A New Radical Clock for Testing the Possibility of Electron Transfer from Carbanions

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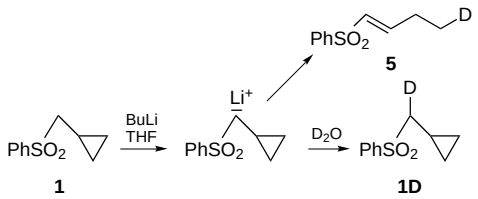
Cyclopropylcarbinyl radical ring opening may be used as an efficient tool for the study of carbanions possibly involved in SET reactions. The question of involvement of electron-transfer processes in organic reactions classically considered to be polar is an active field.[1] In biological systems, unexpected insights have been obtained using free radical clocks.[2]

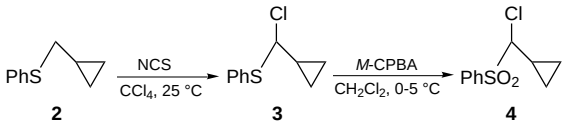
Carbanions may be involved in electron transfer mechanisms.[3] Nevertheless, there is not, at this time, an indisputable rule to predict if a carbanion is going to react through a polar or through an electron-transfer pathway when it reacts with an electrophilic reagent. In depth experimental studies of this mechanistic area could bring new insights on the fundamentals of reactivity.[4]

We have previously described free radical clocks of the norbornenyl type ($k = 10^8-10^9$ s^{-1}, 80 °C) specifically designed for the study of carbanions.[5] The use of this kind of radical probe is governed by the cyclization rate (addition of a C−C centered α-sulfonyl radical to a double bond). The fastest known free radical clocks are based on the cleavage of strained C−C bonds (cyclopropylcarbinyl radical ring opening). This ring opening could become specific for the radical if rearrangement in the corresponding carbanion was prevented by appropriate groups known for their carbanion stabilizing properties (G = NO_2, CN, RSO_2). Accordingly, as shown in Scheme 1, the desired sulfone-stabilized carbanion was prepared from **1**, and after 45 min at 25 °C the mixture was quenched with D_2O. Only deuterated sulfone **1**α-*d* was observed (NMR). No deuterated ring-opened product corresponding to **5** was formed (Scheme 1). Stabilization by the phenylsulfonyl group evidently prevents cyclopropyl ring opening.

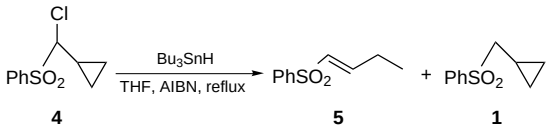
Scheme 1



Scheme 2



Scheme 3



This result prompted us to examine the cyclopropylmethyl phenyl sulfone **4,** the first radical clock involving cyclopropylcarbinyl ring-opening and designed for the study of carbanions in electron-transfer processes. Preparation of α-chlorocyclopropylmethyl phenyl sulfone (**4**) was by chlorination of cyclopropylmethyl phenyl sulfide (**2**) to give **3** and rapid oxidation with *m*-chloroperbenzoic acid in CH_2Cl_2 (17%) (Scheme 2).

In kinetic competition, reduction of chloride **4** with a slight excess of Bu_3SnH (1.4 equiv) in THF with AIBN as initiator gave the ring-opened product **5** (more stable *E* isomer,[7] 70% isolated yield) and a small amount of unrearranged product **1** (5%) (Scheme 3).

