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RESEARCH ARTICLE

Aryl fluoroalkyl sulfoxides: optical stability and pK_a measurement

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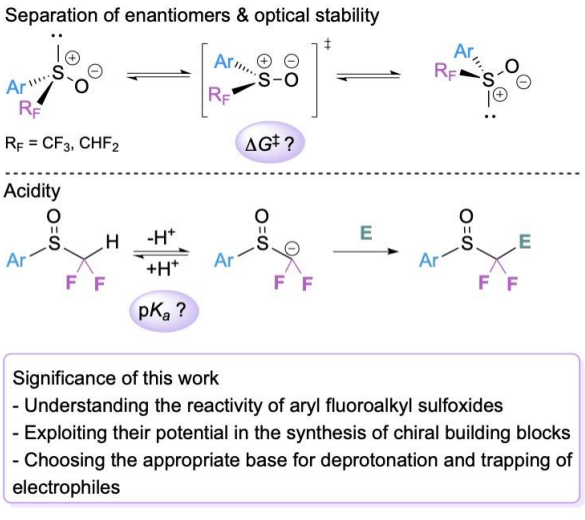
Abstract: The enantiomeric separation of aryl trifluoromethyl and difluoromethyl sulfoxides was realized *via* chiral chromatography. The configurational stability of each set of enantiomers was then studied by thermal enantiomerization. The $\Delta G^{\ddagger}$ values obtained cover a range of 38.2-41.0 kcal.mol^{-1} at 214 °C, thus demonstrating their optical stability at room temperature. However, a shorter half-life time has been observed for difluoromethyl sulfoxides. Furthermore, the acidities of six aryl difluoromethyl sulfoxides were determined in DMSO by an overlapping indicator method using UV-visible spectrophotometric titrations. The pK_a values fall in range of 20.3-22.5 and differ by about 10 log units compared to non-fluorinated analogues.

Introduction

Fluorinated moieties such as $-CF_3$, $-CHF_2$, $-OCF_3$, $-SCF_3$ or $-SF_5$ can deeply modify the lipophilicity, the metabolic stability, the acidity or the conformational preference of compounds.[1] Such perfluoroalkyl groups have shown a growing interest in pharmaceutical and agrochemical fields due to their ability to impact the properties of bioactive molecules. Among the various strategies used to introduce the prized $-CF_3$ and $-CHF_2$ groups, the use of α-fluorinated sulfur derivatives proved highly resourceful in various types of nucleophilic, electrophilic and radical reactions.[2] In particular, when the trifluoromethyl moiety is bonded to a sulfinyl moiety, a very original and versatile group is then created. The most illustrative examples of its importance include its use as a precursor of CF_3^- as demonstrated by Prakash *et al*.[3], or as a source of *in situ* generation of trifluoromethylcopper as shown by the group of Hu.[4] Another major application is the use of difluoro- and trifluoromethyl sulfoxides as common precursors of both sulfoniums[5] and sulfoximines[6], two of the most widely used classes of electrophilic and radical di- or trifluoromethylation reagents.[7] Considering difluoromethyl sulfoxides, one of our groups (Leroux and coworkers) employed the enantiopure difluoromethanesulfinyl moiety as a chiral auxiliary to access highly enantioenriched α-difluoromethyl alcohols by deprotonation and trapping with electrophiles such as aldehydes or prochiral ketones.[8] Indeed, the valuable properties of the $-CHF_2$ group, a motif known to be a good hydrogen bond donor and a bioisostere of hydroxy, thiol and amine groups,[9] have motivated the development of numerous methods for its non-stereoselective introduction;[10] however, the enantioselective synthesis of CHF_2-containing scaffolds is less described.[11]

Regarding the access to such α-polyfluorinated alkyl aryl sulfoxides, Magnier and coworkers developed methods for either the direct introduction of the trifluoromethanesulfinyl group onto aryl derivatives,[5b,6a] or its construction *via* simple oxidation of the corresponding sulfides using TFPAA.[12] Unfortunately, all the attempts of asymmetric synthesis of aryl trifluoromethyl sulfoxides led to racemates.[13] To the best of our knowledge, there is only one example of preparation of an enantioenriched trifluoromethyl sulfoxide[14] and no example with an aryl group. On the other hand, Leroux and coworkers recently succeeded in developing an efficient synthesis of enantiopure aryl α,α-difluoromethyl sulfoxides, starting with a Reformatsky-type reaction on a sulfinyloxazolidinone and followed by a Krapcho dealkoxycarbonylation.[8] As mentioned above, the subsequent use of the obtained difluoromethyl sulfoxides required a deprotonation, which brought to our attention that the pK_a of aryl difluoromethyl sulfoxides was unknown and deserved to be explored (Scheme 1).



