The Oxide Anion Accelerated Retro-Diels–Alder Reaction

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Abstract: The widespread application of the retro-Diels–Alder reaction in synthesis has been hampered by the high temperatures usually required to effect cycloreversion. The discovery of the anionic oxy-Cope reaction was followed by predictions that the accelerating effect of the oxide anion should also be observed with other pericyclic reactions. Recently, such predictions have been confirmed for the retro-Diels–Alder reaction, which often proceeds rapidly at room temperature by oxide anion rate acceleration. Such mild retro-Diels–Alder reactions have now been employed in the synthesis of a range of molecular targets, including temperature-sensitive enediynes.

Keywords: Diels–Alder reactions · pericyclic reactions · retro reactions · oxide anion · synthetic methods

Introduction

The Diels–Alder [4+2] cycloaddition reaction has proven to be one of the most versatile strategies for six-membered carbocycle synthesis, allowing the ready union of diene and dienophile components in a highly predictable stereo- and regiochemical manner. Although countless synthetic applications of the Diels–Alder reaction have been described, the corresponding retrograde process has attracted much less attention.[1] Although the retro-Diels–Alder reaction could also have many potential applications in synthetic organic chemistry, particularly as a method for masking an alkene moiety, its use has generally been hampered by the high temperatures required to effect cycloreversion.[1] We recently disclosed a novel method for the synthesis of sensitive cyclic enediynes,[2] which utilised a retro-Diels–Alder reaction (rDA) to generate the central "ene" moiety (vide infra). The success of this approach stemmed from the ability to effect cycloreversion at room temperature through the utilisation of an oxide anion accelerating effect. In the present article, the background to the oxide anion accelerated retro-Diels–Alder reaction, and prospects for the future of this process, are discussed.

The classic thermally induced Diels–Alder coupling of an electron-deficient dienophile and a conjugated diene is known to proceed through a concerted pericyclic mechanism, and can be represented schematically by the energy profile depicted in Figure 1.[3] Clearly, cycloreversion of such a Diels–Alder adduct would not generally be feasible since the reaction would be thermodynamically "up hill" and have a high activation energy (Figure 1). Nevertheless, one strategy by which these barriers have been overcome is through the use of flash vacuum pyrolysis.[1] In this technique elevated temperatures (e.g., 500–800 °C) are employed to surmount the high activation barrier, and the diene or dienophile component are separated in vacuo, thus driving the reaction to completion. Despite these rather extreme conditions, this procedure has found a number of useful applications in total synthesis.[1] Nevertheless, it is unlikely that complex or highly reactive molecules could withstand such treatment, and a more general and convenient strategy for effecting the retro-Diels–Alder reaction would evidently be preferred.

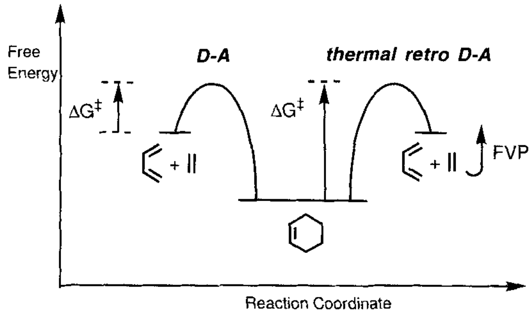

Figure 1. Schematic representation of thermal Diels–Alder and retro-Diels–Alder reactions (FVP: flash vacuum pyrolysis).

Discussion

Acceleration of Pericyclic Reactions by the Oxide Anion: In a landmark paper in 1975,[4] Evans and Golob reported that the oxy-Cope [3,3] sigmatropic rearrangement underwent a spectacular increase in rate (by factors of up to 10^{17}!) upon conversion of the alcohol to the potassium alkoxide (Scheme 1). In this

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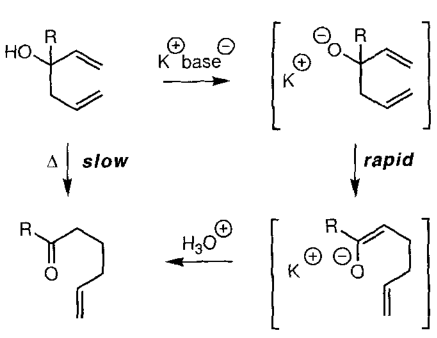
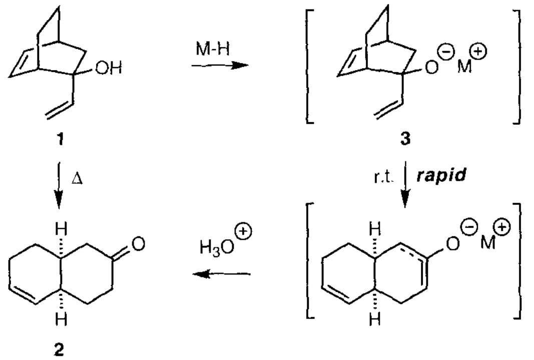


