PAPER

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Sigmatropic proton shifts: a quantum chemical study†

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A quantum chemical study of [1,j] sigmatropic proton shifts in polyenyl anions and related conjugated systems has been performed. We found that the Woodward–Hoffmann rules can be applied to understand the stereochemical outcome of these sigmatropic rearrangements, showing that [1,j] sigmatropic proton shift occurs *antarafacially* when $j = 4n + 2$, while *suprafacial* proton shift is symmetry-allowed when $j = 4n$. The activation barriers for [1,j] proton shifts in polyenyl anions $C_jH_{j+3}^{-}$ are 48.2 ($j = 2$), 32.8 ($j = 4$), 21.0 ($j = 6$), 40.5 ($j = 8$), and 49.1 ($j = 10$) kcal mol^{-1}, respectively. This trend can be explained by the trade-off between stereoelectronic requirement and ring strain in the proton shift transition structure. Among these reactions, only the [1,6] proton shift with the lowest activation barrier can occur intramolecularly under mild reaction conditions. The others are unlikely to take place in a direct manner. Consequently, proton shuttles are generally required to facilitate these sigmatropic proton shifts through a protonation/deprotonation mechanism.
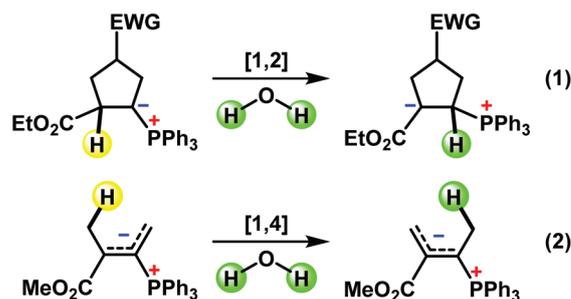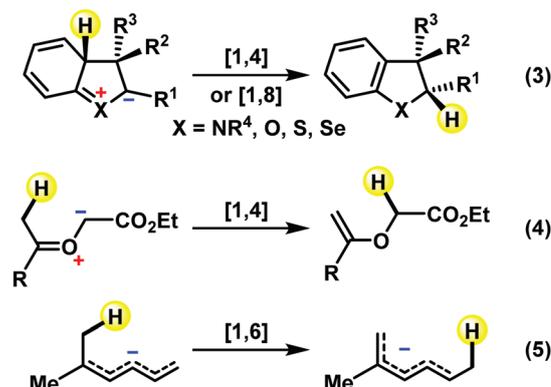
Introduction

Sigmatropic hydrogen shifts are well-known processes in organic reactions and biological transformations.[1] These reactions can be either *suprafacial* or *antarafacial*. For example, the thermal [1,5] hydrogen shift in (Z)-1,3-pentadiene is suprafacial,[2] whereas the thermal isomerization of previtamin D into vitamin D proceeds through an antarafacial [1,7] hydrogen shift.[3] The stereochemical outcome of these sigmatropic rearrangements of polyenes can be understood by the Woodward–Hoffmann rules based on orbital symmetry considerations.[4] Sigmatropic hydride shifts in polyenyl cations have also been discussed by Woodward and Hoffmann in their original paper in 1965.[4a] Nearly four decades later, Hoffmann and Tantillo found that the transition structures for sigmatropic hydrogen shifts in polyenes and polyenyl cations can be viewed as protonated electrocyclic transition structures.[5]

However, no systematic study on sigmatropic proton shifts has been reported, though a few examples of sigmatropic proton shifts within polyenyl anions and related systems have been reported in the literature (Scheme 1).[1b,6–18] Previously we and others found that the [1,2] sigmatropic proton shift in

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(a) Water-assisted formal sigmatropic shifts (refs. 6, 7, 14)

(b) Sigmatropic proton shifts (refs. 15–18)

Scheme 1 Selected examples for sigmatropic proton shifts. The different color codings of hydrogen atoms in substrates and products in eqn (1) and (2) indicate a water-assisted protonation/deprotonation mechanism.

