Organic & Biomolecular Chemistry



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Cite this: Org. Biomol. Chem., 2017, **15**, 7887

Claisen rearrangements of benzyl vinyl ethers: theoretical investigation of mechanism, substituent effects, and regioselectivity[†]

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Recently we reported the aromatic Claisen rearrangements of benzyl ketene acetals, which form one of the few examples of aromatic Claisen rearrangements involving benzyl vinyl ethers (as opposed to allyl aryl ethers, which are the usual substrates for aromatic Claisen rearrangements). Theoretical calculations predict that these rearrangements proceed *via* a concerted [3,3]-sigmatropic transition state, which is similar in geometry to the TS for the Claisen rearrangement of an allyl aryl ether but has a 4 kcal mol⁻¹ higher barrier. The effects of donor (OMe) and acceptor (CN) substituents on the kinetics of the [3,3]-rearrangement mirror those reported for allyl vinyl ethers: the largest substituent effects are seen for 1-OMe, 2-OMe, 2-CN, and 4-CN substituents, which lower the barrier by 5–9 kcal mol⁻¹. Substituents on the aromatic ring have smaller effects on the barrier (≤ 2 kcal mol⁻¹). The regioselectivities of Claisen rearrangements of *meta*-substituted benzyl ketene acetals favour 1,2,3-trisubstituted products in preference to the less sterically congested 1,2,4-isomers due to favourable orbital interactions in the 1,2,3 transition state.

Received 7th July 2017, Accepted 1st September 2017 DOI: 10.1039/c7ob01666b

Introduction

The Claisen rearrangement is an important pericyclic reaction with many applications in organic synthesis.¹ In general, Claisen rearrangements can be divided into three categories depending on whether one of the C=C bonds of the substrate is part of an aromatic ring (Scheme 1): allyl vinyl ethers (1), allyl aryl ethers (3) and benzyl vinyl ethers (6). Claisen



Scheme 1 Claisen rearrangements of aliphatic and aromatic substrates.

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†Electronic supplementary information (ESI) available: Computational methods and data. See DOI: 10.1039/c7ob01666b

rearrangements of aromatic substrates are more difficult than those of aliphatic substrates because the [3,3]-sigmatropic shift leads to a loss of aromaticity (*e.g.* **4**, 7) which is only regained during the subsequent tautomerisation step. For example, at 200 °C, the aliphatic Claisen rearrangement of allyl vinyl ether² has a rate constant $k = 3.8 \times 10^{-3} \text{ s}^{-1}$ while the aromatic Claisen rearrangement of allyl *p*-tolyl ether³ has k = $1.6 \times 10^{-5} \text{ s}^{-1}$. The rearrangements of benzyl vinyl ethers are even more difficult, and few examples have been achieved.⁴⁻¹⁴

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We recently reported synthetic methodology enabling some of the first examples of these challenging Claisen rearrangements to be achieved (Scheme 2a).¹⁴ Central to our approach was the incorporation of an alkoxy substituent at the 2-position on the vinyl moiety (**10**). The alkoxy group lowers the activation barrier for [3,3]-rearrangement, similar to the Johnson–Claisen rearrangement¹⁵ (and related variants such as those of Ireland¹⁶ and Eschenmoser^{7,8}), enabling the [3,3]-sigmatropic rearrangement to become feasible in solution. In our optimised synthetic protocol, the Claisen rearrangements of benzyl ketene acetals **10** were conducted in a tandem operation starting from α -bromoacetals **9**; dehydrobromination of **9** with KO^tBu and Claisen rearrangement of **10** were conducted in one pot in DMF or diglyme. After saponification, *ortho*-tolylacetic acids **12** were obtained in 24–60% yield.¹⁴

Being the least established of the three classes of Claisen rearrangements, the mechanism of the rearrangements of benzyl vinyl ethers remains relatively unexplored. During our





Scheme 2 (a) Claisen rearrangements of benzyl ketene acetals 10 derived from α -bromoacetals 9. (b) Evidence for an intermediate isotoluene 14 trapped by an intramolecular Alder-ene reaction. (c) Regioselective Claisen rearrangements of *meta*-substituted benzyl ketene acetals 17.

synthetic work,¹⁴ we uncovered the following four mechanistically relevant phenomena:

(1) The rearrangement of benzyl ketene acetal **13** (Scheme 2b), containing a tethered alkene, gave a 1:2 mixture of the normal Claisen rearrangement product **15** and the cyclised product **16**. The latter is consistent with the formation of an intermediate isotoluene **14** which is trapped by an intra-molecular Alder–ene reaction.

(2) The outcomes of the rearrangements were sensitive to solvent. When the reaction was conducted in refluxing anhydrous DMF or diglyme (b.p. 153 °C and 162 °C, respectively), the [3,3]-rearrangement products 11/12 were obtained, but when the reaction was conducted in refluxing xylenes (b.p. 137 °C), the products were those derived from C–O bond homolysis and radical recombination reactions.

(3) The Claisen rearrangement tolerated a range of moderate-to-strong electron-donating groups on the aromatic ring (*p*-Me, Ph, Cl, Br, OMe, SMe). More powerful electron-donating (*p*-NMe₂) or electron-withdrawing groups (*p*-CN, NO₂, CO₂Bn, SO₂Me, CF₃) led to decomposition.