Scheme 1. Thermal and anionic oxy-Cope rearrangements.

initial study, the effect was exemplified with the rearrangement of the dienol **1** to the ketone **2** (Scheme 2), and it was shown that the magnitude of the rate acceleration was directly related to the degree of alkoxide–metal dissociation, with maximum accelerations obtained with a more "naked" anion.[4] Thus, under identical conditions (THF, reflux), the potassium alkoxide (**3**, M = K) rearranged at a much greater rate ($t_{1/2}$ = 1.4 min) than the sodium alkoxide ($t_{1/2}$ = 1.2 h), whereas the lithium and magnesium (M = MgBr) alkoxides proved to be stable. Moreover, it was found that the rate of the potassium alkoxide rearrangement could be further accelerated by addition of [18]crown-6 as a K^+ ionophore. Since 1975 the anionic oxy-Cope rearrangement has been widely used in total synthesis[5] owing to its predictable regio- and stereochemical outcome, and ability to proceed at ambient temperature (e.g., 20 °C), which allows many sensitive functional groups to be tolerated.



Scheme 2. Acceleration of the oxy-Cope rearrangement by alkoxide ion formation, as first demonstrated by Evans and Golob [4]. When M = K rate enhancements of up to 10^{17} are observed compared to the thermal process.

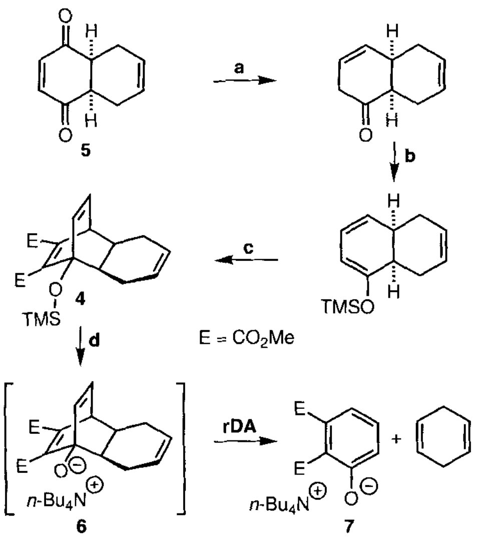
Importantly, the oxide anion effect is not restricted to the oxy-Cope rearrangement, and many other thermal pericyclic reactions, including [1,3] sigmatropic shifts[6] and vinylcyclopropane rearrangements,[7] have been found to be similarly accelerated. One can rationalise this oxide anion rate enhancement by considering the degree of conjugation of the substituent in the ground state relative to the transition state of the reaction. In the oxy-Cope setting, for example, the oxide anion is isolated in the ground state; however, in the transition state it can undergo a degree of delocalisation into the cycle of fully conjugated orbitals, which are present, by definition, in a pericyclic reaction. This stabilisation of the oxide anion in the transition state relative to the ground state leads to a decrease in the activation energy ($\Delta G^{\ddagger}$) and an increase in rate for the reaction. This effect should be more pronounced as the ground state increases in energy (i.e., when the oxide anion is more "naked"). The oxy-Cope rearrangement ultimately affords an enolate product that is more thermodynamically stable than the alkoxide precursor, and so the reaction is generally highly exothermic and irreversible. It is noteworthy that, although a weakening of the C–C bond adjacent to the oxide anion may facilitate the rearrangement,[8] the anionic oxy-Cope reaction has been shown to be a true pericyclic reaction, which occurs in a concerted manner.[9]

The assumption that the change in degree of delocalisation is the sole determinant of substituent influence on the reaction rate led Carpenter to develop, in 1978,[10] a simple model for predicting the effect of various substituents (including the oxide anion) on the rates of a range of thermal pericyclic reactions. Interestingly, Carpenter's model also suggested that the retro-Diels–Alder reaction would undergo rate acceleration by the appropriate incorporation of an oxide anion substituent. Thus, in the prototype retro-Diels–Alder reaction delineated in Scheme 3, the presence of an oxide anion at either positions 1 or 2 was predicted to increase the rate of cycloreversion, whilst its incorporation at position 3 was anticipated to cause a rate retardation. As detailed below, Carpenter's predictions have now been experimentally validated, and the oxide anion assisted retro-Diels–Alder reaction has emerged as a powerful reaction for use in organic synthesis.