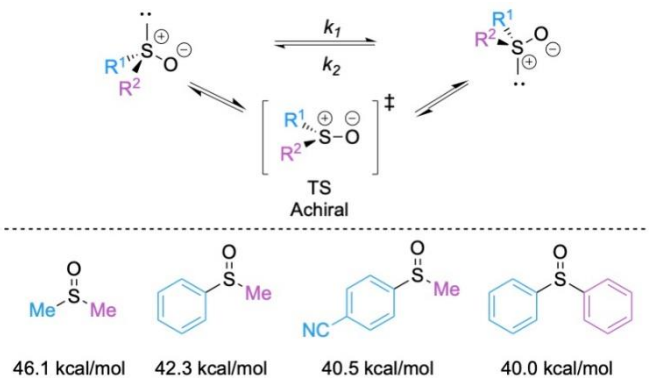
Scheme 1. Investigated properties of aryl fluoroalkyl sulfoxides.

In view of our precedent works on the synthesis of fluoroalkyl sulfoxides, it appeared essential to tackle several issues, in particular the isolation of enantiomerically pure trifluoromethyl sulfoxides, the study of the configurational stability of difluoro- and trifluoromethyl sulfoxides as well as the acidity of the difluoromethyl species (Scheme 1). Consequently, the first objective of the present study was to isolate for the first time the enantiomers of trifluoromethyl sulfoxides. The second was the determination of the inversion energy barriers for the enantiomerization of aryl fluoroalkyl sulfoxides by a kinetic study. Thirdly, the acidity of several aryl α,α-difluoromethyl sulfoxides was evaluated by UV-visible absorption spectrophotometric means in DMSO to determine the impact of the two α-fluorine atoms on the pK_a value of sulfoxides as well as the electronic effects of the aryl substituent on the α,α-difluoromethanesulfinyl moiety. These results are fully detailed in the following text.

Results and discussion

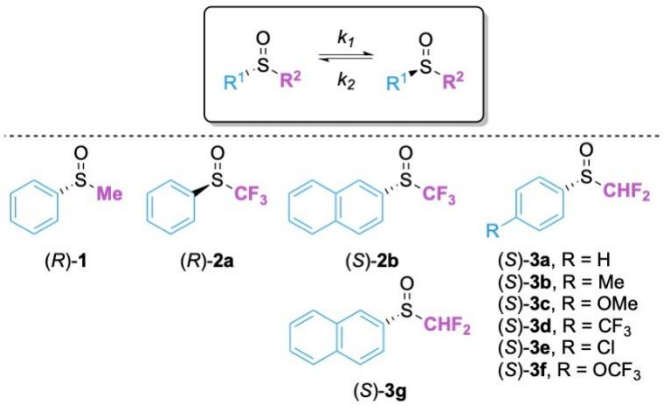
Determination of inversion energy barriers.

In the non-fluorinated series, the physico-chemical properties of sulfoxides have been thoroughly investigated. Non-fluorinated sulfoxides are known to be highly configurationally stable. Only the enantiomerization of allyl,[15] benzyl,[16] vinyl[17] sulfoxides and arenethiolsulfinates[18] requires milder conditions. For dialkyl, diaryl and alkyl aryl sulfoxides, the thermal enantiomerization is suggested to occur through a pyramidal inversion mechanism with a planar non-chiral transition state (Scheme 2).[19] However, this process only happens at temperatures above 200 °C. Agranat *et al.*[20] reported a theoretical study on the inversion energy barriers of some chiral and achiral sulfoxides. The energies were calculated by DFT methods and were found to be in a range of 40-46 kcal.mol^{-1} (Scheme 2). They demonstrated that with the presence of a phenyl ring, the transition state is stabilized by a resonance effect, decreasing the energy barrier compared to an alkyl sulfoxide. By introducing an electron-withdrawing moiety such as a cyano group at the *para* position of the aromatic ring, the energy is further reduced. To the best of our knowledge, in the fluorinated series, the only example of enantiomerization was reported by Cahard *et al.*[14] They demonstrated the spontaneous enantiomerization of allylic trifluoromethyl sulfoxides *via* a [2,3]-sigmatropic rearrangement with inversion energy barriers approaching 22 kcal.mol^{-1}.