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Org. Biomol. Chem., 2017, **15**, 7439–7446 | 7439

Lu's (3 + 2) cycloaddition of allenoates with electron-deficient olefins[6] is not concerted, but is assisted by water *via* a stepwise protonation/deprotonation mechanism (Scheme 1a, eqn (1)).[7] In this case, the term "formal sigmatropic shift" should be used. Similar formal [1,2] sigmatropic proton shifts have been proposed in the Reimer–Tiemann reaction,[8,9] *N*-heterocyclic carbene (NHC) catalysis,[10,11] transition-metal-catalyzed hetero-atom–hydrogen bond insertions,[12,13] *etc*. Similarly, we found that the [1,4] proton shift involved in the phosphine-promoted (3 + 2) cycloaddition of 2-methyl-2,3-butadienoate with fumarates is an intermolecular event occurring with the assistance of water (Scheme 1a, eqn (2)).[14] However, the thermal [1,4] sigmatropic proton shifts in azomethine, carbonyl, thiocarbonyl, and selenocarbonyl ylides have been proven to occur intra-molecularly and suprafacially (Scheme 1b, eqn (3) and (4)).[15–17] The physical origins underlying the different mechanisms of these similar [1,4] sigmatropic reactions are quite interesting, yet unknown to the best of our knowledge. Furthermore, [1,6] sigmatropic proton shifts in pentadienyl lithiums have been proven to proceed intramolecularly and antarafacially under thermal conditions (Scheme 1b, eqn (5)).[18]

Generally, the Woodward–Hoffmann rules can be applied to understand the facial selectivity of these sigmatropic proton shifts[15–18] and to rule out the symmetry forbidden pathways. Our quantum chemical calculations also supported this point of view (*vide post*). However, one question remains: whether a symmetry allowed sigmatropic proton shift is facile or not; in other words, whether a sigmatropic proton shift is direct (if the intramolecular pathway is facile) or assisted by proton shuttles (if the intramolecular pathway is difficult).

Recently we reported our computational study on the trans-locations of carbanions *via* proton transfers, showing that the tether length and substituent effect play important roles in determining the relative ease of intramolecular proton transfers in nonconjugated systems (Scheme 2a).[19,20] Here we report our quantum chemical study on sigmatropic proton shifts in conjugated systems (Scheme 2b).[21] We aimed to discuss the difference between σ- and π-frameworks and the influence of the thermodynamic driving force. We expect that these computational results would be useful in understanding whether a sigmatropic proton shift of a polyenyl anion (or a related conjugated system) occurs intramolecularly or with the assistance of proton shuttles.
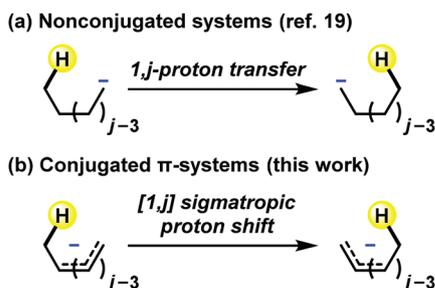
Computational methods

All density functional theory (DFT) calculations were performed with Gaussian 09.[22] Pruned integration grids with 99 radial shells and 590 angular points per shell were used. Geometry optimizations of all the minima and transition structures involved were carried out using the ωB97XD functional[23] and the 6-311+G(d,p) basis set[24] without any constraints. Unscaled harmonic frequency calculations at the same level were performed to validate each structure as either a minimum or a transition structure and to evaluate its zero-point energy (ZPE). Based on the optimized structures at the ωB97XD/6-311+G(d,p) level, single-point energy calculations employing the spin-component-scaled second-order Møller–Plesset perturbation theory (SCS-MP2)[25] and the aug-cc-pVTZ basis set[26] were carried out using ORCA 3.0.3.[27] The convergence thresholds were set to "TIGHTSCF". Frozen core approximations and the resolution of the identity (RI)[28] using the aug-cc-pVTZ/C auxiliary basis set[29] were used to speed up the correlation calculations. All discussed energy differences were based on the ZPE-corrected electronic energies at the SCS-MP2/aug-cc-pVTZ//ωB97XD/6-311+G(d,p) level unless otherwise specified. We chose this level of theory based on our previous *ab initio* benchmark study on intramolecular carbon-to-carbon proton transfers.[19] For bimolecular reactions, to take the entropy changes into account, Gibbs energies of activation at 298 K were also provided for reference. For unimolecular reactions, discussions based on Gibbs energies of activation or theoretical rate constants (with and without quantum tunneling) at 298 K did not change the conclusions of our work and therefore are only listed in the ESI.†[30]

3D structures were prepared with CYLview.[31]