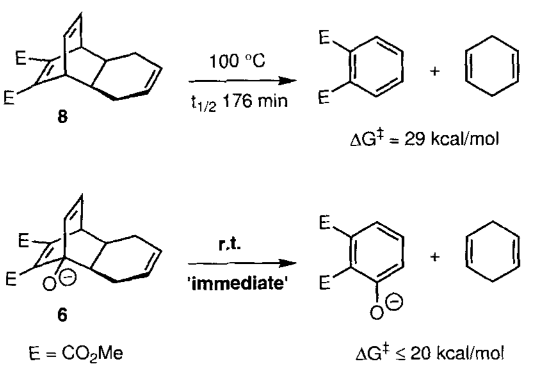
position	rate
1 & 2	Pol > Con > H
3	H > Con > Pol

Scheme 3. Carpenter's predictive model [10] for the effect of polar (Pol, e.g. oxide anion) and conjugating (Con, e.g. vinyl) groups on the rate of retro-Diels–Alder cycloreversion. Note that the polar classification describes both electron donor *and* electron acceptor substituents.

Oxide Anion Accelerated Retro-Diels–Alder Reactions: The first analysis of oxide-anion acceleration in a retro-Diels–Alder context was described by Papies and Grimme in 1980.[11, 12] The model compound **4** used in this study was prepared from **5** (the Diels–Alder adduct of *p*-benzoquinone and butadiene), through the sequence of transformations illustrated in Scheme 4. It was discovered that treatment of **4** with anhydrous tetra-*n*-butylammonium fluoride (TBAF) in THF at room temperature resulted in the immediate formation of a burgundy colour, consistent with rapid desilylation to **6** and subsequent retro-Diels–Alder reaction to form the 2,3-dicarbomethoxyphenolate ion **7**. In contrast, the parent diester **8** (Scheme 5), readily obtained by cycloaddition of 1,4,9,10-tetrahydronaphthalene and dimethylacetylene dicarboxylate, was only found to undergo sluggish cycloreversion at 100 °C ($t_{1/2}$ = 176 min). The dramatic oxide anion accelerating effect observed in this system (> 10^6) stems from the significant increase in conjugative stabilisation at-



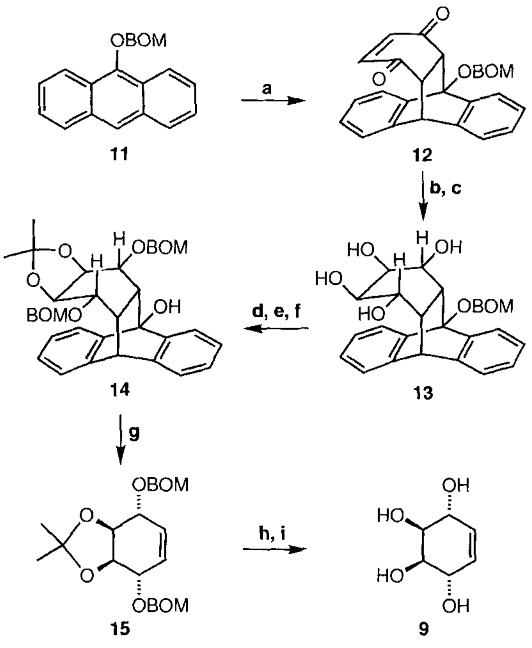
Scheme 4. Synthesis of **4** and oxide anion accelerated retro-Diels–Alder reaction of desilylation product **6**, as described by Papies and Grimme [11]. Reagents and conditions: a) $TsNHNH_2$, Na_2CO_3, HI; b) LDA, THF, TMSCl; c) $MeO_2CC{\equiv}CCO_2Me$, 25 °C; d) TBAF, THF, 25 °C. TBAF = tetra-*n*-butylammonium fluoride.



Scheme 5. Free energies of activation ($\Delta G^{\neq}$) for retro-Diels–Alder cycloreversion of adducts **8** and **6**, as calculated by Papies and Grimme [11].

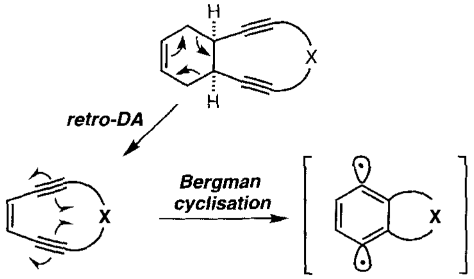
tained in transformation of the alcoholate ion of the precursor into the phenolate ion of the product "diene fragment".