Scheme 2. Pyramidal inversion mechanism and inversion energy barriers calculated at 25 °C of alkyl aryl, dialkyl and diaryl sulfoxides.[20]

Understanding the stereomutation of aryl fluoroalkyl sulfoxides that cannot undergo such a rearrangement is therefore essential to control the optical stability of enantiomers for synthetic applications and its investigation is unfortunately still lacking. Previously, we were able to separate perfluorinated sulfilimines by SFC while demonstrating their enantiomeric stability.[13] Herein, the enantiomeric separation of trifluoromethyl (**2a-2b**) and difluoromethyl (**3a-3g**) sulfoxides (Scheme 3) was first performed by chiral HPLC before investigating their enantiomerization kinetics.



Scheme 3. Enantiomerization process and sulfoxides investigated in this approach.

The racemic sulfoxides **1**, **2a**-**b** and **3a**-**g** were synthesized by our previously reported methods.[8,12] Enantiomers were then separated by preparative HPLC on a chiral stationary phase and obtained up to the gram scale (see ESI). Their absolute configuration was determined by comparing experimental and TD-DFT calculated electronic circular dichroism spectra (see ESI). Solutions of enantiopure sulfoxides were then heated to 214° C (487 K) in 1,2,4-trichlorobenzene and samples were injected on a chiral chromatography column at different times to obtain the corresponding kinetic traces (see ESI). The enantiomerization process is considered as a reversible first order reaction, where k_1 and k_2 are the rate constants of the forward and backward reactions, respectively (Scheme 2 and Scheme 3, i.e., for an enantiomerization process, $k_{enantiomerization} = k_1 = k_2$).[21] The rate constants $k_{enantiomerization}$ were then determined experimentally (see ESI) by monitoring *via* HPLC the percentage of the S_S enantiomer. The rate constant $k_{enantiomerization}$, the inversion energy barrier $\Delta G^{\ddagger}$ and the half-life time $t_{1/2}$ (see ESI) were determined for each compound and are summarized in Table 1.

Table 1. Rate constants, inversion energy barriers and half-life times for sulfoxides **1**, **2a**-**b**, **3a**-**g** at 214 °C (487 K) in 1,2,4-trichlorobenzene.

Sulfoxide	$k_{enantiomerization}$ (s^{-1})	$\Delta G^{\ddagger}$ (kcal.mol^{-1})	$t_{1/2}$ (min or h)
1	3.84.10^{-6}	41.1	25.1 h
2a	4.00.10^{-6}	41.0	24.1 h
2b	4.68.10^{-6}	40.9	20.6 h
3a	3.16.10^{-5}	39.0	183 min

3b	$3.48.10^{-5}$	38.7	166 min
3c	$3.21.10^{-5}$	38.9	180 min
3d	$5.89.10^{-5}$	38.2	98 min
3e	$3.49.10^{-5}$	39.0	166 min
3f	$3.57.10^{-5}$	38.9	162 min
3g	$3.00.10^{-5}$	39.1	192 min

