

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

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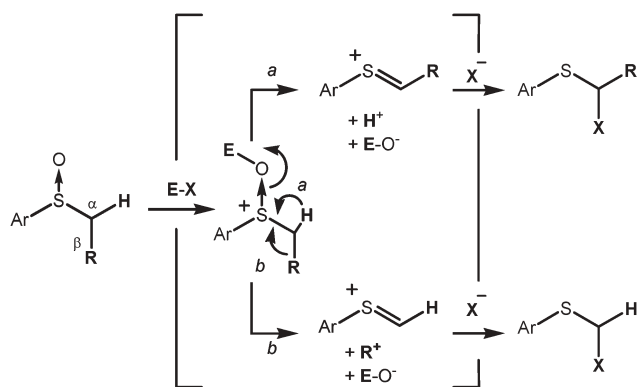
Depending upon the nature of the substituent at the  $\beta$ -position of the sulfoxide moiety, a Pummerer reaction can be oriented “at will” towards  $C_{\alpha}$ -H (rearrangement) or  $C_{\alpha}$ - $C_{\beta}$  (fragmentation) bond cleavage.

The Pummerer reaction, which is the reaction of alkylsulfoxides with electrophilic reagents, has been extensively studied since its discovery in 1909.<sup>1</sup> Numerous synthetic applications have been developed as *in situ*-generated thionium ion intermediates can be trapped by a variety of nucleophiles<sup>2</sup> either intramolecularly (cyclization reactions) or intermolecularly.<sup>3,4</sup> Stereoselective reactions,<sup>5</sup> cascade processes,<sup>6</sup> as well as additive, vinylogous or aromatic Pummerer reactions,<sup>7</sup> have extended further the scope of its applications. Unusual Pummerer rearrangements, including “interrupted” Pummerer reactions, have also been reported,<sup>8</sup> as well as novel experimental conditions (fluorous or solid phase)<sup>9</sup> 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  $C_{\alpha}$ -H bonds results in the release of a proton and the formation of a thionium moiety,<sup>10</sup> 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  $\alpha$ -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).<sup>11</sup> The single enantiomers of this [4]helicinium ion were isolated through a Pummerer fragmentation of diastereomerically pure sulfoxides that released the enantiopure cation  $1^+$  by  $C_{\alpha}$ - $C_{\beta}$  bond rupture instead of the usual  $C_{\alpha}$ -H bond cleavage (Scheme 1, route b over route a,  $R^+ = 1^+$ ).

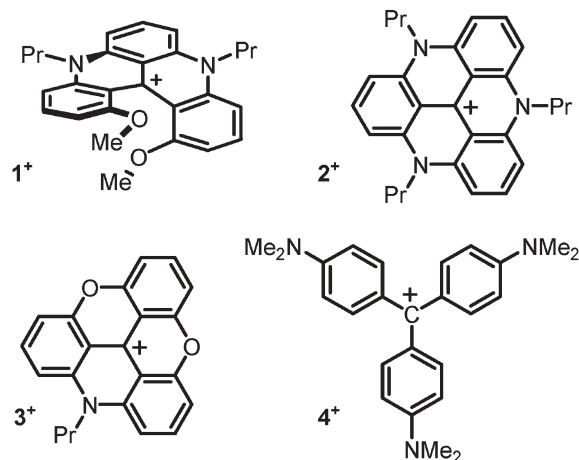
To our knowledge, this was the first example of such a Pummerer fragmentation pathway, and hence came the question of the origin of this mechanistic “switch”; the driving force possibly being the stronger electrofugal character of carbenium  $1^+$  vs.  $H^+$ . In other words, we wondered whether the high chemical stability of cation  $1^+$ —translated in quantitative terms into a



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

highly positive  $pK_{R^+}$  value ( $\geq 19$ )<sup>12</sup>—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  $C_{\alpha}$ -H or  $C_{\alpha}$ - $C_{\beta}$  bond cleavage through careful selection of the  $\beta$ -carbon substituent.

In the literature, there are relatively few examples of elimination reactions using isolable carbenium ions as electrofugal groups,<sup>13,14</sup> the nature of these carbenium ions being relatively stable carbocations of, for instance, tropylium nature ( $pK_{R^+} = 4.75$ ).<sup>15,16</sup> 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  $C_{\alpha}$ - $C_{\beta}$  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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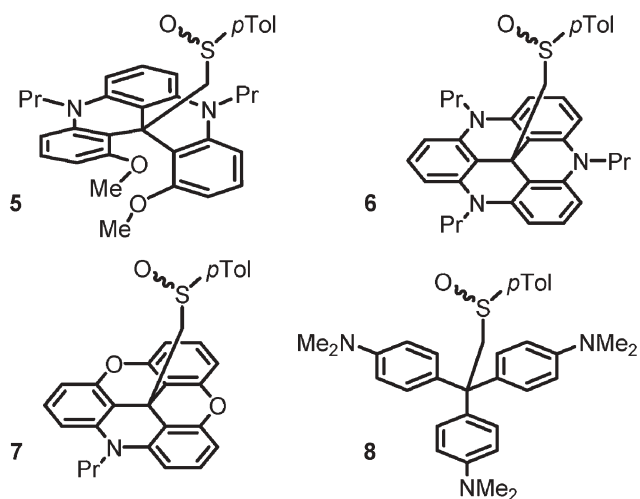


Fig. 2 Sulfoxides **5**, **6**, **7** and **8** derived from cations  $1^+$ ,  $2^+$ ,  $3^+$  and  $4^+$ , respectively.