An application of the oxide anion accelerated retro-Diels–Alder in total synthesis was provided by Knapp et al. in 1983.[13] In this study, a stereospecific synthesis of (±)-conduritol A (**9**) from *p*-benzoquinone (**10**) was achieved by using 9-[(benzyloxy)methoxy)]anthracene (**11**) (vide infra) as a protecting and directing group. Thus, Diels–Alder coupling of **10** with **11** gave the adduct **12** (Scheme 6) in which one double bond and one face of **10** were now protected from attack by reagents. Consequently, Luche reduction of **12** occurred from the top face to give the corresponding *syn*-diol, and dihydroxylation of this intermediate afforded **13** as a single (racemic) diastereoisomer. In preparation for the liberation of the masked double bond, **13** was then transformed into **14** by standard protecting group manipulations (Scheme 6). Treatment of **14** with potassium hydride in dioxane at 35 °C initiated the key oxide anion accelerated retro-Diels–Alder reaction, affording the desired alkene **15** in excellent yield (84%). Finally, deprotection of **15** afforded (±)-conduritol A (**9**) in 39% overall yield from **10** (Scheme 6).

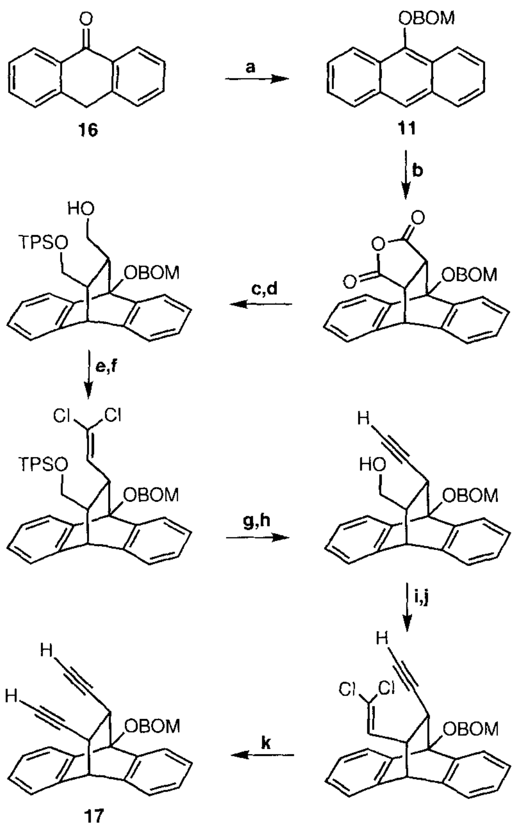


Scheme 6. Synthesis of (±)-conduritol A (**9**) by means of an accelerated retro-Diels–Alder approach [13]. Reagents and conditions: a) *p*-benzoquinone (**10**), toluene, 68 °C, 15 h, 92%; b) $NaBH_4$, $CeCl_3$, MeOH, toluene, −78 °C, 96%; c) OsO_4, NMO, acetone, H_2O; d) TFA, MeOH, 40 °C, 78% (2 steps); e) acetone, TFA, 65 °C; f) BOMCl, NaH, THF, 84% (2 steps); g) KH, dioxane, 35 °C, 12 h, 84%; h) Na, NH_3, ether, −78 °C; i) TFA, MeOH, 80% (2 steps). BOM = CH_2OCH_2Ph; NMO = 4-methylmorpholine *N*-oxide; TFA = trifluoroacetic acid.

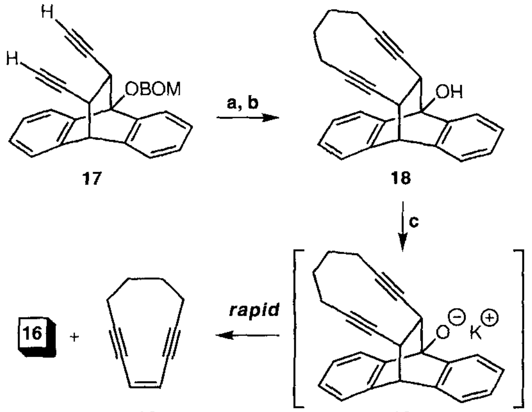
Our interest in the retro-Diels–Alder reaction arose from its potential as a method for the synthesis of enediynes from stable 1,5-diyne progenitors, as delineated in Scheme 7. Since the enediyne moiety is highly reactive and prone towards Bergman cycloaromatisation (Scheme 7), a prerequisite for the success of such a strategy is the ability to trigger the retro-Diels–Alder process when desired and for it to proceed at ambient temperature. The oxide anion accelerated retro-Diels–Alder reaction thus appeared ideal for our requirements, and we investigated the use of **11** as a platform for the generation of enediynes. The generation of **11** from anthrone (**16**), and its conversion to the 1,5-diyne **17** is illustrated in Scheme 8 and has been described in detail.[2] Since the two alkyne moieties in **17** are locked into a *syn* orientation, the intramolecular bisalkylation of the corresponding dialkynyl dianion proceeded cleanly to give the cyclic 1,5-diyne (52% yield), which was readily deprotected to give the alcohol **18** (Scheme 9). Although **18** proved to be highly stable