(4) Rearrangements of *meta*-substituted benzyl ketene acetals 17 displayed unexpected regioselectivity (Scheme 2c). The sterically congested 1,2,3-trisubstituted products 18 were favoured (3:2-4:1) relative to the less crowded 1,2,4-trisubstituted isomers 19.

Herein, we report a theoretical investigation of this lesserknown member of the Claisen rearrangement family. We examine the fundamental features of the reaction mechanism and the effect of solvent on the reaction outcome. We then analyse the effects of substituents on reactivity and examine the regioselectivities observed in the rearrangements of *meta*substituted benzyl ketene acetals.

Results and discussion

Mechanism of the Claisen rearrangements of benzyl vinyl ethers

Our initial calculations aimed to determine whether the Claisen rearrangements of benzyl vinyl ethers **6** follow a concerted pericyclic [3,3]-sigmatropic mechanism, as typical of other Claisen rearrangements,^{17–21} or whether they instead follow a radical pathway in which the initial step is homolysis of the C–O bond leading to oxallyl and benzyl radical intermediates.

Houk and co-workers previously assessed the performance of a range of *ab initio* and density functional theory methods for calculating the activation enthalpies of the prototypical aliphatic and aromatic Claisen rearrangements of 1 and 3.²² They showed that the values of ΔH^{\ddagger} obtained from calculations with SCS-MP2²³/cc-pVQZ using geometries optimised with M06-2X²⁴ agreed closely with the experimental ΔH^{\ddagger} values (within 0.3 kcal mol^{-1}). We previously explored the free energy profiles for the Claisen rearrangements of 1, 3, and 6 in the gas phase with CBS-OB3.¹⁴ Here, we have performed calculations on the rearrangements of 1, 3, and benzyl vinyl ether 6 with several other theoretical methods (Table 1). We find that energies calculated with SCS-MP2/cc-pVTZ using geometries optimised with B3LYP²⁵/6-31G(d) also give relatively reliable predictions of ΔH^{\ddagger} for **1** and **3**, within 0.6 kcal mol⁻¹ of experiment. These results are comparable or superior in accuracy to high-level CBS-QB3²⁶ calculations, which agree to within 0.9 kcal mol⁻¹ of experiment. In contrast, calculations with M06-2X and ω B97X-D²⁷ gave poorer agreement, with errors of >3 kcal mol⁻¹.

For each theoretical method in Table 1, the calculations predict that the activation enthalpy for the Claisen rearrangement of benzyl vinyl ether 6 is 4-5 kcal mol⁻¹ higher than that for allyl phenyl ether 3. This casts benzyl vinyl ethers as the least reactive of the three classes of Claisen rearrangement substrates (Scheme 1) and is consistent with the paucity of examples of this kind of rearrangement in the literature.

 Table 1
 Activation enthalpies for Claisen rearrangements of 1, 3, and 6, calculated with different theoretical methods^a



	1	3	6
B3LYP/6-31G(d)	27.2	34.9	39.6
M06-2X/cc-pVTZ//B3LYP/6-31G(d)	32.5	40.3	45.1
ωB97X-D/cc-pVTZ//B3LYP/6-31G(d)	32.1	39.2	44.0
SCS-MP2/cc-pVTZ//B3LYP/6-31G(d)	29.8	35.6	39.6
CBS-QB3	28.5	34.2	38.3
Expt.	29.2^{b}	35.1 ± 0.2^c	—

^{*a*} ΔH^{\ddagger} in kcal mol⁻¹. ^{*b*} Ref. 2. ^{*c*} Ref. 3.



Fig. 1 Concerted transition states for Claisen rearrangements of **1**, **3**, **6**, and **6**b, calculated with CBS-QB3. Distances in Å. ΔH^{\ddagger} , ΔG^{\ddagger} , and ΔG in kcal mol⁻¹. Numbers in blue indicate the amount of charge transferred from the allyl or benzyl moiety to the enol moiety on going from the reactant to the TS. ${}^{a}\Delta G^{\ddagger}$ in implicit (SMD) zylenes. ${}^{b}\Delta G^{\ddagger}$ in implicit (SMD) DMF.

Experimentally, Burgstahler *et al.* reported that benzyl vinyl ether **6** did not rearrange to **8** even at >225 °C, instead undergoing polymerisation and decomposition.⁵

Fig. 1 shows the geometries of the concerted transition states (TSs) for [3,3]-rearrangements of **1**, **3**, **6**, and benzyl ketene acetal **6b**, calculated with CBS-QB3 [which uses geometries optimised with B3LYP/6-311G(2d,d,p)]. The aromatic substrates **3** and **6** exhibit similar TS geometries. The breaking C–O and forming C–C bond lengths in **TS-6** are 2.19 and 2.23 Å, respectively, compared with 2.17 and 2.24 Å in **TS-3**. Similar to other Claisen rearrangements,^{17,28} the rearrangement of benzyl vinyl ether **6** prefers a chair-like TS. The boat transition state **TS-6-boat** is 2.8 kcal mol⁻¹ higher in energy than the chair, **TS-6**. This boat/chair energy difference is smaller than those calculated for **1** (4.3 kcal mol⁻¹) and **3** (3.9 kcal mol⁻¹).²⁹