Results and discussion

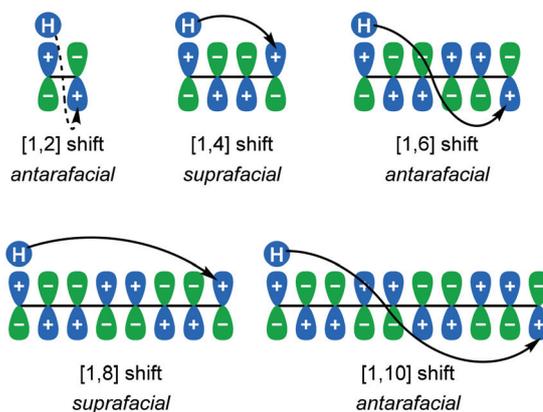### Degenerate sigmatropic proton shifts in polyenyl anions

We commenced our study with degenerate sigmatropic proton shifts in polyenyl anions **A–E** under thermal conditions (Table 1). These reactions are thermoneutral ($\Delta E_{rxn} = 0$), and thus can be discussed without consideration of the thermodynamic driving forces. The optimized geometries for the sigmatropic proton shift transition structures are depicted in Fig. 1.

According to the analysis by Woodward and Hoffmann, the transition structure for the [1,*j*] sigmatropic proton shift can be divided into two parts, the migrating hydrogen atom and the polyenyl anion radical.[4] To maintain a constructive overlap between the migrating hydrogen orbital and the singly occupied molecular orbital (SOMO) of the polyenyl anion radical, the sigmatropic proton shift should occur antarafacially when $j = 4n + 2$, while suprafacial shift is permitted when $j = 4n$ (Fig. 2). Our quantum chemical calculations indicated that the facial selectivity of the sigmatropic proton shifts can be correctly predicted according to the Woodward–Hoffmann rules, except that the [1,2] proton shift occurs

(a) Nonconjugated systems (ref. 19)

1,j-proton transfer

(b) Conjugated π-systems (this work)

[1,j] sigmatropic proton shift

Scheme 2 Proton transfer and sigmatropic proton shift.

Table 1 [1,j] sigmatropic proton shifts in polyenyl anions $C_jH_{j+3}^-$ under thermal conditions
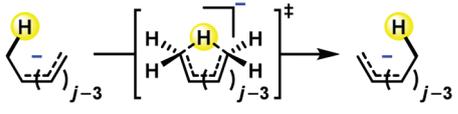
j	Polyenyl anion	TS	Stereochemistry	$\Delta E^{\ddagger}$ [kcal mol^{-1}]
2	Ethyl anion, **A**	**TS1**	Suprafacial	48.2 (48.2)
4	But-2-enyl anion, **B**	**TS2**	Suprafacial	32.8 (32.8)
6	Hexa-2,4-dienyl anion, **C**	**TS3**	Antarafacial	21.0 (14.2)
8	Octa-2,4,6-trienyl anion, **D**	**TS4**	Suprafacial	40.5 (31.2)
10	Deca-2,4,6,8-tetraenyl anion, **E**	**TS5**	Antarafacial	49.1 (34.6)