Scheme 7. General concept for the retro-Diels–Alder generation of enediynes [2] and their Bergman cycloaromatisation.



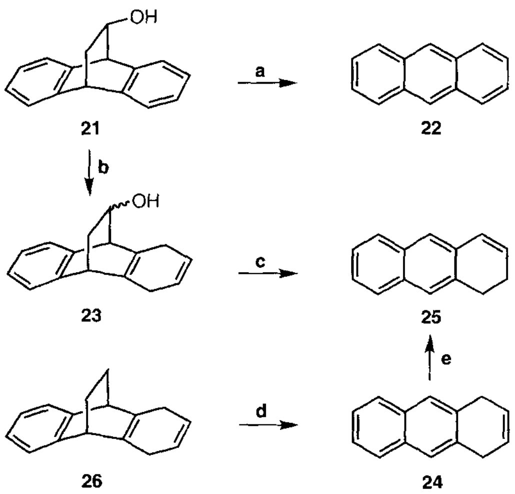
Scheme 8. Synthesis of **17** [2]. Reagents and conditions: a) 1.2 equiv NaH, THF, 0 °C, 45 min; 1.2 equiv BOMCl, 1.5 h, 85 %; b) 1.0 equiv maleic anhydride, PhH, reflux, 8 h, 100 %; c) 4.25 equiv $LiAlH_4$, THF, reflux, 12 h, 95 %; d) 1.0 equiv TPSCl, 2.0 equiv imidazole, 0 → 25 °C, 2.0 h, 63 % (+ 25 % regioisomer); e) 1.5 equiv NMO, 0.025 equiv TPAP, MeCN, 25 °C, 0.5 h, 95 %; f) 6 equiv CCl_4, 3 equiv $P(NMe_2)_3$, THF, −30 → 0 °C, 1.5 h, 83 %; g) 2.1 equiv *n*BuLi, THF, −78 → 0 °C, 0.5 h, 100 %; h) 10 equiv TBAF, THF, 25 °C, 2 h, 94 %; i) 1.5 equiv NMO, 0.05 equiv TPAP, CH_2Cl_2/MeCN (9:1), 25 °C, 15 min, 80 %; j) 6 equiv CCl_4, 3 equiv $P(NMe_2)_3$, THF, −30 °C, 15 min, 84 %; k) 3.2 equiv *n*BuLi, THF, −78 °C, 0.5 h, 45 %. TPS = tBuPh$_2$Si; TPAP = tetra-*n*-propylammonium perruthenate(VII).



Scheme 9. Synthesis of cyclic 1,5-diyne **18** and oxide anion accelerated retro-Diels–Alder reaction to form enediyne **20** [2]. Reagents and conditions: a) 2.3 equiv *n*BuLi, 4 equiv HMPA, THF, −78 °C, 0.5 h; 1.2 equiv $I(CH_2)_4I$, −78 → 25 °C, 12 h, 52 %; b) 10 % TFA in MeOH, reflux, 1 h, 94 %; c) KH, THF, 25 °C, 30 min, 90 %. HMPA = hexamethylphosphoric triamide.

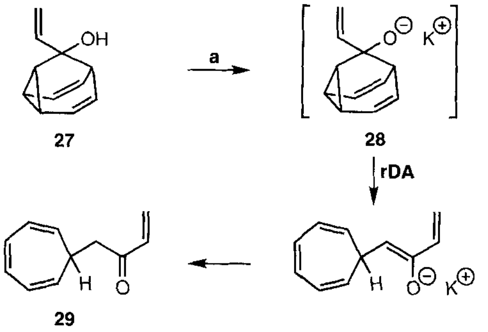
under neutral or acidic conditions, deprotonation to form the oxide anion **19** immediately initiated the desired cycloreversion. Thus, treatment of **19** with potassium hydride in THF at 25 °C (Scheme 9) resulted in rapid development of a deep orange colouration, consistent with the generation of the potassium salt of anthrone, and the clean generation of cyclodecenediyne **20**. Although **20** does undergo Bergman cycloaromatisation at ambient temperature ($t_{1/2}$ = *18 h at 37 °C*), it was stable enough to permit isolation and was secured in 90 % yield from **18**.[2] This methodology offers significant scope for the synthesis of new cyclic enediynes and structures of type **18** have the potential to be developed into novel enediyne prodrug systems. These opportunities are currently under investigation in our laboratories.