The TS for benzyl ketene acetal 6b is somewhat less synchronous than that for benzyl vinyl ether 6, with breaking and forming bond lengths of 2.12 and 2.40 Å, respectively. The methoxy group lowers ΔG^{\ddagger} by 10.2 kcal mol⁻¹ (relative to 6) and also makes the rearrangement thermodynamically favorable ($\Delta G = -5.0$ kcal mol⁻¹ for **6b** compared with +13.0 kcal mol⁻¹ for **6**). The TS for **6b** is more reactant-like than that for 6, consistent with the Hammond postulate.³⁰ We analyse the effects of substituents on the barriers and energetics of this type of Claisen rearrangement in more detail below. The boat/chair energy difference for **6b** is 2.3 kcal mol^{-1} , which is $0.5 \text{ kcal mol}^{-1}$ smaller than that for **6**. In the boat TSs for both 6 and 6b, the breaking C-O bond lies at an angle of about 70° relative to the OCC π system (similar to the boat TSs for 1 and 3). This indicates that the boat TSs are best described as pericyclic, in contrast to the pseudopericyclic TSs which have previously been described³¹ for related [3,3]-rearrangements involving esters.

Experimentally, the Claisen rearrangements of benzyl ketene acetals are conducted at relatively high temperatures (DMF or diglyme, >150 °C) where the possibility of competing C–O bond homolysis is a concern. The benzylic and oxallylic radicals generated by C–O bond homolysis may recombine by C–C bond formation or may react with the solvent.^{5,14,32} We computed the C–O bond dissociation energies of allyl vinyl ether **1**, allyl phenyl ether **3**, benzyl vinyl ether **6**, and benzyl

 Table 2
 Comparison between [3,3]-rearrangements and C-O bond homolysis of 1, 3, 6, and 6b^a



6b	OMe	29.9	-5.0	29.5
^a CI	BS-QB3, kcal mol ⁻¹ .			

ketene acetal **6b** (Table 2). For C–O homolysis, the calculated dissociation barriers (ΔG^{\ddagger}) are likely to be very similar to the dissociation energies (ΔG), assuming that the reverse reaction (radical recombination) is effectively barrierless. For **1**, **3**, and **6**, the free energy (ΔG) of C–O homolysis is higher than the barrier (ΔG^{\ddagger}) for concerted [3,3]-rearrangement, while for **6b** the C–O homolysis energy (29.5 kcal mol⁻¹) is close to the rearrangement barrier (29.9 kcal mol⁻¹). It is clear from the relatively weak C–O bond strengths in **6** and **6b** that radical fission/recombination reactions involving these substrates or the isotoluene intermediates derived from their [3,3]-rearrangements are more likely to be competitive than in the conventional aromatic Claisen rearrangements of allyl aryl ethers such as **3**.

Solvent effects

Previous theoretical studies of the Claisen rearrangement of allyl vinyl ether have shown that the transition state has weak dipolar character. Approximately 0.3e of negative charge is transferred from the allyl moiety onto the enolate moiety on going from the reactant to the TS.^{17–20} The amounts of charge transfer for **1**, **3**, **6**, and **6b** are shown in Fig. 1 (blue typeface).³³ The TSs for both allyl phenyl ether **3** and benzyl vinyl ether **6** display greater charge transfer than the TS for allyl vinyl ether **1**, consistent with the ability of the aromatic ring to delocalise the charge, but the charge transfer for **6** (±0.17*e*) is smaller than for **3** (±0.22*e*). Benzyl ketene acetal **6b** shows significantly more charge transfer, with a net charge of 0.38e transferred from the benzyl moiety onto the enolate moiety.

Despite their polar TSs, the ΔG^{\ddagger} values for the Claisen rearrangements of **6** and **6b** are predicted to be relatively insensitive to solvent. Fig. 1 shows the ΔG^{\ddagger} values resulting when solvation energies computed with the SMD implicit model³⁴ are added to the gas-phase barriers. For **6**, the value of ΔG^{\ddagger} decreases from 40.1 kcal mol⁻¹ in the gas phase to 39.5 kcal mol⁻¹ in xylenes and 38.8 kcal mol⁻¹ in DMF.³⁵ The ΔG^{\ddagger} for rearrangement of **6b** actually increases slightly (0.2–0.3 kcal mol⁻¹) in these two solvents. Previous theoretical studies have shown that the Claisen rearrangements of 2-OH and 2-NH₂ substituted allyl vinyl ethers display a similar insensitivity to continuum solvent.^{18,19}

The insensitivity of the ΔG^{\ddagger} for **6b** to solvent appears at odds with our earlier experimental observations.¹⁴ We found that reactions conducted in DMF or diglyme led to [3,3]rearranged products but the reaction in xylenes gave only radical fission/recombination products. Since the calculated barriers in DMF and xylenes are almost identical (DMF: 30.2, xylenes: $30.1 \text{ kcal mol}^{-1}$), the difference in reaction outcomes points toward some factor other than the rate of [3,3]rearrangement. Previous studies of the Claisen rearrangements of allyl aryl ethers have suggested that the tautomerisation of 4 may be rate-determining, and a variety of tautomerisation mechanisms have been proposed.³⁶ It is likely that the tautomerisation of isotoluenes 7 in the rearrangements of benzyl vinyl ethers 6 (and their derivatives such as benzyl ketene acetals 10) are also rate-determining.³⁷ Under the conditions of the reaction (Scheme 2a), tautomerisation of the isotoluene intermediate is likely to be catalysed by the small excess of KO^tBu present in the reaction mixture. The solvents DMF and diglyme would assist the tautomerisation by enhancing the basicity of KO^tBu. In xylenes, by contrast, slower tautomerisation of the isotoluene to the ortho-tolylacetate would set the stage for the isotoluene to revert to the benzyl ketene acetal.