Computed at the SCS-MP2/aug-cc-pVTZ//ωB97XD/6-311+G(d,p) level. The reaction barriers were computed starting from the most stable conformers. Those starting from the reactive conformers are given in parentheses. ΔE_{rxn} = 0 in all cases. rxn = reaction.
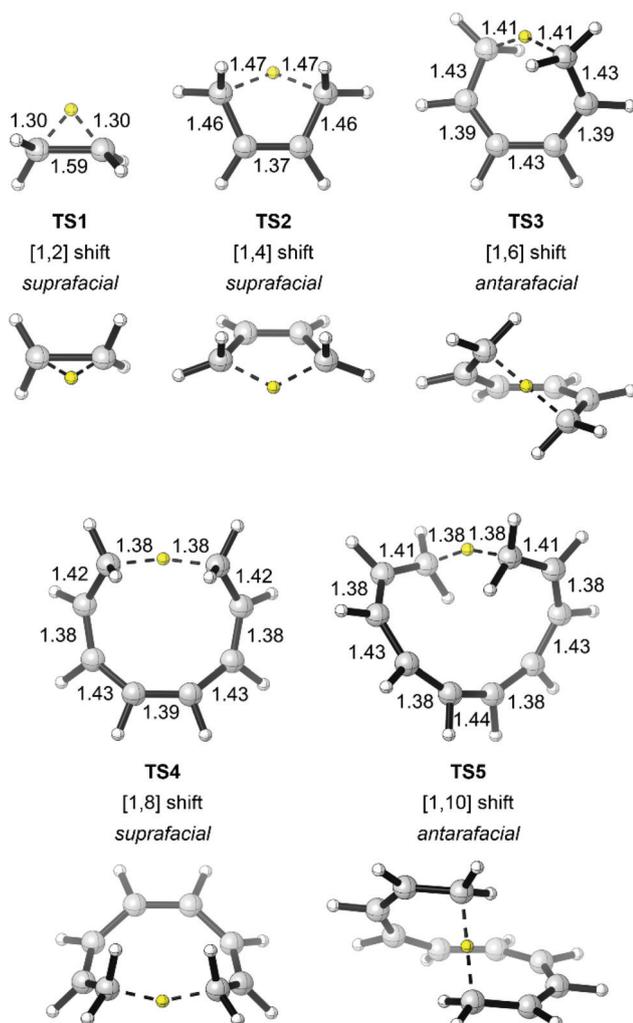
Fig. 1 Optimized geometries for sigmatropic proton shift transition structures **TS1–5**. The bond lengths are reported in Å. Computed at the ωB97XD/6-311+G(d,p) level. Color scheme: C, gray; H, white; the migrating hydrogen, yellow.

Fig. 2 Analysis of sigmatropic proton shifts according to the Woodward–Hoffmann rules.[4]

suprafacially because the antarafacial [1,2] shift is geometrically unrealizable.

The activation barriers for the [1,j] sigmatropic proton shifts in polyenyl anions **A–E** are 48.2 (j = 2), 32.8 (j = 4), 21.0 (j = 6), 40.5 (j = 8), and 49.1 (j = 10) kcal mol^{-1}, respectively (Table 1). We reasoned that this trend is due to the trade-off between ring strain and stereoelectronic requirement, *i.e.*, the linear C···H···C displacement in the transition structure (Fig. 3). Previously we have shown that the minimization of the Pauli repulsion between carbon acid and carbanion results in the linear C···H···C arrangement of the intermolecular proton transfer transition structure (Fig. 3a).[19] Similarly, in the transition structure for the [1,j] sigmatropic proton shift, the optimal C···H···C bond angle is expected to be around 180°. To
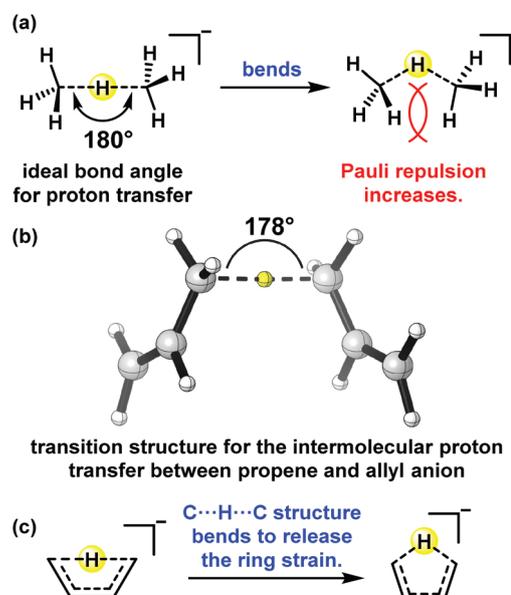
Fig. 3 The trade-off between stereoelectronic requirement and ring strain in the transition structure. Computed at the ωB97XD/6-311+G(d,p) level. Color scheme: C, gray; H, white; the migrating hydrogen, yellow.

verify this hypothesis, we have located the transition structure for the intermolecular proton transfer between propene and allyl anion, and found that the C⋯H⋯C bond angle is 178°, which is indeed very close to 180° (Fig. 3b). However, in the intramolecular case, the attempt to achieve a C⋯H⋯C bond angle of 180° leads to an increase of the ring strain. As a result, the C⋯H⋯C structure bends to balance the stereoelectronic requirement and ring strain in the transition structure (Fig. 3c).