The above examples have demonstrated that dramatic increases in the rate of retro-Diels–Alder cycloreversions can be achieved by incorporating an oxide substituent at the terminus of the 4π component, that is, position 2 in the Carpenter model (Scheme 3). As predicted by this model, it is also reasonable that the rate of cycloreversion should be enhanced if the oxide anion substituent were connected to the 2π component (i.e., position 1, Scheme 3). Indeed, Rajanbabu et al.[14] have shown that 11-hydroxy-9,10-dihydro-9,10-ethanoanthracene (**21**) affords anthracene (**22**) in good yield (60 %) upon treatment with potassium hydride in THF/HMPA at room temperature (Scheme 10), albeit after a long reaction time (66 h). In contrast, the thermally induced retro-Diels–Alder reaction only proceeded at temperatures above 200 °C.[14] Interestingly, the 1,4-dihydro derivative **23**, readily prepared from **21** by Birch reduction (Scheme 10), underwent more facile debridging than **21** by deprotonation with KH (with or without added HMPA). In this system, mixtures of the 1,4-dihydro- (**24**) and 1,2-dihydroanthracene (**25**) products were generated depending on the reaction conditions, with prolonged reaction times leading almost exclusively to **25** (18 h, 69 % yield). It thus appeared that the initial product of the retro-Diels–Alder reaction (i.e. **24**) was undergoing isomerisation under the reaction conditions. This was confirmed by the independent synthesis of **24** through thermally induced cycloreversion of **26** and its isomerisation to **25** with KH in THF (Scheme 10).[14]

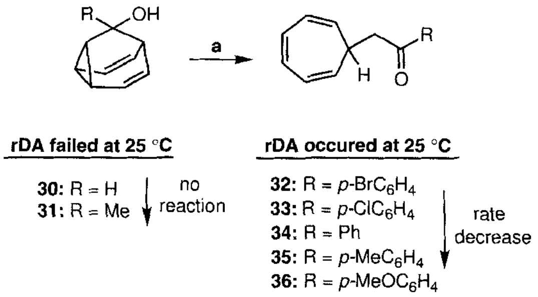


Scheme 10. Retro-Diels–Alder reactions of 9,10-dihydro-9,10-ethanoanthracenes [14]. Reagents and conditions: a) KH, THF, HMPA, 25 °C, 66 h, 60 %; b) Li, liq. NH_3, *t*BuOH, 59 %; c) KH, THF, 18 h, 25 °C, 69 %; d) Δ, 1,3,5-trichlorobenzene, 18 h, 28 %; e) KH, THF, 17 h, 25 °C, 71 %.

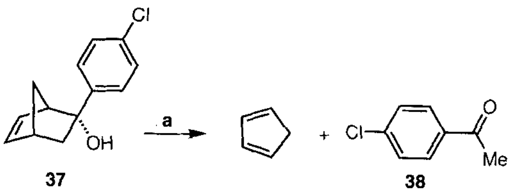
Rajanbabu et al. correlated the differing rates of cycloreversion of **21** and **23** with the greater resonance stabilisation energy of naphthalene over that of anthracene, and further suggested that cycloreversions could only occur if the 4π component were destined to be incorporated into an aromatic system.[14] However, Miyashi et al.[15] discovered that the 4π component need not be incorporated into an aromatic system if a group capable of conjugation is introduced at the centre bearing the oxide anion. Thus, conversion of the barbaralane **27** to the potassium alkoxide **28** (Scheme 11) gave rise to a facile retro-Diels–Alder reaction, affording the cycloheptatriene **29** (60% yield) upon protic workup. Replacement of the vinyl group by a hydrogen atom (**30**) or a methyl group (**31**) completely curtailed the cycloreversion process (Scheme 12) and rates for a range of aromatic substituents (**32**–**36**) indicated that the reaction was facilitated by electron-withdrawing conjugating groups (Scheme 12).



Scheme 11. Oxide anion accelerated retro-Diels–Alder reaction in a barbaralane system [15]. Reagents and conditions: a) KH, [18]crown-6, THF, 25 °C, 60%.



