Pummerer fragmentation *vs.* Pummerer rearrangement: a mechanistic analysis†

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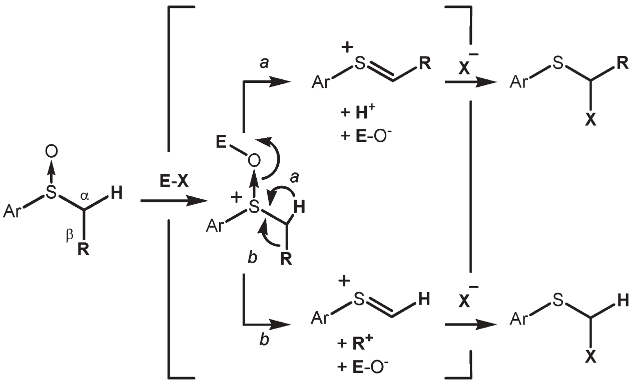
Depending upon the nature of the substituent at the β-position of the sulfoxide moiety, a Pummerer reaction can be oriented "at will" towards C_α–H (rearrangement) or C_α–C_β (fragmentation) bond cleavage.

The Pummerer reaction, which is the reaction of alkylsulfoxides with electrophilic reagents, has been extensively studied since its discovery in 1909.[1] Numerous synthetic applications have been developed as *in situ*-generated thionium ion intermediates can be trapped by a variety of nucleophiles[2] either intramolecularly (cyclization reactions) or intermolecularly.[3,4] Stereoselective reactions,[5] cascade processes,[6] as well as additive, vinylogous or aromatic Pummerer reactions,[7] have extended further the scope of its applications. Unusual Pummerer rearrangements, including "interrupted" Pummerer reactions, have also been reported,[8] as well as novel experimental conditions (fluorous or solid phase)[9] in their implementation.

Technically, the Pummerer reaction is most often realized by the addition of a stoichiometric amount of strong acid or anhydride to an alkylsulfoxide. The reaction is then thought to proceed by protonation or esterification of the oxygen atom of the sulfoxide to generate a sulfonium intermediate. Subsequent cleavage of the S–O and C_α–H bonds results in the release of a proton and the formation of a thionium moiety,[10] which is trapped by the counterpart of the electrophilic reagent or by any other (better) nucleophile present in the reaction medium. This Pummerer rearrangement affords α-substituted sulfides in generally good yields (Scheme 1, route a).

Recently, we reported a mechanistic alternative to this usual Pummerer rearrangement in the context of the resolution of chiral cationic dyes of type 1^+ (Fig. 1, *P*-enantiomer).[11] The single enantiomers of this [4]helicenium ion were isolated through a Pummerer fragmentation of diastereomerically pure sulfoxides that released the enantiopure cation 1^+ by C_α–C_β bond rupture instead of the usual C_α–H bond cleavage (Scheme 1, route b over route a, $R^+ = 1^+$).

To our knowledge, this was the first example of such a Pummerer fragmentation pathway, and hence came the question of the origin of this mechanistic "switch"; the driving force possibly being the stronger electrofugal character of carbenium 1^+ *vs.* H^+. In other words, we wondered whether the high chemical stability of cation 1^+—translated in quantitative terms into a highly positive pK_{R+} value ($\geqslant 19$)[12]—is the driving force for the unusual fragmentation. Herein, we report that this is indeed the case; the Pummerer reaction being oriented "at will" towards C_α–H or C_α–C_β bond cleavage through careful selection of the β-carbon substituent.



Scheme 1 Mechanistic rationalization of the Pummerer (a) rearrangement and (b) fragmentation pathways. (E–X: reactive electrophile).