Among the five sigmatropic proton shifts within the polyenyl anions that we investigated, the [1,6] shift has the lowest activation barrier due to the relatively small ring strain in the transition structure (the average C–C–C bond angle is 125°, which is close to the typical magnitude of bond angles around a trigonally bonded carbon, *ca.* 120°). Our quantum chemical calculations indicated that the activation barrier of the antarafacial [1,6] proton shift in the carbanion **C** is 21.0 kcal mol^{-1}, suggesting that such a process might take place intramolecularly. These results are in accordance with the experimental investigations on the [1,6] shifts in pentadienyl lithiums by the Bates group (Scheme 1b, eqn (5)).[18b,32]

For other sigmatropic proton shifts, large deviations of the C⋯H⋯C and/or C–C–C bond angles from their optimal values (180° and *ca.* 120°, respectively) arise. For example, the C⋯H⋯C bond angle in **TS1** (the [1,2] proton shift transition structure) is only 76° (the ideal value is 180°), while the average C–C–C bond angle in **TS5** (the [1,10] proton shift transition structure) is 137° (the ideal value is *ca.* 120°). As a result, the activation barriers for [1,2], [1,4], [1,8], and [1,10] shifts are very high (more than 30 kcal mol^{-1}). We suggested that these sigmatropic reactions cannot occur intramolecularly under mild reaction conditions, yet could take place *via* a protonation/deprotonation mechanism with the help of proton shuttles.

Herein we use a [1,4] proton shift in the but-2-enyl anion **B** as an example to support this point of view (Fig. 4). If there

exists a trace amount of water (or other proton shuttles) in the reaction system, the [1,4] proton shift will have two reaction pathways.[14,33] One is the concerted pathway, which requires an activation barrier of 32.8 kcal mol^{-1}. The other is the stepwise pathway.[34] First, the carbanion **B** and water form a hydrogen-bond complex **F**, which may undergo rapid protonation (the reaction barrier is only 5.2 kcal mol^{-1}) to generate another hydrogen-bond complex **G** consisting of (*Z*)-but-2-ene and a hydroxyl ion. Then, deprotonation at the C4 position takes place *via* **TS6'** (the reaction barrier is only 1.5 kcal mol^{-1}), followed by the release of a water molecule, leading to the formal [1,4] sigmatropic proton shift product **B'**. Therefore, the assistance of water can indeed reduce the activation barrier by a magnitude of *ca.* 20 kcal mol^{-1} (*ca.* 30 kcal mol^{-1} in terms of the Gibbs energy of activation). We reasoned that the stepwise pathway is favored over the concerted one because the intermolecular proton transfer does not suffer from ring strain and therefore can better fulfill the stereoelectronic requirement, *i.e.*, the linear C⋯H⋯X (X = O or C) displacement in the transition structure.

Influence of the π-framework

In this part, to shed light on the difference between π- and σ-frameworks, we compared the activation barriers for sigmatropic proton shifts with those for proton transfers induced by nonconjugated carbanions (Scheme 3). We found that sigmatropic proton shifts generally require higher activation barriers than the corresponding proton transfers (21.0 kcal mol^{-1} for a [1,6] sigmatropic proton shift *versus* 15.1 kcal mol^{-1} for a 1,6-proton transfer in an *n*-hexyl anion **H**, Scheme 3a; 32.8 kcal mol^{-1} for [1,4] sigmatropic proton shift *versus* 18.2 kcal mol^{-1} for 1,4-proton transfer in an *n*-butyl anion **I**, Scheme 3b).