Increasing the excess of Bu_3SnH yielded increasing amounts of **1**. The second-order reaction can be treated as a pseudo-first-order process, and the rate constant of the ring opening of the α-sulfonyl radical can be estimated, the relation being $k = k_H$ [**5**]/[**1**] − $[Bu_3SnH]_0$[8] where $[Bu_3SnH]_0$ is the initial concentration of reductant and k_H is the rate constant for the abstraction of H• from Bu_3SnH by the C-centered α-sulfonyl radical. Since the effect of the phenylsulfonyl group on this radical is weak,[9] for k_H and the Arrhenius parameters we used the values calculated by Ingold and co-workers for a secondary radical (3×10^6 M^{-1} s^{-1}, 80 °C).[10] From these results, in refluxing cyclohexane or benzene, ring opening of the α-sulfonyl cyclopropylmethyl radical was estimated to have $k = 10^7$ s^{-1} (80 °C). The radical undergoes ring opening more slowly than does the parent α-methylcyclopropylcarbinyl radical (secondary to primary radical rearrangement, $k^{80\ °C} = 2.2 \times 10^8$ s^{-1}). Previous studies of substituted cyclopropylcarbinyl radicals with stabiliz-

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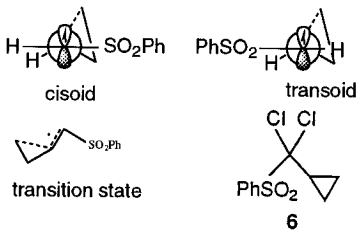
Chart 1



ing groups such as α-CO_2Me, α-NO_2, α-Ph, O^- (ketyl), or α-CO_2tBu also showed dramatic decreases in ring-opening rates[2e,11b,12] but the decrease of the rate constant was unexpected with the phenylsulfonyl group since this substituent has no capacity for radical delocalization.[9] This result could be explained by nonbonded interactions between α-phenylsulfonyl and ring C−H groups disfavoring the transition-state geometry which is necessary for orbital overlap between the SOMO and the C−C bond which is to be cleaved (Chart 1).[2b] The stereoselectivity (*E* isomer formation, transoid transition state) of the ring opening is also determined by steric repulsions between the α-phenylsulfonyl substituent and the ring in the cisoid versus transoid transition state (Chart 1).[2b,11b] Nevertheless, the α-sulfonylcyclopropylcarbinyl radical ring opening remains efficient and may be used as a mechanistic tool in SET process studies involving α-sulfonylcarbanion species.

Note added in proof: To illustrate an application of this radical clock **1**, we have run the reaction with CCl_4 in a *t*-BuOK−*t*-BuOH medium. The dichlorosulfone **6** was isolated in 80% yield, showing that if electron transfer to give the α-sulfonyl radical is involved, the subsequent intermolecular reaction of the radical is faster than ring fission.

Conclusions

These preliminary results open the way to a new radical-probe family designed for the study of carbanions possibly involved in SET reactions. There is potential to trap intermediates of very short lifetime, and the system is readily tunable with substituents in order to increase the efficiency of this kind of radical probe. The comparative stabilization of the carbanion by substituents present on the cyclopropyl group has to be kept in mind.

Experimental Section

Cyclopropylmethyl Phenyl Sulfone 1. Sulfide **2** (2.10 g 0.0128 mol) was dissolved in acetic acid (39 mL). This solution was heated to 60 °C, and then hydrogen peroxide was added dropwise (8.3 mL, 0.085 mol of a 30% solution in water). The mixture was kept at 100 °C for 1 h, and after being cooled to room temperature, the solution was diluted with water and extracted with three portions of CH_2Cl_2. The combined organic extracts were washed with $Na_2S_2O_5$, saturated aqueous $NaHCO_3$ (three times), and water. Drying over Na_2SO_4 was followed by evaporation. The crude product was flash chromatographed on silica gel (elution: 10%, 20%, 30%, and 40% ethyl acetate in cyclohexane) to yield sulfone **1** (1.64 g, 65% yield) as a transparent oil. ^{1}H NMR: 7.49−7.94 (m, 5H), 2.99 (d, J = 7 Hz, 2H), 0.97 (m, 1H), 0.52 (m, 2H), 0.09 (m, 2H). IR (cm^{-1}): 1148 (SO_2), 1303 (SO_2). Anal. Calcd for $C_{10}H_{12}SO_2$: C, 61.22; H, 6.12; S, 16.32. Found: C, 60.94; H, 6.10; S, 16.57.