Substituent effects

Our synthetic experiments¹⁴ demonstrated that the Claisen rearrangements of benzyl ketene acetals **10** tolerate a range of moderate-to-strong electron-donating groups (Me, Ph, Cl, Br, OMe, SMe) at the *para* position of the aromatic ring, but more powerful electron-donating (NMe₂) or electron-withdrawing Table 3Effects of substituents on the kinetics and thermodynamics ofClaisen rearrangements of benzyl vinyl ethers 6^a



			$\Delta G_0^{\ddagger b}$	$\Delta\Delta G^{\ddagger}_{ m thermo}$
Substituent R	$\Delta G^{\ddagger} \left[\Delta G^{\ddagger}_{\mathrm{rel}} \right]$	$\Delta G \left[\Delta G_{\rm rel} \right]$	$\left[\Delta G_{0,\mathrm{rel}}^{\ddagger}\right]$	$[\Delta\Delta G_{\rm thermo, rel}^{\ddagger}]$
None (6)	41.3	11.7	35.3	6.1
1-OMe $(6a)^d$	34.6 [-6.7]	10.4[-1.3]	29.2 [-6.1]	5.4[-0.6]
2-OMe (6b)	32.5 [-8.8]	-6.2 [-17.9]	35.5 [+0.3]	-3.1 [-9.1]
4-OMe (6c)	39.5 [-1.8]	13.9 [+2.3]	32.2 [-3.1]	7.3 [+1.3]
6-OMe (6d)	43.3 [+2.0]	13.5 [+1.8]	36.3 [+1.0]	7.1 [+1.0]
7-OMe (6e)	39.3 [-2.1]	9.0[-2.7]	34.6 [-0.6]	4.6[-1.4]
8-OMe (6f)	40.7[-0.7]	10.1[-1.6]	35.5 [+0.2]	5.2[-0.9]
9-OMe (6g)	40.1[-1.3]	9.3 [-2.3]	35.2 [0.0]	4.8 [-1.3]
10-OMe (6h)	41.5[+0.2]	10.8[-0.9]	35.9 [+0.7]	5.6[-0.5]
1-CN $(6i)^d$	40.9[-0.4]	17.7 [+6.0]	31.5 [-3.8]	9.4 [+3.4]
2-CN (6j)	36.9 [-4.5]	13.5[+1.9]	29.7 [-5.6]	7.2 [+1.1]
4-CN (6k)	34.2 [-7.2]	4.8[-6.9]	31.7 [-3.5]	2.4[-3.7]
6-CN (61)	42.6 [+1.3]	16.6[+4.9]	33.8 [-1.4]	8.8 [+2.7]
7-CN (6m)	41.1[-0.2]	10.9[-0.8]	35.5 [+0.2]	5.6[-0.4]
8-CN (6n)	41.2[-0.1]	11.8[+0.1]	35.1 [-0.2]	6.1[+0.1]
9-CN (60)	42.0 [+0.7]	11.1[-0.5]	36.2 [+1.0]	5.8 [-0.3]
10-CN (6p)	41.4[+0.1]	11.5[-0.2]	35.5 [+0.2]	6.0[-0.1]
2-OMe,8-NMe ₂ (6q)	32.0 [-9.3]	-6.9 [-18.5]		
2-OMe,8-CN (6r)	32.2 [-9.2]	-6.1[-17.8]		

^{*a*} SCS-MP2/cc-pVTZ//B3LYP/6-31G(d), kcal mol⁻¹. Values in brackets are relative to **6**. ^{*b*} ΔG_0^+ : intrinsic barrier. ^{*c*} $\Delta G_{\text{thermo}}^+$: thermodynamic contribution to the barrier. ^{*d*} *Trans* substitution of the C1=C2 double bond.

groups (CN, NO₂, CO₂Bn, SO₂Me, CF₃) at this position led to decomposition. To determine how donor and acceptor substituents influence the [3,3]-rearrangement, we studied all possible monosubstituted benzyl vinyl ethers containing a methoxy or cyano substituent. The calculated values of ΔG^{\ddagger} and ΔG for the rearrangements of these derivatives are reported in Table 3. These calculations employed SCS-MP2/cc-pVTZ// B3LYP/6-31G(d) and use the numbering convention shown in Table 3. In several pairs of reactions (*e.g.* **6e** and **6g**), the reacting benzyl vinyl ether is identical but the TSs and intermediates differ due to the regiochemical placement of the substituent.