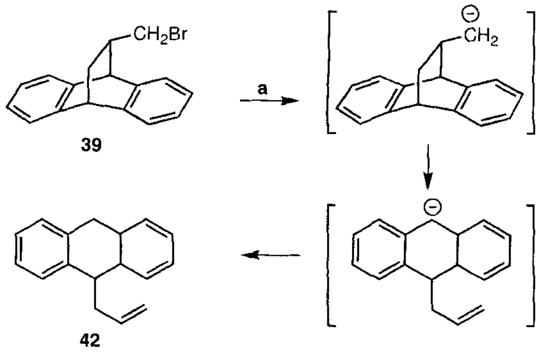
Scheme 12. Dependence of the rate on the nature of substituent R in retro-Diels–Alder reactions of barbaralane systems [15]. Reagents and conditions: a) KH, [18]crown-6, THF, 25 °C.



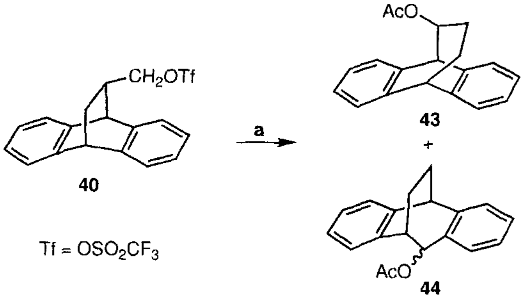
Scheme 13. Accelerated retro-Diels–Alder reaction in the norbornene system [14]. Reagents and conditions: a) KH, [18]crown-6, THF, 25 °C, 100%.

The rate acceleration in this system may be due to the vinyl and phenyl groups providing conjugative stabilisation of the partially anionic transition state. The generality of this effect was demonstrated by its application in the norborene system. Thus, although the parent system was inert towards potassium alkoxide induced cycloreversion,[16] the 2-aryl derivative **37** gave rise to quantitative generation of *p*-chloroacetophenone (**38**) under identical conditions (Scheme 13).

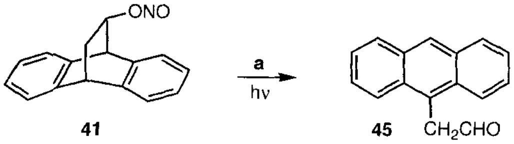
Although the discussion has so far focussed on an oxide anion as the accelerating substituent, Carpenter predicted that other anions, carbocations and possibly radicals might also be able to accelerate pericyclic reactions since all substituents should benefit from conjugative stabilisation in the transition state. To test this contention in the context of the retro-Diels–Alder reaction,[17] Rajanbabu et al. also prepared the bromide **39** (Scheme 14), the triflate **40** (Scheme 15), and the nitrite **41** (Scheme 16).[14] Unfortunately, the carbanion resulting from metal–halogen exchange of **39** did not undergo a retro-Diels–Alder reaction, but instead gave rise to single-bond cleavage leading to the dihydroanthracene **42** (Scheme 14).[18] The potential for carbocation acceleration was examined by solvolysis of the triflate **40**, but only the known Wagner–Meerwein rearrangement products **43** and **44** (Scheme 15) could be detected.[14] Finally, the potential for oxygen-centred radical rate acceleration was investigated by photolysis of the nitrite **41**,[14] but



Scheme 14. The carbanion derived from **39** undergoes a one-bond cleavage rather than a retro-Diels–Alder reaction [14]. Reagents and conditions: a) *n*BuLi, −78 °C, 10 min; AcOH, 31% (+69% unreacted **39**).



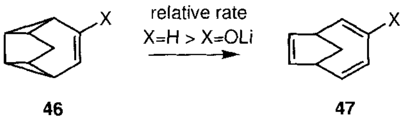
Scheme 15. Solvolysis of **40** leads to Wagner–Meerwein rather than retro-Diels–Alder products [14]. Reagents and conditions: a) AcOH, NaOAc, reflux.



Scheme 16. Generation of the oxygen-centred radical leads to a single-bond cleavage rather than a retro-Diels–Alder pathway [14]. Reagents and conditions: a) hv, benzene, 66 min, 23%.

the major product was the aldehyde **45** (Scheme 16), resulting from one-bond cleavage, and no traces of the anthracene expected from a retro-Diels–Alder pathway were observed. Although these results suggest that only an oxide anion substituent can be employed to initiate the retro-Diels–Alder reaction *in this system,* it by no means precludes the potential for other anions,[18] carbocations or indeed radicals to accelerate cycloreversion when alternative reaction pathways are not available.