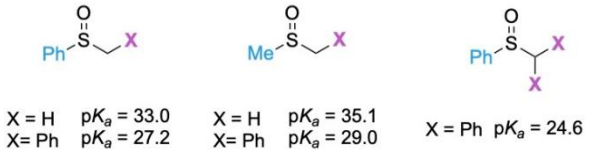
In the non-fluorinated series, the configurationally stable diaryl, alkyl aryl or dialkyl sulfoxides enantiomerize with activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ ranging from 35 to 42 kcal.mol^{-1} and from -8 to 4 e.u. (*i.e.*, entropy unit, 1 e.u. = 4.184 J.K^{-1}.mol^{-1}), respectively.[19b] For methyl phenyl sulfoxide **1** (Scheme 3), we measured an inversion energy barrier of 41.1 kcal mol^{-1} at 214 °C. Inversion energies determined for aryl trifluoromethyl sulfoxides **2a**-**b** were found to be comparable to those measured for non-fluorinated analogues. By contrast, aryl difluoromethyl sulfoxides **3a**-**g** were found to be less optically stable (i.e., faster inversion process, Table 1) with a difference of up to ~3 kcal.mol^{-1} units when compared to non-fluorinated analogues (e.g., **2a** versus **3a** and **2b** versus **3g**). For fluorinated aryl sulfoxides, much lower inversion energy barriers were initially expected taking into account the strong electron-withdrawing effect of fluorine. For non-fluorinated analogues,[19] it has been suggested that the four atoms (C, C, O, S) of the sulfinyl group are positioned in a planar array in the transition state of the pyramidal inversion mechanism (Scheme 2). This induces a resonance effect between the π-electrons of the aromatic ring, the unshared electron pair of the sulfur atom and the electrons of the sulfur–oxygen "double"[22] bond, which stabilizes the planar transition state. Hyperconjugation of the methyl group to the partially positively charged sulfur centre also contributes to stabilize this transition state.[19b,20] Substitution on the alkyl moiety of the sulfoxide by a fluorine atom would therefore destabilize the planar transition state by: 1) disfavouring the delocalization of the electron density at sulfur into the phenyl ring by resonance, 2) weakening or fully suppressing the (α-CH)-sulfur hyperconjugation, and 3) depleting the electron density at sulfur *via* the known hyperconjugation between non-bonding electrons at sulfur and the antibonding σ^*_{C-F} orbital. On the other hand, steric effects could also play a significant role and increase the inversion energy barriers due to repulsion interactions between the unshared electron pairs of the fluorine atoms, the oxygen and the sulfur atoms in the planar transition state. This repulsion would be minimized in the tetrahedral geometry. In summary, given the relative size of the –CF_3 group (*A* value = 2.37 kcal.mol^{-1}) compared to the –CH_3 group (*A* value = 1.74 kcal.mol^{-1}),[23] the steric effect most likely compensates for the electronic effect, leading to similar inversion energy barriers for the corresponding sulfoxides. In contrast, the size of the –CHF_2 unit (*A* value = 1.85 kcal.mol^{-1})[24] is much smaller than the –CF_3 moiety and only slightly larger than a –CH_3 substituent. Therefore, for aryl difluoromethyl sulfoxides, the electron-withdrawing effect overwhelms the steric one, resulting in lower inversion energy barriers.

We then evaluated the influence of the aromatic ring on the inversion energy barriers of the corresponding sulfoxides. The comparison of compounds **2a** and **2b** clearly shows that the inversion properties are not significantly altered, with however a slightly faster enantiomerization for **2b** (i.e., stronger resonance effect with a naphthalene ring). The comparison of compounds **2b** (CF_3) and **3g** (CHF_2) supports our hypotheses on the electronic/steric effects of these substituents.

We next turned our attention to the effects of the substituents at the *para* position of the phenyl ring. In the non-fluorinated series, Mislow and co-authors[19b] showed that the more electron-rich the benzene ring, the slower the enantiomerization; however, these electronic effects were assumed to play a minor role (for diaryl sulfoxides R-C_6H_4S(O)*p*-Tol with R = H, Cl, CF_3 or OCH_3, the energy difference does not exceed 0.7 kcal.mol^{-1}). Electrostatic repulsion between the π electrons of the aryl ring and the lone electron pair on the sulfur atom was proposed to explain this property. With electron-donating groups (EDG), this effect is reinforced in the planar transition state leading to higher inversion barrier. For electron-withdrawing groups (EWG), the planar transition state will be stabilized due to a conjugation from the lone electron pair on the sulfur atom to the EWG causing a decrease of the energy barrier. Similarly to non-fluorinated sulfoxides, we observed negligible energy variations for difluoromethyl sulfoxides **3a**-**f**, which do not exceed 0.8 kcal mol^{-1} (**3d** – R = CF_3 *versus* **3a** – R = H). Our results follow the same reasoning and are therefore consistent with the reported data.

Determination of the pK_a values.

