Vanier, N. *J. Org. Chem.* **1976**, *41*, 1885.
10. Pearson, R.; Dillon, R. *J. Am. Chem. Soc.* **1953**, *75*, 2439.
11. Richard, J. P.; William, G.; Gao, J. *J. Am. Chem. Soc.* **1999**, *121*, 715; Terrier, F.; Kizilian, E.; Goumont, N.; Faucher, N.; Wakselman, C. *J. Am. Chem. Soc.* **1998**, *120*, 9496; Wodziński, S.; Bunting, J. W. *J. Am. Chem. Soc.* **1994**, *116*, 6910.
12. Bordwell, F. G.; Vanier, N. R.; Matthews, W. S.; Hendrickson, J. B.; Skipper, P. L. *J. Am. Chem. Soc.* **1975**, *97*, 7160.
13. Bordwell, F. G.; Bares, J. E.; Bartmess, J. F.; Amcker, G. E.; Gerhold, J.; McCollum, G. J.; Van Der Puy, M.; Vanier, N. R.; Matthews, W. S. *J. Org. Chem.* **1977**, *42*, 326; Bordwell, F. G. *Am. Chem. Res.* **1988**, *21*, 456.
14. Gronert, S.; Azizian, K.; Friedman, M. A. *J. Am. Chem. Soc.* **1998**, *120*, 3220.
15. Fleming, F.; Shook, B. *Tetrahedron* **2002**, *58*, 1.
16. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03W, Revision B.05*; Gaussian: Wallingford, CT, 2004.
17. Smith, B. J.; Radom, L. *Chem. Phys. Lett.* **1995**, *245*, 123.
18. Wong, M. W. *Chem. Phys. Lett.* **1996**, *256*, 391.
19. Danikiewicz, W., in preparation.
20. *GaussView 3.0*; Gaussian: Wallingford, CT, 2004.
21. Inbasekaran, M.; Peet, N. P.; McCarthy, J. R.; Le Tournean, M. E. *Chem. Commun.* **1985**, 678.
22. King, J. F.; Rajendra, R.; Guo, Zh; Li, M.; Payne, N. C. *J. Am. Chem. Soc.* **2000**, *122*, 10308.
23. Mąkosza, M.; Judka, M. *Synthesis* **2003**, 820.
24. Waldron, W. R.; Reid, E. E. *J. Am. Chem. Soc.* **1923**, *24*, 2399.
25. Bird, R.; Stirling, C. J. M. *J. Chem. Soc. B* **1968**, 111.