We reasoned that, as compared with the nonconjugated systems, sigmatropic proton shifts suffer from two disadvan-
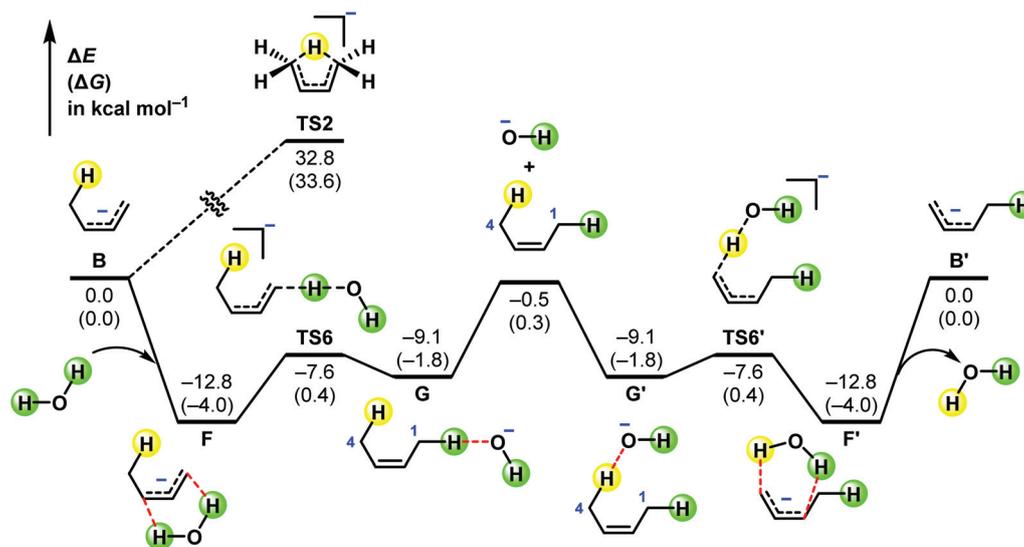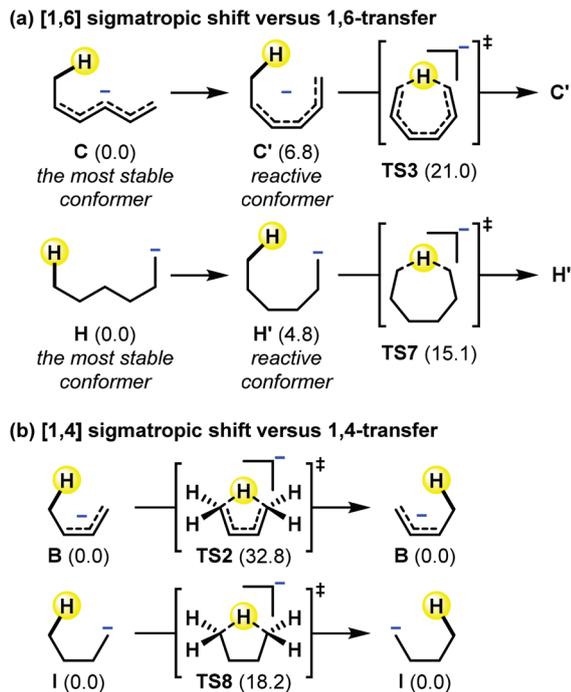

Fig. 4 Concerted *versus* stepwise pathways for [1,4] proton shift in the carbanion **B**. Computed at the SCS-MP2/aug-cc-pVTZ//ωB97XD/6-311+G(d, p) level.

7442 | *Org. Biomol. Chem.*, 2017, **15**, 7439–7446

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(a) [1,6] sigmatropic shift versus 1,6-transfer

(b) [1,4] sigmatropic shift versus 1,4-transfer

Scheme 3 Difference between π- and σ-frameworks. ZPE-corrected electronic energies are reported in kcal mol^{-1}. Computed at the SCS-MP2/aug-cc-pVTZ//ωB97XD/6-311+G(d,p) level.

tages. One is the larger conformational energy change originating from the partial loss of the conjugation energy. For example, the energy for the conversion of the most stable conformer of the dienyl anion **C** into its reactive conformer **C′** is 6.8 kcal mol^{-1}, whereas such energy penalty in the corresponding nonconjugated counterpart, **H → H′**, is smaller (4.8 kcal mol^{-1}). Additionally, if we subtract the conformational energy changes from the overall activation barriers, the resulting reaction barriers for the [1,6] sigmatropic proton shift and 1,6-proton transfer are 14.2 and 10.3 kcal mol^{-1}, respectively. We suggested that this is due to the worse fulfillment of the stereoelectronic requirement (linear C···H···C displacement) in the sigmatropic proton shift transition structure **TS3** (the C···H···C bond angle in **TS3** is 146°) compared to the corresponding nonconjugated system (the C···H···C bond angle in **TS7** is 162°). The reason behind this difference is that the π-framework in the polyenyl anion **C′** is more rigid than the σ-framework of the nonconjugated carbanion **H′** with flexible carbon–carbon single bonds.