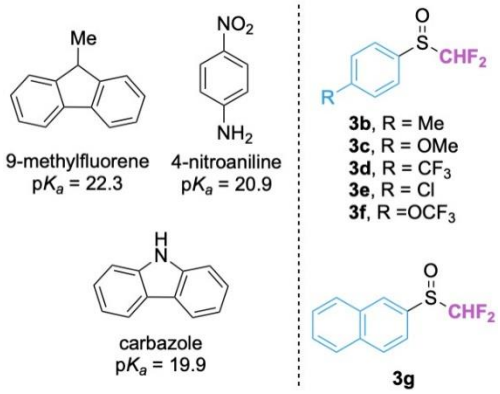
Another interesting property of aryl alkyl sulfoxides that has been investigated in depth is the acidity of the α-protons of sulfoxides. A survey of literature shows that their pK_a values are ranging from 24.6 to 35.1 in DMSO (e.g., pK_a = 33.0 for **1**) depending on the nature of the group linked to the sulfur atom (Scheme 4).[25,26] Besides, aryl sulfoxides are more acidic than their alkyl congeners with two pK_a units less due to the resonance effect of the aryl ring that stabilizes the anionic form. It is also worth mentioning that sulfoxides are also weakly basic and can be protonated at their oxygen centres (e.g., pK_a = -0.488 for **1** in acetic anhydride).[27] Substitution at the *para*-position of methyl phenyl sulfoxide markedly affects this corresponding pK_a value as a consequence of the resonance effect of the substituent. A difference of 4 pK_a units is indeed observed between an EDG (pK_a = 0.555 for OCH_3 substitution) and an EWG (pK_a = -3.51 for NO_2 substitution). Introducing two fluorine atoms in α-position (i.e., affording a difluoromethyl group) is anticipated to significantly lower the pK_a value of the α-protons of sulfoxides due to the strong electron-withdrawing character of the fluorine atoms. Nonetheless, no pK_a value of difluoromethyl aryl sulfoxides has been reported in the literature. So far, only one pK_a value for difluoromethylated compounds has been reported by Bordwell *et al.* who determined a pK_a value of 20.2[25c] for 2,2-difluoroacetophenone in DMSO. Introduction of one (2-fluoroacetophenone, pK_a = 21.7) or two fluorine (2,2-difluoroacetophenone, pK_a = 20.2) atoms thus induces a significant stepwise increase of the acidity of the compound when compared to acetophenone (pK_a of 24.7).[25c] On the other hand, Xue *et al.* recently reported the pK_a values of a series of (α-monofluoro)(phenylsulfonyl)methane derivatives.[28] Surprisingly, introduction of a α-fluorine substituent weakens the α-C_{sp3}–H acidity of most the investigated derivatives. Destabilization of α-fluorocarbanions by lone-pair repulsions, attenuation of the stabilizing inductive effect of fluorine by the polar saturation effect, as well as stabilization of the parent acid form by the double bond-no bond resonance were proposed to explain this peculiar behaviour.[28]



Scheme 4. pK_a values of selected non-fluorinated sulfoxides in DMSO.[25,26]

These reported data highlight that physico-chemical characterizations of sulfoxide derivatives remain scarce and their reactivity difficult to predict.

Several bases were shown to be effective to deprotonate aryl α,α-difluoromethyl sulfoxides. Strong bases such as KHMDS or LiHMDS (pK_a = 25.8 in THF),[29] *t*-BuOK (pK_a = 32.2 in DMSO),[25c] Schwesinger's superbase (pK_a = 42.6 in acetonitrile)[8,30] were found to be suitable,[8,31] in contrast to DBU (pK_a = 24.2 in THF).[32]



Scheme 5. Indicators with their pK_a values in DMSO[18b] and aryl difluoromethyl sulfoxides investigated in this approach.

Aryl difluoromethyl sulfoxides are weakly absorbing in the UV region either under neutral (protonated, see ESI) or negatively (deprotonated) charged states and, therefore, not valuable chromophores to directly assess their deprotonation properties. An indirect colorimetric method previously applied to non-fluorinated sulfoxides by Bordwell[25b] (i.e., Bordwell's indicator overlapping method) was consequently used for compounds **3b**-**3g** (Scheme 5). Using absorption spectrophotometry (i.e., an original setup composed of optical fibres and a quartz suprasil immersion probe was used to measure the absorption in a two-necked round-bottom tube under strict argon atmosphere), a deprotonated coloured indicator (noted In$^-$; freshly prepared from dimsyl potassium) was titrated by aryl difluoromethyl sulfoxides (noted HA; **3b**-**3g**) in DMSO.[33] The proton exchange (K_{ex}) between HA and In$^-$ was monitored and quantified by measuring the absorption alterations. The pK_a values of the investigated aryl difluoromethyl sulfoxides were then evaluated from the exchange constant K_{ex} and the pK_a value of the indicator used.