The largest effects on the kinetics of the Claisen rearrangement are seen for 1-OMe, 2-OMe, 2-CN, and 4-CN substituents, which decrease ΔG^{\ddagger} by 5–9 kcal mol⁻¹ relative to the parent compound **6**. These substituents are all located on nonaromatic sites. Substituents attached to the aromatic ring have smaller effects on ΔG^{\ddagger} . Among them, the largest $\Delta \Delta G^{\ddagger}$ value is that of 7-OMe, which decreases the barrier by 2.1 kcal mol⁻¹. In most cases, a methoxy substituent at the *meta* or *para* position of the aromatic ring accelerates the rearrangement to a greater extent than a cyano substituent at the same position does, consistent with the ability of OMe groups to stabilise the partial positive charge on the benzyl moiety in the TS. Of special note are the 6-substituted derivatives (**6d, 61**), which lead to the formation of a new C–C bond to a substituted carbon of the aromatic ring. The isotoluene intermediate in these two cases cannot rearomatise. Both an OMe and a CN group disfavour bond formation to C-6. Instead, the isomeric rearrangement with formation of a bond to C-10 (**6h**, **6p**) is favoured by 1–2 kcal mol⁻¹.

In general, the large effects of methoxy and cyano substituents at C-1, C-2, and C-4 resemble those reported for allyl vinyl ethers, whose rearrangements are likewise accelerated by donors at C-1 and C-2 and by acceptors at C-2 and C-4.^{18–20}

In order to understand the origins of the large substituent effects at C-1, C-2, and C-4, we performed a Marcus Theory³⁸ analysis. This approach was originally proposed by Murdoch³⁹ and was utilised by Houk and coworkers¹⁸⁻²⁰ to analyse the effects of substituents on aliphatic Claisen rearrangements of allyl vinyl ethers. In the Marcus Theory analysis, the effect of an individual substituent on the activation energy for the rearrangement is considered to have two origins: (1) the direct stabilisation or destabilisation of the TS relative to the reactant, and (2) the barrier-lowering/raising influence of the reaction exergonicity/endergonicity. These two contributions are represented, respectively, by an "intrinsic barrier" (ΔG_0^{\ddagger}) and a "thermodynamic contribution" ($\Delta \Delta G^{\ddagger}_{\text{thermo}}$), both of which may be calculated from the ΔG^{\ddagger} and ΔG values of the reaction. The intrinsic barrier ΔG_0^{\ddagger} (which is equivalent to the barrier for a hypothetical thermoneutral process) is given by eqn (1):^{18–20,39}

$$\Delta G^{\ddagger} = \Delta G_0^{\ddagger} + \frac{1}{2} \Delta G + (\Delta G)^2 / 16 \Delta G_0^{\ddagger}.$$
 (1)

The thermodynamic contribution $\Delta\Delta G_{\text{thermo}}^{\ddagger}$ is calculated as the difference between the actual and intrinsic barriers, $\Delta G^{\ddagger} - \Delta G_{0}^{\ddagger}$.

The intrinsic barriers ΔG_0^{\ddagger} and thermodynamic contributions $\Delta \Delta G_{\text{thermo}}^{\ddagger}$ calculated from the quantum mechanical ΔG^{\ddagger} and ΔG values are shown in the fourth and fifth columns of Table 3. The numbers in brackets show how each quantity for a given substituted derivative differs from that for the parent benzyl vinyl ether **6**.

A methoxy group at C-1 (6a) has a strong barrier-lowering effect, decreasing the total activation barrier ΔG^{\ddagger} by 6.7 kcal mol⁻¹. The 1-OMe group has a large effect on the intrinsic barrier ΔG_0^{\ddagger} (-6.1 kcal mol⁻¹) but only a small effect on the thermodynamic contribution $\Delta \Delta G_{\text{thermo}}^{\ddagger}$ (-0.6 kcal mol⁻¹). Thus, the lowering of the barrier by the 1-OMe substituent can be ascribed primarily to an intrinsic effect. Its origins are twofold: firstly, the 1-OMe group destabilises the reactant through a 4-electron interaction with the C=C π orbital, and secondly, the 1-OMe group lowers the TS energy by inductively stabilising the negative charge on the enolate moiety.

A methoxy group at C-2 (**6b**) has an even stronger barrierlowering effect (8.8 kcal mol⁻¹). This effect is primarily thermodynamic in origin. The 2-OMe group destabilises the reactant through its 4-electron interaction with the C=C π orbital, and it strongly stabilises the carbonyl group of the product through resonance.

A cyano group at C-2 (6j) lowers the barrier by 4.5 kcal mol⁻¹. This is primarily an intrinsic effect which originates from

inductive stabilisation of the negative charge on the enolate moiety in the TS. A cyano group at C-4 (**6k**) lowers the barrier by 7.2 kcal mol⁻¹. This reflects a combination of intrinsic and thermodynamic factors. In their study of cyano substituent effects on the Claisen rearrangements of allyl vinyl ether, Aviyente and Houk²⁰ attributed the barrier-lowering effects of 2-CN and 4-CN groups to the stabilisation of diradical TS resonance contributors (cyclohexane-1,4-diyl and bis-allyl, respectively). Conjugative stabilisation of the product accounts for the thermodynamic contribution of 4-CN.