Similarly, the C···H···C bond angle in the [1,4] sigmatropic proton shift transition structure **TS2** is 123°, which is smaller than that in its nonconjugated counterpart (the C···H···C bond angle in the 1,4-proton transfer transition structure **TS8** is 136°). As a result, the [1,4] sigmatropic proton shift is more sluggish than the corresponding 1,4-proton transfer (the activation barriers for the [1,4] sigmatropic proton shift and 1,4-proton transfer are 32.8 and 18.2 kcal mol^{-1}, respectively). Based on these discussions, we conclude that, compared to the flexible σ-frameworks, the rigid π-frameworks lead to larger

ring strains in the proton shift transition structures, and consequently induce higher activation barriers.

Influence of the thermodynamic driving force

According to the Marcus equation (eqn (6)), the activation barrier ($\Delta E^{\ddagger}$) can be divided into two parts, namely the intrinsic barrier ($\Delta E_i^{\ddagger}$) and the thermodynamic contributions.[35] In most cases, the stronger the thermodynamic driving force is, the lower the activation barrier will be. To verify whether the same conclusions hold for sigmatropic proton shifts, we investigated six [1,4] proton shifts with thermodynamic bias (Table 2), and compared them with the thermoneutral parent system, the [1,4] shift in carbanion **B** with an activation barrier of 32.8 kcal mol^{-1}. We chose these model reactions because of their relevance to the experimental studies (Scheme 1, eqn (3) and (4)).[15,16]

$$\Delta E^{\ddagger} = \Delta E_i^{\ddagger} + \Delta E_{rxn}/2 + (\Delta E_{rxn})^2/(16\Delta E_i^{\ddagger}) \qquad (6)$$

For the [1,4] proton shift in azomethine ylide **J**, the activation barrier decreases to 23.0 kcal mol^{-1} due to the existence of a strong thermodynamic driving force of −24.4 kcal mol^{-1} (possibly originating from the transformation of a carbon–nitrogen double bond into a more stable carbon–carbon double bond). According to the Marcus equation, we calculated the intrinsic barrier of this process to be 34.1 kcal mol^{-1},

Table 2 [1,4] sigmatropic proton shifts under thermal conditions
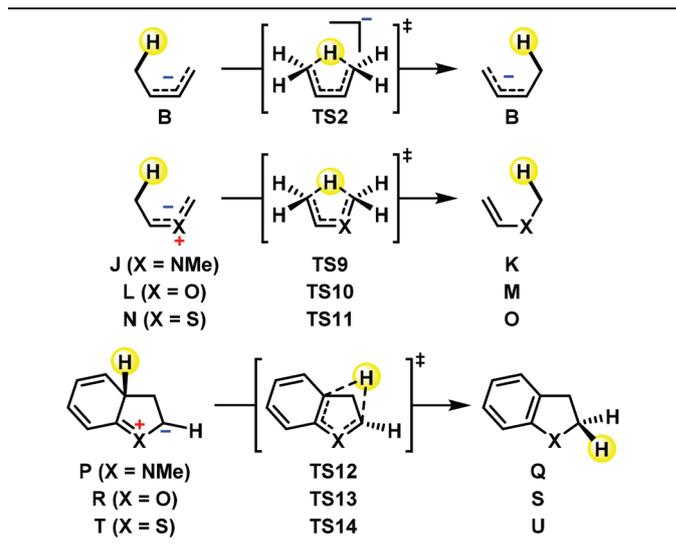
Entry	Reaction	TS	ΔE_{rxn}	$\Delta E^{\ddagger}$	$\Delta E_i^{\ddagger}$ [a]
1	**B → B**	**TS2**	0.0	32.8	32.8
2	**J → K**	**TS9**	−24.4	23.0	34.1
3	**L → M**	**TS10**	−45.4	14.9	33.8
4	**N → O**	**TS11**	−32.5	21.4	35.8
5	**P → Q**	**TS12**	−51.0	15.4	36.4
6	**R → S**	**TS13**	−66.5	9.4	34.7
7	**T → U**	**TS14**	−62.0	10.5	34.5

Energies are reported in kcal mol^{-1}. Computed at the SCS-MP2/aug-cc-pVTZ//ωB97XD/6-311+G(d,p) level. rxn = reaction. [a] Intrinsic barriers.