α-Methylcyclopropylmethyl Phenyl Sulfone (4). *N*-Chlorosuccinimide (1.37 g, 0.01 mol) was added to a solution of sulfide **1** (1.67 g, 0.01 mol) in CCl_4 (33 mL). After being stirred at room temperature for 4.5 h, the solution was filtered and the solvent was evaporated at room temperature. The oil obtained was dissolved in CH_2Cl_2 (120 mL), and 12.05 g of *m*-CPBA (48%, 3 equiv) was added at 0−5 °C. After being stirred for 1.5 h at 0 °C, the mixture was filtered. The filtrate was washed with 10% aqueous $Na_2S_2O_5$, 10% aqueous K_2CO_3 (six times), and water. Drying over Na_2SO_4 was followed by evaporation, and a few drops of ethanol were added to the crude product. Chloro sulfone **4** crystallized on standing at −5 °C. The crystals were washed with EtOH at −20 °C, (0.39 g, 17% yield): mp = 57−58.4 °C; ^{1}H NMR 7.58 (m, 2H), 7.71 (m, 1H), 7.98 (m, 2H), 4.23 (d, J = 9.0, 1H), 1.37 (m, 1H), 0.60−0.90 (m, 3H), 0.44 (m, 1H); IR (cm^{-1}): 1320 (SO_2)(s), 1150 (SO_2)(s). Anal. Calcd for $C_{10}H_{11}ClSO_2$:C, 52.06; H, 4.77; Cl, 15.40; S, 13.88. Found: C, 52.21; H, 4.85; Cl, 15.25; S, 13.96.

Reductions of Chlorosulfone 4 with Bu_3SnH. Formation of 1-(Phenylsulfonyl)-1-butene (5). Chlorosulfone **4** (0.093 g 0.4 mmol) and a few crystals of AIBN were dissolved in degassed THF (4 mL) under an argon atmosphere (a slight positive pressure of argon was maintained and additions were performed by syringe). At reflux, Bu_3SnH (0.15 mL, 1.4 equiv) was added. The mixture was refluxed for 21 h, and after the solvent was removed, the residue was dissolved in CH_3CN (15 mL). The solution was washed three times with hexane and evaporated to yield the crude product (99 mg). The ratio **5**/**2** = 95/5 was determined by ^{1}H NMR. Flash chromatography on silica gel (elution with 20% ethyl acetate in cyclohexane) afforded the ring-opened reduction product **5** (*E* isomer, 0.055 g, 70% yield) as an oil. Other reductions were performed at 80 °C for 1.5 h in refluxing cyclohexane $[Bu_3SnH]_0$ = 0.16 M (5 equiv) and 0.27 M (8.4 equiv) when the ratio of **5**/**2** was 92/8. In refluxing benzene, same results were obtained: for $[Bu_3SnH]_0$ = 0.16 M (5 equiv) the ratio of **5**/**2** was 94/6.[14]

Note Added in Proof. The Radical Clock in Halogenation. Sulfone **1** (0.12 g, 0.6 mmol), finely ground KOH (0.279 g), *t*-BuOH (2.6 mL), and CCl_4 (2.6 mL) were stirred for 113 h at 25 °C. Additional CCl_4 (1 mL) and KOH (0.17 g and 0.34 g) were added after 17 h and 96 h, respectively. Addition of water and extraction (CH_2Cl_2) gave a crude product whose ^{1}H NMR spectrum showed no vinylic protons. Flash chromatography (elution: cyclohexane then 10% ethyl acetate in cyclohexane) gave halosulfone **6** (80%): mp 36−37.5 °C; ^{1}H NMR 8.08 (m, 2H), 7.74 (tt, J = 7.5 and 1.7 Hz, 1H), 7.59 (m, 2H), 1.94 (m, 1H), 0.82 (m, 4H). Anal. Calcd for $C_{10}H_{10}Cl_2SO_2$: C, 45.45; H, 3.79; Cl, 26.52; S, 12.12. Found: C, 45.46; H, 3.64; Cl, 26.70; S, 12.33.

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