In the literature, there are relatively few examples of elimination reactions using isolable carbenium ions as electrofugal groups;[13,14] the nature of these carbenium ions being relatively stable carbocations of, for instance, tropylium nature ($pK_{R+} = 4.75$).[15,16] As mentioned, cation 1^+ is more stable than the tropylium ion by several orders of magnitude. As such, 1^+ should depart readily without the two electrons of the C_α–C_β bond as soon as a positive

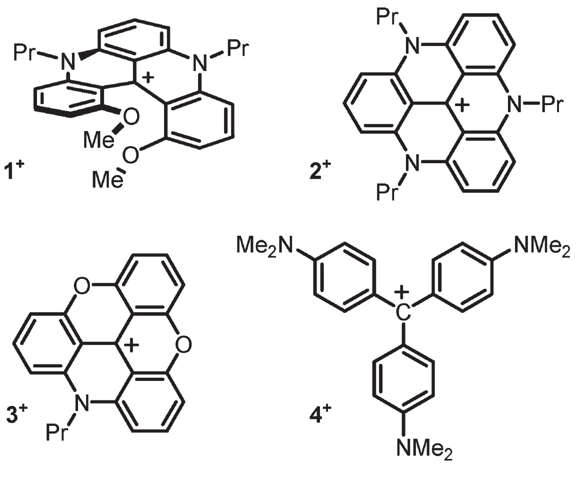


Fig. 1 Carbenium ions 1^+ ($pK_{R+} \sim 19$, *P*-enantiomer depicted), 2^+ ($pK_{R+} \sim 23.7$), 3^+ ($pK_{R+} \sim 14.5$) and crystal violet 4^+ ($pK_{R+} \sim 9.4$).

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† Electronic supplementary information (ESI) available: Spectral data for **5**, **6**, **7**, **8** and **10**. See DOI: 10.1039/b605187a

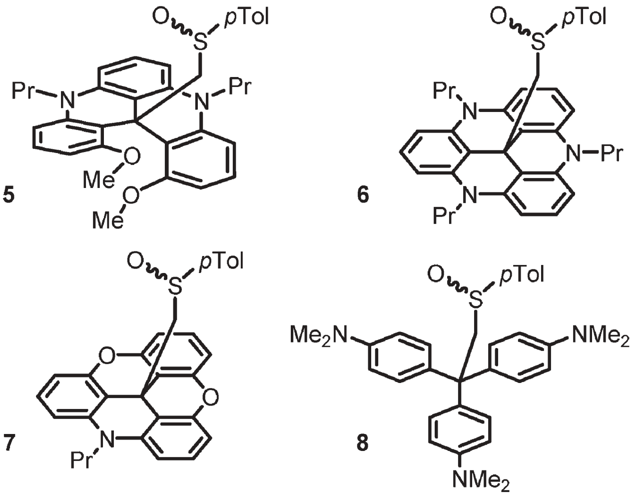

Fig. 2 Sulfoxides **5**, **6**, **7** and **8** derived from cations $\mathbf{1}^+$, $\mathbf{2}^+$, $\mathbf{3}^+$ and $\mathbf{4}^+$, respectively.

charge develops on the neighboring sulfur atom. Any reduction in carbenium ion stability ought to reduce the electrofugality of the moiety[17] and favor the classical rearrangement pathway. On the contrary, sulfoxides made from carbenium ions more stable than $\mathbf{1}^+$ should also cleave exclusively by C_α–C_β bond fragmentation. To validate this hypothesis, carbenium ions of both lower and higher chemical stability than $\mathbf{1}^+$ were selected ($9.4 \leqslant pK_{R+} \leqslant 23.7$) and treated with the carbanion of racemic methyl-*para*-tolylsulfoxide. The resulting sulfoxides **5**, **6**, **7** and **8**, derived from $\mathbf{1}^+$ ($pK_{R+} \sim 19$), $\mathbf{2}^+$ ($pK_{R+} \sim 23.7$), $\mathbf{3}^+$ ($pK_{R+} \sim 14.5$) and crystal violet $\mathbf{4}^+$ (pK_{R+} 9.4), respectively, are reported in Fig. 2.

Traditional reaction conditions (TFAA,[18] CH_2Cl_2) were then chosen to promote the Pummerer rearrangement of these derivatives. Care was first taken to reproduce the chemistry reported previously for the enantio- and diastereomerically pure analogues with racemic **5** (*rac*-**5**, 1.5 : 1 mixture of diastereomers).[11] Treatment of *rac*-**5** with TFAA (1.1 equiv., 20 °C) resulted in the immediate appearance of a dark green color, indicative of the presence of $\mathbf{1}^+$. After 20 min, the crude mixture was concentrated *in vacuo* and analyzed by ^{1}H and ^{19}F NMR spectroscopy, revealing only two products: salt $[\mathbf{1}^+][CF_3CO_2^-]$, isolated almost quantitatively after chromatography (SiO_2, CH_2Cl_2/MeOH = 97 : 3, 96%), and *para*-tolylthiomethyl 2,2,2-trifluoroacetate (**9**) (Fig. 3).[19] This compound resulted from a reaction of the thionium ion with the trifluoroacetate anion.