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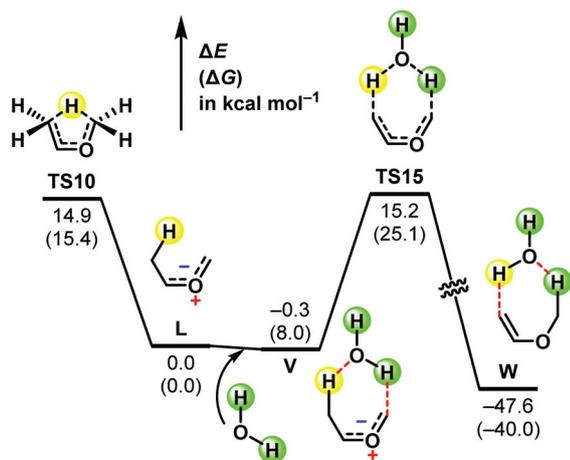*Org. Biomol. Chem.*, 2017, **15**, 7439–7446 | 7443

Fig. 5 Direct *versus* water-assisted mechanisms for [1,4] proton shift in the carbonyl ylide **L**. Computed at the SCS-MP2/aug-cc-pVTZ//ωB97XD/6-311+G(d,p) level.

which is close to that of the parent system (32.8 kcal mol^{-1}). In the presence of an even stronger driving force of −45.4 kcal mol^{-1}, the activation barrier for the [1,4] shift (in the carbonyl ylide **L**) can be further reduced to only 14.9 kcal mol^{-1} even though the intrinsic barrier is still as high as 33.8 kcal mol^{-1}.

Then, we investigated the [1,4] shifts in benzobicyclic systems **P**, **R**, and **T** (Table 2, entries 5–7). Although the intrinsic barriers of these reactions are similar to their acyclic counterparts **J**, **L**, and **N**, respectively (Table 2, entries 2–4), the sigmatropic shifts in bicyclic systems are much more facile due to the utility of aromatization as an additional driving force.

Furthermore, to verify whether these sigmatropic proton shifts with thermodynamic bias can also be accelerated by proton shuttles, we considered the water-assisted pathway in the carbonyl ylide **L** as an example (Fig. 5).[36] Unlike the stepwise pathway of the carbanion **B** (Fig. 4), the assisted pathway of the carbonyl ylide **L** is concerted. The reaction barrier is 15.5 kcal mol^{-1}, which is similar to that of the intramolecular pathway (14.9 kcal mol^{-1}). However, due to the entropy penalty, the assisted mechanism is strongly disfavored over the direct mechanism by 9.7 kcal mol^{-1} in terms of the Gibbs energy of activation (25.1 kcal mol^{-1} for the assisted mechanism *versus* 15.4 kcal mol^{-1} for the direct mechanism). Therefore, the [1,4] proton shift in the carbonyl ylide **L** cannot be accelerated by proton shuttles. For sigmatropic proton shifts in **R** and **T** (and perhaps the related systems), whose reaction barriers are even lower than the diffusion limit, proton shuttles have no chance to be involved.

Conclusions

Based on quantum chemical calculations, we found that the Woodward–Hoffmann rules can be applied to understand the facial selectivity of thermal [1,*j*] sigmatropic proton shifts. The

antarafacial proton shift is symmetry allowed when $j = 4n + 2$, whereas the sigmatropic proton shift occurs suprafacially when $j = 4n$. The activation barriers for the [1,*j*] sigmatropic proton shifts within the polyenyl anions $C_jH_{j+3}{}^-$ are 48.2 ($j = 2$), 32.8 ($j = 4$), 21.0 ($j = 6$), 40.5 ($j = 8$), and 49.1 ($j = 10$) kcal mol^{-1}, respectively. This trend is due to the trade-off between ring strain (mainly caused by the deviation of the C–C–C bond angles from their optimal values) and stereoelectronic requirement (the linear C···H···C displacement in the transition structure). Moreover, these activation barriers were found to be higher than those for the corresponding proton transfers in nonconjugated carbanions due to the penalties from larger conformational energy changes and worse fulfillments of the stereoelectronic requirements (the rigid π-frameworks lead to larger ring strains in the proton shift transition structures). Among the sigmatropic proton shifts within polyenyl anions, only the [1,6] proton shift with the lowest activation barrier can take place in a direct manner under mild reaction conditions. The others are unlikely to proceed intramolecularly, but can be assisted by proton shuttles *via* the protonation/deprotonation mechanism (unless strong thermodynamic driving forces are present to facilitate the intramolecular processes; six examples are given in Table 2).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Notes and references

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7446 | *Org. Biomol. Chem.*, 2017, **15**, 7439–7446

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