$$In^- + HA \overset{K_{ex}}{\rightleftharpoons} InH + A^-$$

$$K_{ex} = \frac{[InH][A^-]}{[In^-][HA]}$$

$$\boldsymbol{pK_{HA} = pK_{InH} - \log K_{ex}}$$

For the method to be reliable, the pK_a values of the acid and the indicator must not differ by more than two units. In addition, the indicator must be sufficiently stable over the duration of the titration. Six indicators were first tested for their ability to act as efficient colorimetric reporters in their basic form in DMSO: carbazole (pK_a = 19.9), 2-naphthyl-acetonitrile (pK_a = 20.7)[34], 4-nitro-aniline (pK_a = 20.9)[35], indole (pK_a = 21.0)[36], 9-benzyl-fluorene (pK_a = 21.8)[37] and 9-methyl-fluorene (pK_a = 22.3).[25b] Only the anions derived from carbazole, 9-methyl-fluorene and 4-nitro-aniline were found to be sufficiently stable in solution to allow absorption titrations with aryl difluoromethyl sulfoxides **3b**-**g** (see ESI). The pK_a values of sulfoxides **3b**-**g** were determined in duplicate or triplicate and in some cases several indicators were used to confirm their value (see ESI). As an example, Figure 1 depicts the absorption spectrophotometric titration of the anion (In$^-$) derived from 4-nitroaniline with the aryl difluoromethyl sulfoxide **3d** acting as the acid (HA). Upon addition of **3d**, proton exchange is clearly evidenced by the gradual decrease of the In$^-$ anion absorption and the concomitant formation of a new absorption related to the protonated neutral indicator (see ESI). The presence of an isosbestic point at 412 nm confirms that proton exchange is the only equilibrium that takes place

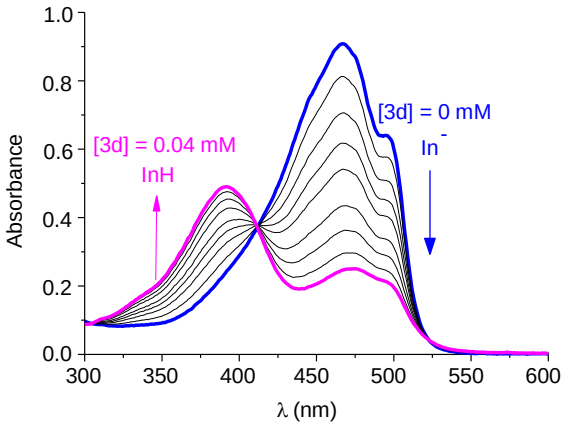


Figure 1. UV-visible absorption spectra of the anion In$^-$ derived from 4-nitroaniline after each addition of the sulfoxide **3d** in DMSO. [In$^-$] = 0.1 mM; T = 25 °C; argon atmosphere. The absorption spectra are not corrected from dilution effects.

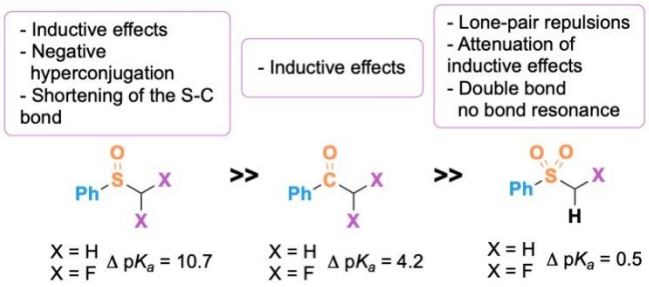
Table 2 gathers the pK_a values which fall between 20.3 and 22.5. Compared to methyl phenyl sulfoxide (Scheme 4, pK_a = 33.0 in DMSO),[18d] the acidity of *p*-tolyl difluoromethyl sulfoxide **3b** decreased by more than 10 pK_a units. This increase in acidity is for example much higher than that observed for compounds of the acetophenone series (ΔpK_a = 4.5). This clearly demonstrates a marked stabilizing effect of the two fluorine substituents on the carbanion, in addition to the previously mentioned stabilization provided by the sulfinyl group in α-position.

Table 2. pK_a values of aryl α,α-difluoromethyl sulfoxides **3b**-**g** measured in DMSO at 25 °C under argon.