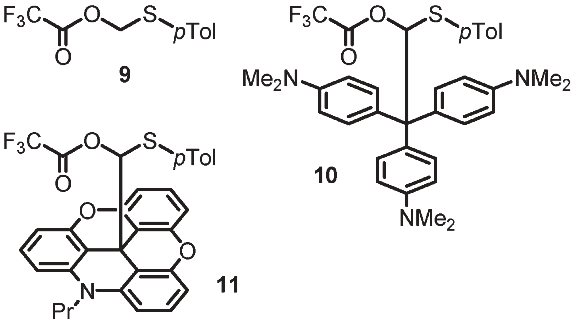

Fig. 3 Trifluoroacetate sulfide derivatives from the Pummerer reactions.

With this result in-hand, the reaction of **6** was considered. As expected, the treatment of **6** with TFAA under analogous conditions yielded salt $[\mathbf{2}^+][CF_3CO_2^-]$ (98% isolated yield) and **9** exclusively; this confirming our mechanistic supposition that a highly stable carbenium ion is indeed a more electrofugal group than H^+.

However, definite validation of our hypothesis was achieved only when the Pummerer reactions of compounds **7** and **8** were studied. In the case of **8**, after treatment with TFAA, no trace of crystal violet $\mathbf{4}^+$ was observed in the UV or ^{1}H NMR spectra of the crude mixture. Purification by chromatography (basic Al_2O_3, CH_2Cl_2/MeOH = 97 : 3) afforded trifluoroacetate-sulfide derivative **10** (Fig. 3) as the major product.[20] The formation of this adduct is consistent with the Pummerer rearrangement pathway (Scheme 1, route a); the lower chemical stability of crystal violet $\mathbf{4}^+$ (pK_{R+} 9.4) rendering this moiety an unlikely leaving group for a fragmentation.

Finally, compound **7** was treated under Pummerer reaction conditions. An immediate red color was observed upon the addition of TFAA. ^{1}H NMR analysis of the crude products revealed a rather complex mixture containing, along with minor unidentified derivatives,[21] both cation $\mathbf{3}^+$ and α-trifluoroacetoxymethyl sulfide **11** (Fig. 3) as products. This observation indicates that both fragmentation and rearrangement pathways are operative for the Pummerer reaction of **7**.

Compound **11** was prone to decomposition and, unlike **10**, the isolation of this moiety was not feasible by chromatography. If one considers that the amount (%) of cation $\mathbf{3}^+$ recovered at the end of the reaction is indicative of the percentage of fragmentation,[22] then the isolation of salt $[\mathbf{3}^+][CF_3CO_2^-]$ by chromatography (basic Al_2O_3, CH_2Cl_2/MeOH = 97 : 3) in 48% yield indicates that the Pummerer rearrangement and fragmentation reactions occur with essentially equal probability. The reaction of sulfoxide **7** is thus indicative of the "turning point" between the two elimination routes—a pK_{R+} value of 14.5 being the requisite for a "fair" competition between H^+ (rearrangement) and R^+ (fragmentation) electrofugal groups.

In conclusion, experimental data indicate that the Pummerer reaction can be oriented "at will" towards two different chemical pathways through the careful selection of the β-carbon substituent—moeties leading to carbocations of pK_{R+} values higher than 14.5 promote Pummerer fragmentation reactions (C_α–C_β bond rupture), whereas the others ($pK_{R+} < 14.5$) lead to the usual Pummerer rearrangement.

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22 This is essentially the case with compounds **5** and **6**, from which salts [$\mathbf{1}^+$][$CF_3CO_2^-$] and [$\mathbf{2}^+$][$CF_3CO_2^-$] were isolated with 96 and 98% yield, respectively.