Oxygen–Carbon β-Bond Effects in Radical Reactions

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The 'β-oxygen effect' can be either activating or deactivating according to the type of radical reaction involved.

The well known Barton and McCombie deoxygenation procedure for secondary alcohols involving tributyltin hydride reduction of the corresponding thiocarbonyl derivatives[1] is a widely used reaction in organic synthesis.[2] The rate of both this reaction, and the closely related radical deamination of isonitriles, was found to be markedly accelerated by the presence of β-oxygen atoms,[3] and this phenomenon has subsequently become known as the β-oxygen effect.

It was orginally suggested[3,4] that β-bonded oxygen stabilises the intermediate carbon-centred radical. However later work by Beckwith and Brumby[5] on hydrogen-atom abstraction from 1,2-dimethoxyethane by *tert*-butoxyl radicals, concluded that the β-oxygen substituent has only a small influence on the rate of formation of the (secondary) carbon-centred radical. More recently, Beckwith[6] has suggested that the presence of a β-oxygen substituent has little effect on the ease of formation and, by implication, on the stability of a carbon-centred radical. Both Beckwith[6] and Motherwell and Crich[2] have concluded that a convincing explanation of the β-oxygen effect has yet to be provided.

Recently, we have carried out an extensive study of hydrogen-atom abstraction from acyclic[7] and cyclic[8] ethers by *tert*-butoxyl radicals using the aminoxyl (nitroxide) radical trapping technique.[9] From this and related work, it has become apparent that, in general, a β-oxygen atom decreases the reactivity towards hydrogen-atom abstraction by *tert*-butoxyl radicals. For example, in the case of 1,2-dimethoxyethane, we have found that the rate of hydrogen abstraction of a methylene hydrogen (*i.e.* the methylene carbon is β- to one oxygen atom) is only half that found for abstraction of a methylene hydrogen in diethyl ether. With dibutyl ether, only abstraction from the α and γ-positions (ratio 9:1) was observed. Products derived from abstraction β- to the oxygen or from the methyl groups were below the level of detection (approximately 1%). Relative reactivities towards hydrogen abstraction (versus cyclohexane, and on a per equivalent hydrogen basis) for these and related ethers are given in Fig. 1. Analogous results have been reported[10] for *n*-butanol, where the relative reactivities of hydrogen atoms on carbons α-, β-, γ- and δ- to the hydroxyl group were 65:2.8:6.3:1.1 respectively.

It is clear then, from these examples, that the β-oxygen effect for hydrogen-atom abstraction by *tert*-butoxyl radicals is deactivating, in sharp contrast to the (activating) β-oxygen effect observed for stannane reductions.

We believe that polar effects[11] are responsible for this apparent contradiction. Thus, in the transition state (Fig. 2) for attack by the *tert*-butoxyl radical (an electrophilic species),[12] the carbon atom would possess a fractional positive charge, which would be destabilised by the inductive effect of the β-oxygen substituent.

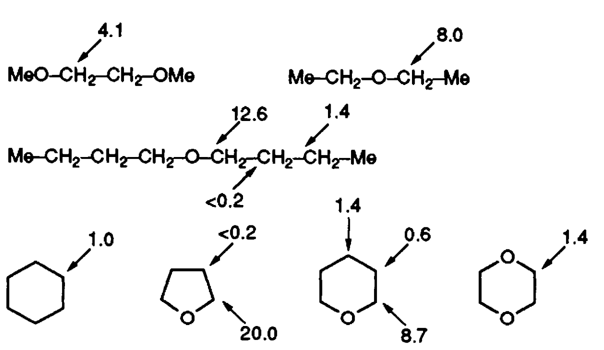


Fig. 1 Relative rates of methylene hydrogen abstraction by *tert*-butoxyl radicals at 60 °C

The generally accepted mechanism[13] for the Barton–McCombie reaction involves (reversible) attack by the tributylstannyl radical on sulphur to give a carbon-centred radical intermediate which then undergoes (rate-determining) β-scission, followed by hydrogen-transfer from tributyltin hydride to the resulting alkyl radical etc. (Scheme 1). We suggest that the transition state (Fig. 3) for the β-scission reaction is also dipolar, but as the 'attacking' radical (*i.e.* the carbon-centred radical) is nucleophilic, the polarity is opposite to that in Fig. 2 (where the attacking radical was electrophilic). By analogy with the arguments used by Beckwith[14] for β-fission, the formation of the transition state (Fig. 3) involves interaction between the semi-occupied orbital and the σ* oribtal of the bond undergoing cleavage. This results in the development of a fractional positive charge at the original radical centre (and presumably stabilisation by the S–SnBu$_3$ and X groups) and the development of a fractional negative charge (relative to the starting material) at the incipient radical centre. Any increase in electron density at this centre (*i.e.* the alkyl carbon) would be stabilised by the inductive effect of a β-oxygen substituent.

These arguments should apply irrespective of whether the respective transition states are early (as is probably the case for hydrogen abstraction by *tert*-butoxyl radicals[15]) or late (as is probably the case for the β-scission reaction, so that product radical stability will also contribute significantly to the rate).

Analogous (dipolar) transition states, involving attack by the (nucleophilic) tributylstannyl radical, presumably occur in the deamination of isonitriles and in the formation of glycosyl radicals from glycosyl halides.

The explanation of the β-oxygen effect offered here is

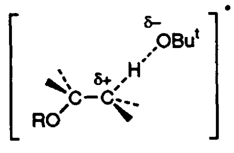
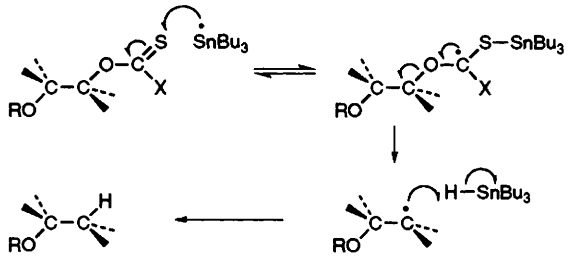


Fig. 2



Scheme 1

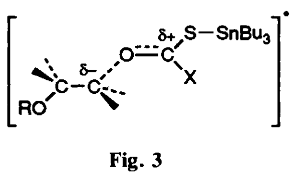


Fig. 3

consistent with the increasing recognition of the importance of polar effects in radical reactions.[11,16–18]

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