Finally, the Carpenter model predicted that an oxide anion substituent at position 3 (Scheme 3) should actually *retard* the rate of cycloreversion. This has been supported by the observations of Miller and Dolce[19] who discovered that the rate of conversion of **46** to **47** is markedly slower with an oxide anion substituent (X = OLi) than in the parent hydrido (X = H) system (Scheme 17).



Scheme 17. An oxide anion *decelerated* retro-Diels–Alder reaction [19], consistent with the Carpenter prediction (Scheme 3).

Conclusions

The discovery of the anionic oxy-Cope reaction has prompted investigations into the accelerating effect of oxide anions on other pericyclic reactions. For example, the utility of the retro-Diels–Alder reaction in synthesis has traditionally been hampered by the high temperatures required to effect cycloreversion; the oxide anion accelerated variant often proceeds rapidly at room temperature. The generation of enediynes[20] by such a protocol demonstrates its potential in the synthesis of sensitive molecular targets, and the oxide anion accelerated retro-Diels–Alder reaction seems destined to find many further applications in the years ahead.

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[1] For a recent review, see: A. Ichihara, *Synthesis* **1987**, 207.

[2] M. E. Bunnage, K. C. Nicolaou, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1110.

[3] For a discussion of the mechanism of both the Diels–Alder reaction and its cycloreversion, see: J. Sauer, R. Sustmann, *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 779.

[4] D. A. Evans, A. M. Golob, *J. Am. Chem. Soc.* **1975**, *97*, 4765.

[5] For a review, see: L. A. Paquette, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 609.

[6] For example, see: R. W. Thies, E. P. Seitz, J. *Org. Chem.* **1978**, *43*, 1050.

[7] For example, see: J. P. Snyder, *J. Org. Chem.* **1980**, *45*, 1340.

[8] M. L. Steigerwald, W. A. Goddard III, D. A. Evans, *J. Am. Chem. Soc.* **1979**, *101*, 1994.

[9] D. A. Evans, J. V. Nelson, *J. Am. Chem. Soc.* **1980**, *102* , 774.

[10] B. K. Carpenter, *Tetrahedron* **1978**, *34*, 1877.

[11] O. Papies, W. Grimme, *Tetrahedron Lett.* **1980**, *21*, 2799.

[12] Although apparently unrecognised, the oxide anion acceleration of a retro-Diels–Alder reaction may have been witnessed over a decade in advance of the Grimme study, see: A. Oku, T. Kakihana, H. Hart, *J. Am. Chem. Soc.* **1967**, *89*, 4554.

[13] S. Knapp, R. M. Ornaf, K. E. Rodriques, *J. Am. Chem. Soc.* **1983**, *105*, 5494.

[14] T. V. RajanBabu, D. F. Eaton, T. Fukunaga, *J. Org. Chem.* **1983**, *48*, 652.

[15] T. Miyashi, A. Ahmed, T. Mukai, *J. Chem. Soc. Chem. Commun.* **1984**, 179.

[16] This system has been shown to undergo a formal retro-Diels–Alder reaction upon treatment with phenylmagnesium bromide, see: J. V. N. Vara Prasad, P. Iyer, C. N. Pillai, *J. Org. Chem.* **1982**, *47*, 1381. Since the corresponding potassium alkoxide does not cyclorevert (ref. [14]), the possibility that the reaction is not concerted seems likely.

[17] Experimental support for carbocation acceleration of the Cope rearrangement is available, see ref. [10].

[18] The acceleration of retro-Diels–Alder reactions by carbanion generation has been demonstrated in other systems, see: E. S. Bowman, G. B. Hughes, J. B. Grutzner, *J. Am. Chem. Soc.* **1976**, *98*, 8273; W. Neukam, W. Grimme, *Tetrahedron Lett.* **1978**, *25*, 2201.

[19] R. D. Miller, D. L. Dolce, *Tetrahedron Lett.* **1977**, *38*, 3329.

[20] For selected reviews, see: a) K. C. Nicolaou, W.-M. Dai, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1387; b) K. C. Nicolaou, A. L. Smith, *Acc. Chem. Res.* **1992**, *25*, 497; c) K. C. Nicolaou, A. L. Smith, E. W. Yue, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 5881; d) A. L. Smith, K. C. Nicolaou, *J. Med. Chem.* **1996**, *39*, 2103; e) J. W. Grissom, G. U. Gunawardena, D. Klingberg, D. Huang, *Tetrahedron* **1996**, *52*, 6453; f) M. E. Maier, *Synlett* **1995**, 13.