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

Traditional reaction conditions (TFAA,<sup>18</sup>  $\text{CH}_2\text{Cl}_2$ ) 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).<sup>11</sup> 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  $1^+$ . After 20 min, the crude mixture was concentrated *in vacuo* and analyzed by  $^1\text{H}$  and  $^{19}\text{F}$  NMR spectroscopy, revealing only two products: salt  $[1^+][\text{CF}_3\text{CO}_2^-]$ , isolated almost quantitatively after chromatography ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2/\text{MeOH} = 97 : 3$ , 96%), and *para*-tolylthiomethyl 2,2,2-trifluoroacetate (**9**) (Fig. 3).<sup>19</sup> This compound resulted from a reaction of the thionium ion with the trifluoroacetate anion.

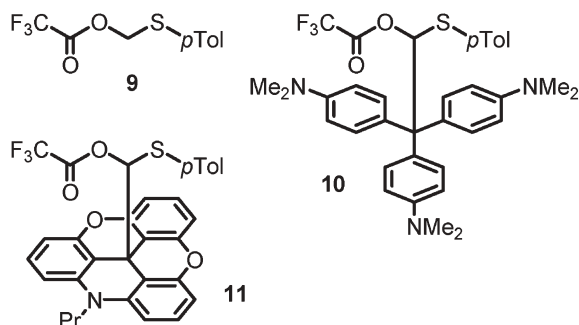


Fig. 3 Trifluoroacetate sulfide derivatives from the Pummerer reactions.

With this result in-hand, the reaction of **6** was considered. As expected, the treatment of **6** with TFAA under analogous conditions yielded salt  $[2^+][\text{CF}_3\text{CO}_2^-]$  (98% isolated yield) and **9** exclusively; this confirming our mechanistic supposition that a highly stable carbenium ion is indeed a more electrofugal group than  $\text{H}^+$ .

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  $4^+$  was observed in the UV or  $^1\text{H}$  NMR spectra of the crude mixture. Purification by chromatography (basic  $\text{Al}_2\text{O}_3$ ,  $\text{CH}_2\text{Cl}_2/\text{MeOH} = 97 : 3$ ) afforded trifluoroacetate-sulfide derivative **10** (Fig. 3) as the major product.<sup>20</sup> The formation of this adduct is consistent with the Pummerer rearrangement pathway (Scheme 1, route a); the lower chemical stability of crystal violet  $4^+$  ( $pK_{R^+} 9.4$ ) 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.  $^1\text{H}$  NMR analysis of the crude products revealed a rather complex mixture containing, along with minor unidentified derivatives,<sup>21</sup> both cation  $3^+$  and  $\alpha$ -trifluoroacetoxy-methyl 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  $3^+$  recovered at the end of the reaction is indicative of the percentage of fragmentation,<sup>22</sup> then the isolation of salt  $[3^+][\text{CF}_3\text{CO}_2^-]$  by chromatography (basic  $\text{Al}_2\text{O}_3$ ,  $\text{CH}_2\text{Cl}_2/\text{MeOH} = 97 : 3$ ) 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  $\text{H}^+$  (rearrangement) and  $\text{R}^+$  (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  $\beta$ -carbon substituent—moieties leading to carbocations of  $pK_{R^+}$  values higher than 14.5 promote Pummerer fragmentation reactions ( $C_\alpha$ – $C_\beta$  bond rupture), whereas the others ( $pK_{R^+} < 14.5$ ) lead to the usual Pummerer rearrangement.

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  - 18 TFAA: Trifluoroacetic anhydride.
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  - 20 This compound is prone to decomposition and could be isolated only in 59% yield.
  - 21 The use of trapping agents for cationic intermediates such as hydride transfer reagents (e.g. Et<sub>3</sub>SiH) or electron-rich aromatic moieties (e.g. mesitylene or indole) did not allow “cleaner” crude mixtures.
  - 22 This is essentially the case with compounds **5** and **6**, from which salts [1<sup>+</sup>][CF<sub>3</sub>CO<sub>2</sub><sup>-</sup>] and [2<sup>+</sup>][CF<sub>3</sub>CO<sub>2</sub><sup>-</sup>] were isolated with 96 and 98% yield, respectively.