Also included in Table 3 are benzyl ketene acetal 6q, which bears a 2-OMe group and a para-NMe₂ group, and 6r, which bears a 2-OMe group and a para-CN group. Experimentally, the 2-OEt analogues of these two benzyl ketene acetals did not undergo [3,3]-rearrangements, instead decomposing under the reaction conditions.¹⁴ The ΔG^{\ddagger} values for the Claisen rearrangements of both 6q and 6r are 9 kcal mol⁻¹ lower than that for benzyl ketene acetal 6b, which did undergo rearrangement in 60% yield. Thus, the strong donor NMe₂ or strong acceptor CN at the para position activates a benzyl ketene acetal towards Claisen rearrangement. The calculations suggest that the failure of these types of substrates to furnish rearranged products under our synthetic conditions is not due to their inherently low reactivity toward [3,3]-rearrangement; instead, sensitivity toward side reactions under the strongly basic reaction conditions may be responsible.

Regioselectivity of Claisen rearrangements of *meta*-substituted benzyl vinyl ethers

Our final mechanistic question concerns the regioselectivity of Claisen rearrangements of benzyl ketene acetals 17 containing a meta substituent (Scheme 2c). Benzyl ketene acetals containing either a meta-OMe or meta-Br substituent were found to rearrange regioselectively, favouring the sterically crowded 1,2,3-trisubstituted products 18 relative to the 1,2,4-trisubstituted isomers **19**. The calculated ΔG^{\ddagger} values in Table 3 are consistent with this regioselectivity. System 6e (7-OMe) corresponds to the formation of a 1,2,3-trisubstituted product, and 6g (9-OMe) to the formation of a 1,2,4-trisubstituted product. The ΔG^{\ddagger} values for **6e** and **6g** are 39.3 and 40.1 kcal mol⁻¹, respectively. Calculations on dimethoxy-substituted analogues containing one OMe group at C-2 and another at either C-7 or C-9 mirror this result. The C-2, C-7 substituted system is predicted to rearrange with a 0.8 kcal mol⁻¹ lower barrier (30.8 kcal mol⁻¹) than the C-2, C-9 substituted system (31.6 kcal mol⁻¹), favouring the 1,2,3-trisubstituted product.²⁹ The 0.8 kcal mol⁻¹ difference in ΔG^{\ddagger} favouring **6e** agrees well with the 4:1 regioselectivity observed experimentally for 17 (R = OMe). Thermodynamic effects appear to be equivalent in these reactions, the C-7 substituted [3,3]-rearranged product 7e being only slightly (0.3 kcal mol⁻¹) more stable than the C-9 analogue 7g. The difference in barriers is traced to intrinsic effects, i.e. differences in TS stabilisation for the two regioisomeric pathways for this substrate. The HOMO and LUMO of the TS for the parent benzyl vinyl ether 6, shown Fig. 2, provide an explanation for the regioselectivity. In the TS



Fig. 2 HOMO and LUMO of the transition state for Claisen rearrangement of benzyl vinyl ether 6.

LUMO, the orbital coefficient at C-7 is significant but the coefficient at C-9 is very small. Thus, the electron pair of an OMe group can overlap in a stabilising manner with the TS LUMO when the OMe group is bound to C-7, but less so when it is bound to C-9.⁴⁰ This explains the lower energy of the TS for the rearrangement with an OMe group at C-7 leading to the 1,2,3-trisubstituted product.

Conclusions

Theoretical calculations predict that the Claisen rearrangements of benzyl vinyl ethers proceed via a concerted [3,3]rearrangement mechanism. The ΔG^{\ddagger} for rearrangement of benzyl vinyl ether (6) is 4 kcal mol^{-1} higher than that for allyl phenyl ether (3) and 10 kcal mol⁻¹ higher than for allyl vinyl ether (1). Implicit solvent (xylenes or DMF) leads to small accelerations of the rearrangement of benzyl vinyl ether 6, but does not accelerate the rearrangement of benzyl ketene acetal 6b. The importance of using a solvent such as DMF or diglyme (rather than xylenes) for the Claisen rearrangements of benzyl ketene acetals is proposed to reflect the ability of these solvents to enhance the availability of the base (KO^tBu) that catalyses the tautomerisation of the intermediate isotoluene. The effects of donor and acceptor substituents at different positions on the benzyl vinyl ether were analysed. The largest effects are those for 1-OMe, 2-OMe, 2-CN, and 4-CN derivatives, which lower the ΔG^{\ddagger} by 5–9 kcal mol⁻¹ relative to the parent. Donor and acceptor substituents on the aromatic ring have smaller effects on ΔG^{\ddagger} ($\leq 2 \text{ kcal mol}^{-1}$). Two manifestations of the effects of the substituents on the aromatic ring are that: (i) ortho-substituted benzyl vinyl ethers are predicted to rearrange favouring C-C bond formation to the unsubstituted carbon C-10 rather than to the substituted carbon C-6, and (ii) meta-substituted benzyl ketene acetals (R = electron donor) rearrange regioselectively to give 1,2,3-trisubstituted products through bond formation to C-7, in preference to the less crowded 1,2,4-isomers through bond formation to C-9, due to favourable overlap between the meta-substituent and the LUMO in the 1,2,3 transition state.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the Australian Research Council (FT120100632 to E. H. K.) for financial support. Computational resources were provided by the Australian National Computational Infrastructure National Facility through the National Merit Allocation Scheme, and by the University of Queensland Research Computing Centre.