Sulfoxide	pK_a	Indicator used (number of replicates)
3b	22.3 ± 0.2	9-Methylfluorene
3c	22.5 ± 0.4	9-Methylfluorene

3d	20.3 ± 0.6	4-Nitroaniline Carbazole
3e	21.7 ± 0.6	9-Methylfluorene 4-Nitroaniline Carbazole
3f	21.8 ± 0.2	9-Methylfluorene
3g	21.7 ± 0.1	9-Methylfluorene

Furthermore our observations are in contrast to the properties of the (α-fluoro)(phenylsulfonyl)methane derivatives recently reported.[28] Weak to no effect (ΔpK_a = 0.5) was observed between α-fluoro(phenylsulfonyl)methane and its non-fluorinated analogue (Scheme 6).



Scheme 6. Comparison of the pK_a values for selected compounds in DMSO.

For aryl difluoromethyl sulfoxides, stabilization of the anion could be rationalized by combined factors, starting with the attractive inductive effect of the two fluorine atoms, decreasing electron density at the negatively charged carbon. Moreover, a shortening of the sulfur-carbon bond can be proposed on the basis of, on the one hand, the same inductive effect of the two fluorine atoms and, on the other hand, the negative hyperconjugation between the sulfur lone pair and the antibonding σ^*_{C-F} orbital, both contributing in bringing closer the negative charge to the electron-deficient sulfinyl group. Altogether, the formed carbanion would be more stabilized than the non-fluorinated analogue and the acidity of the corresponding sulfoxide would increase.

As observed for the enantiomerization process (*i.e.*, weak influence of the phenyl substitution on the inversion energy barrier), the nature of the substituent in the *para* position of aryl difluoromethyl sulfoxides has a very slight influence on their acidity, with variations not exceeding 2 pK_a units. Compound **3c** is the least acidic derivative due to the mesomeric electron-donating effect of the methoxy group, while with the strong electron-withdrawing inductive effect of the trifluoromethyl group, compound **3d** displays the lowest pK_a value. Furthermore, comparison of compound **3g** (pK_a = 21.7) with **3b** (pK_a = 22.3) demonstrates the weak impact of an extended resonance effect on the α-C_{sp3}–H acidity.

Conclusion

The present study allowed us to unravel the optical stability of aryl fluoroalkyl sulfoxides by thermal enantiomerization *via* enantioselective chromatography. The results indicate that the enantiomers of these compounds are strongly configurationally stable at room temperature and have a reasonable stability up to 214 °C. However, the shorter half-life time obtained for difluoromethyl sulfoxides shows that their enantiomerization is faster when reaching 214 °C. Besides, the pK_a values in DMSO of six aryl α,α-difluoromethyl sulfoxides were determined by means of the overlapping indicator method using UV-visible absorption spectrophotometric titrations. Introduction of two fluorine atoms significantly increases the α-C_{sp3}–H acidity by more than 10 pK_a units whereas substitution in the *para*-position of the phenyl group only weakly modulated the acidity of the sulfoxide. The data obtained are important to deepen our understanding of the reactivity of aryl fluoroalkyl sulfoxides, in particular the effect of fluorine substitution on key properties such as inversion energy barriers or acidities compared to non-fluorinated analogues. This will help fully exploiting the potential of fluoroalkyl sulfoxides in the synthesis of (chiral) fluorinated building blocks.

Experimental Section

Synthetic procedures, calculations and experimental details for the enantiomeric separation and the determination of inversion energy barriers as well as for pK_a measurements are provided in the supporting information.

Acknowledgements

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Keywords: Absorption • Acidity • Enantiomerization • Fluorine • Sulfoxide

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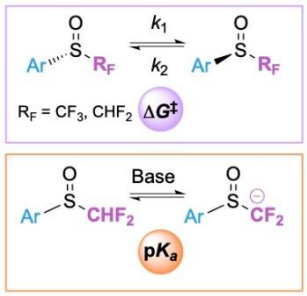

Key properties of chiral aryl fluoroalkyl sulfoxides with strong synthetic potential were studied. After resolution by enantioselective chromatography, their optical stability was investigated by thermal enantiomerization *via* enantioselective chromatography. Their $\Delta G^{\ddagger}$ values range from 38.2 to 41.0 kcal mol^{-1} at 214 °C. In addition, the pK_a values of six aryl difluoromethyl sulfoxides were determined *via* indirect UV-visible spectrophotometric titrations in DMSO and are in the range of 20.3-22.5.