References

- The Claisen Rearrangement: Methods and Applications, ed. M. Hiersemann and U. Nubbemeyer, Wiley-VCH, Weinheim, 2007.
- 2 F. W. Schuler and G. W. Murphy, J. Am. Chem. Soc., 1950, 72, 3155.
- 3 W. N. White and E. F. Wolfarth, J. Org. Chem., 1970, 35, 2196.
- 4 S. M. McElvain, H. I. Anthes and S. H. Shapiro, J. Am. Chem. Soc., 1942, 64, 2525.
- 5 A. W. Burgstahler, L. K. Gibbons and I. C. Nordin, *J. Chem. Soc.*, 1963, 4986.
- 6 W. J. Le Noble, P. J. Crean and B. Gabrielsen, *J. Am. Chem. Soc.*, 1964, **86**, 1649.
- 7 A. E. Wick, D. Felix, K. Steen and A. Eschenmoser, *Helv. Chim. Acta*, 1964, 47, 2425.
- 8 D. Felix, K. Gschwend-Steen, A. E. Wick and A. Eschenmoser, *Helv. Chim. Acta*, 1969, **52**, 1030.
- 9 C. R. Costin, C. J. Morrow and H. Rapoport, *J. Org. Chem.*, 1976, **41**, 535.
- 10 S. Raucher and A. S.-T. Lui, J. Am. Chem. Soc., 1978, 100, 4902.
- 11 V. Valerio, C. Madelaine and N. Maulide, *Chem. Eur. J.*, 2011, **17**, 4742.
- 12 A. A. Tudjarian and T. G. Minehan, *J. Org. Chem.*, 2011, **76**, 3576.
- 13 D. M. D'Souza, W.-W. Liao, F. Rominger and T. J. J. Müller, *Org. Biomol. Chem.*, 2008, **6**, 532.
- 14 J. M. Burns, E. H. Krenske and R. P. McGeary, *Eur. J. Org. Chem.*, 2017, 252.
- 15 W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T.-T. Li, D. J. Faulkner and M. R. Petersen, *J. Am. Chem. Soc.*, 1970, **92**, 741.
- 16 (a) R. E. Ireland and R. H. Mueller, *J. Am. Chem. Soc.*, 1972, 94, 5897; (b) R. E. Ireland, R. H. Mueller and A. K. Willard, *J. Am. Chem. Soc.*, 1976, 98, 2868.
- 17 (a) R. L. Vance, N. G. Rondan, K. N. Houk, F. Jensen, W. T. Borden, A. Komornicki and E. Wimmer, *J. Am. Chem. Soc.*, 1988, **110**, 2314; (b) O. Wiest, K. A. Black and K. N. Houk, *J. Am. Chem. Soc.*, 1994, **116**, 10336.
- 18 H. Y. Yoo and K. N. Houk, J. Am. Chem. Soc., 1997, 119, 2877.
- 19 V. Aviyente, H. Y. Yoo and K. N. Houk, *J. Org. Chem.*, 1997, 62, 6121.
- 20 V. Aviyente and K. N. Houk, J. Phys. Chem. A, 2001, 105, 383.

- 21 For other theoretical studies of Claisen rearrangements, see: (a) O. Wiest and K. N. Houk, J. Am. Chem. Soc., 1995, 117, 11628; (b) A. Sehgal, L. Shao and J. Gao, J. Am. Chem. Soc., 1995, 117, 11337; (c) J. M. Guest, J. S. Craw, M. A. Vincent and I. H. Hillier, J. Chem. Soc., Perkin Trans. 2, 1997, 71; (d) F. C. Gozzo, S. A. Fernandes, D. C. Rodrigues, M. N. Eberlin and A. J. Marsaioli, J. Org. 2003, 68, 5493; (e) M. Ρ. Repasky. Chem. C. R. W. Guimarães, J. Chandrasekhar, J. Tirado-Rives and W. L. Jorgensen, J. Am. Chem. Soc., 2003, 125, 6663; (f) C. Ozturk, V. Aviyente and K. N. Houk, J. Org. Chem., 2005, 70, 7028; (g) J. Rehbein and M. Hiersemann, J. Org. Chem., 2009, 74, 4336; (h) C. Uyeda and E. N. Jacobsen, J. Am. Chem. Soc., 2011, 133, 5062; (i) N. Celebi-Ölçüm, Y.-H. Lam, E. Richmond, K. B. Ling, A. D. Smith and K. N. Houk, Angew. Chem., Int. Ed., 2011, 50, 11478; (*j*) R. Ghadari and A. Shaabani, J. Mol. Model, 2012, 18, 319; (k) E. Lyngvi, J. W. Bode and F. Schoenebeck, Chem. Sci., 2012, 3, 2346; (1) S. Hou, X. Li and J. Xu, J. Org. Chem., 2012, 77, 10856; (m) V. Srinivasadesikan, J.-K. Dai and S.-L. Lee, Org. Biomol. Chem., 2014, 12, 4163; (n) M. F. L. Parker, S. Osuna, G. Bollot, S. Vaddypally, M. J. Zdilla, K. N. Houk and C. E. Schafmeister, J. Am. Chem. Soc., 2014, 136, 3817; and ref. 13, 22, 28 and 36.
- 22 S. Osuna, S. Kim, G. Bollot and K. N. Houk, *Eur. J. Org. Chem.*, 2013, 2823.
- 23 (a) S. Grimme, J. Chem. Phys., 2003, 118, 9095;
 (b) M. Gerenkamp and S. Grimme, Chem. Phys. Lett., 2004, 392, 229; (c) S. Grimme, J. Phys. Chem. A, 2005, 109, 3067.
- 24 Y. Zhao and D. G. Truhlar, Theor. Chem. Acc., 2008, 120, 215.
- 25 (a) C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B: Condens. Matter*, 1988, 37, 785; (b) A. D. Becke, *J. Chem. Phys.*, 1993, 98, 1372; (c) A. D. Becke, *J. Chem. Phys.*, 1993, 98, 5648; (d) P. J. Stephens, F. J. Devlin, C. F. Chabalowski and M. J. Frisch, *J. Phys. Chem.*, 1994, 98, 11623.
- 26 (*a*) J. A. Montgomery Jr., M. J. Frisch, J. W. Ochterski and G. A. Petersson, *J. Chem. Phys.*, 1999, **110**, 2822;
 (*b*) J. A. Montgomery Jr., M. J. Frisch, J. W. Ochterski and G. A. Petersson, *J. Chem. Phys.*, 2000, **112**, 6532.
- 27 J.-D. Chai and M. Head-Gordon, *Phys. Chem. Chem. Phys.*, 2008, **10**, 6615.
- 28 (a) M. M. Khaledy, M. Y. S. Kalani, K. S. Khuong,
 K. N. Houk, V. Aviyente, R. Neier, N. Soldermann and
 J. Velker, *J. Org. Chem.*, 2003, 68, 572; (b) S. Gül,
 F. Schoenebeck, V. Aviyente and K. N. Houk, *J. Org. Chem.*, 2010, 75, 2115.

- 29 See the ESI† for details.
- 30 G. S. Hammond, J. Am. Chem. Soc., 1955, 77, 334.
- 31 Birney *et al.* have shown that related [3,3]-sigmatropic rearrangements of esters have pseudopericyclic TSs. See:
 (*a*) S. Sharma, T. Rajale, D. B. Cordes, F. Hung-Low and D. M. Birney, *J. Am. Chem. Soc.*, 2013, 135, 14438;
 (*b*) D. M. Birney, X. Xu and S. Ham, *Angew. Chem., Int. Ed.*, 1999, 38, 189.
- 32 (a) F. M. Elkobaisi and W. J. Hickinbottom, J. Chem. Soc., 1959, 1873; (b) F. M. Elkobaisi and W. J. Hickinbottom, J. Chem. Soc., 1960, 1286.
- 33 Charges reported in Fig. 1 are Mulliken charges calculated during the CCSD(T)/6-31+G(d') component of the CBS-QB3 calculation.
- 34 A. V. Marenich, C. J. Cramer and D. G. Truhlar, *J. Phys. Chem. B*, 2009, **113**, 6378.
- 35 When fully optimised in implicit DMF, **TS-6** becomes slightly more dissociative: the breaking C–O and forming C–C bonds are 0.05 and 0.03 Å longer, respectively, than in the gas phase. See the ESI† for details.
- 36 (a) S. Yamabe, S. Okumoto and T. Hayashi, J. Org. Chem., 1996, 61, 6218; (b) Y. Zheng and J. Zhang, J. Phys. Chem. A, 2010, 114, 4325.
- 37 Computations on the tandem [3,3]-rearrangement/Alderene sequence $13 \rightarrow 14 \rightarrow 16$ indicate that the Alder-ene step is much more facile than the [3,3]-rearrangement. The calculated barriers (ΔG^{\ddagger}) are 30.7 kcal mol⁻¹ for the [3,3]rearrangement and 15.9 kcal mol⁻¹ for the Alder-ene reaction (modelling OEt as OMe). See the ESI[†] for details.
- 38 (a) R. A. Marcus, J. Chem. Phys., 1956, 24, 966;
 (b) R. A. Marcus, J. Phys. Chem., 1968, 72, 891.
- 39 (a) J. R. Murdoch, J. Am. Chem. Soc., 1983, 105, 2660;
 (b) M. Y. Chen and J. R. Murdoch, J. Am. Chem. Soc., 1984, 106, 4735.
- 40 Natural bond orbital analysis (A. E. Reed, L. A. Curtiss and F. Weinhold, *Chem. Rev.*, 1988, **88**, 899) with a secondorder perturbation theory treatment gave estimates of the stabilisation arising from donor-acceptor orbital interactions in transition states **TS-6e** and **TS-6g**. The analysis predicted that the interaction of a 7-OMe lone pair with a $C=C \pi^*$ orbital in **TS-6e** (which leads to the 1,2,3-trisubstituted product **7e**) is 0.36 kcal mol⁻¹ more stabilising than the interaction of a 9-OMe lone pair with a $C=C \pi^*$ orbital in **TS-6g** (which leads to the 1,2,4-trisubstituted product **7g**), consistent with the conclusion reached by analysis of the HOMO and LUMO of **TS-6** in Fig. 2.