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Perspectives

Bent bonds and the antiperiplanar hypothesis as a simple model to predict Diels–Alder reactivity: retrospective or perspective?

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1. Introduction

In a previous disclosure,[1] we presented a revival of the Slater/Pauling 'bent bond' valence model[2] (τ-bonds, tau-bonds, banana bonds) drawing specific attention to its stereoelectronic consequences. Bent bond model[3] 1 is mathematically equivalent to the familiar Hückel σ/π model[4] 2 from the standpoint of molecular orbital theory, both models being interconvertible via unitary transformation of the basic atomic orbital functions (Fig. 1).[5] However, the theoretical work of Messmer and Shultz found that

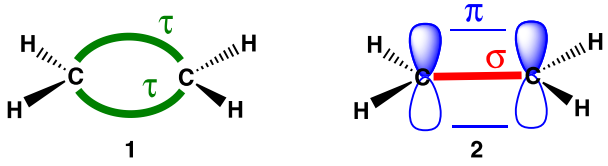

Fig. 1. Slater/Pauling τ-bond model (left) versus Hückel σ/π model (right) of ethylene.

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the bent bond description was energetically superior to the symmetry-restricted σ/π bond representation in the theoretical limit of wave functions (within the context of correlated wave functions, which allows the more appropriate bonding scheme to be determined variationally).[3i–m]

A fundamental aspect of the bent bond model is that it confers 'tetrahedral character' to unsaturated carbons, including those in olefins and carbonyl compounds, and allows one to apply concepts normally associated with saturated systems. For instance, the preferred staggering of groups on adjacent saturated centers can be applied to unsaturated systems if the olefinic bonds are represented as bent bonds (Fig. 2), and account for their preferred conformation.[3f,6]

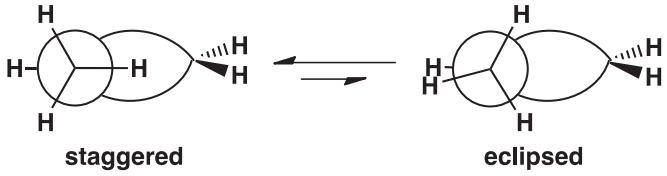

Fig. 2. Newman projections of propene conformations, bent bond view.

Likewise, the notion of antiperiplanar interactions, a foundational stereoelectronic concept,[7] can be extended by considering bent bonds and their particular alignment with neighboring lone pairs and bonds (Fig. 3). The resulting "augmented" bent bond model was applied universally to the conformational analysis and reactivity of compounds bearing C–C=C and C–C=O groups, and to esters, amides, enol ethers, enamines, etc.[1,3f,8] In fact, a complete monograph on stereoelectronic effects in organic chemistry can be redescribed using the bent bond/antiperiplanar (BBA) hypothesis with the same predictive outcomes concerning conformation and reactivity![7a]

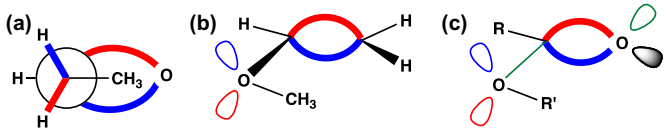

Fig. 3. (a) Newman projection for the most stable conformer of propanal, highlighting C–H bonds antiperiplanar to bent bonds of the carbonyl group; (b) perspective view of the most stable conformer of methyl vinyl ether; (c) perspective view of a *Z*-ester highlighting the two ether oxygen lone pairs antiperiplanar to bent bonds of the carbonyl group.

Our investigations of how the bent bond model could be used qualitatively to rationalize chemical reactivity and stereoselectivity proved to be much more far reaching than originally anticipated. In our initial disclosure,[1] we described the analysis of many stereoselective reactions using the BBA hypothesis, including carbonyl additions, E′ eliminations, enolizations, conjugate additions, even electrocyclic reactions that one generally assumes to be governed by the Woodward–Hoffmann rules.[9] Aromaticity/antiaromaticity was also rationalized, all from a simple analysis of delocalization between antiperiplanar bent bonds. A similar analysis of sigmatropic reactions yielded the same outcome, in which preferred reactivities and stereoselectivities were self-evident from the BBA hypothesis.[10] Thus, using the bent bond model with consideration of antiperiplanar interactions provided a qualitative yet novel basis for understanding electron delocalization and the reactivity inherent to a surprisingly wide range of unsaturated organic systems.

Turning our attention to the Diels–Alder reaction, it became quite clear that application of the BBA hypothesis yielded a simple reaction model that not only predicted the all too numerous outcomes of the reaction (vide infra), but also was qualitatively consistent with the latest computational and mechanistic studies while providing new insight into its mechanistic origins. Although quantum mechanical calculations provide precise geometric and energetic parameters on ground states and transitions states, they do not necessarily shed light on the underlying electronic mechanisms that may govern a given chemical reaction. For example, computational methods have yet to produce a consensus on the fundamental origins of the anomeric effect[11] and the preferred conformation of ethane.[12]

To this day, organic chemists continue to make use of simple, often visual, conceptual models to predict the outcome of organic processes (Markovnikov's rule, Alder rule, Cram's rule, Felkin–Anh model, Woodward–Hoffmann rules, antiperiplanar lone pair hypothesis, etc.), all *sine silico*. They continue to conceive simple theories where intuition, supported by experimentation, is at the basis of conceptual advancements. And as stated by Berson "*Chemists are pragmatic and don't give much thought to the shortcomings of a theory as long as it remains useful.*"[13]

The simple theoretical model presented herein is based on traditional concepts including the Slater/Pauling model for tau-bonds, Wheland's theory of resonance, the Walden inversion, and the antiperiplanar lone pair hypothesis, yet accounts for so many problems of conformational analysis and reactivity, and for such a wide scope of organic reactions. Ultimately, is this a retrospective of outdated concepts or a fresh perspective for organic chemistry? We hope to convince the reader of the latter and to provide, on the one hand, a simple and practical visual model for practicing synthetic chemists to predict the outcome of the Diels–Alder reaction, and on the other hand, to stimulate thought and discussion about the possible mechanistic underpinnings of the reaction.

2. The Diels–Alder reaction revisited

2.1. 1,3-Butadiene

Both dienes and dienophiles can be represented with the bent bond model. Let us first examine 1,3-butadiene, the prototypical Diels–Alder diene. 1,3-Butadiene should exist in either *s-trans* or *s-cis* conformations, assuming conjugation of the two double bonds. The *s-trans* conformer is the most stable with a ≈3.9 kcal/mol rotational barrier to produce the *s-cis* form, but the latter form is not detected at equilibrium.[14] The bent bond model accounts well for the preferred *s-trans* conformer by staggering the substituents about the central C–C bond (Fig. 4a) and, provides an alternate model for conjugation as the opposing bent bonds are antiperiplanar to each other.

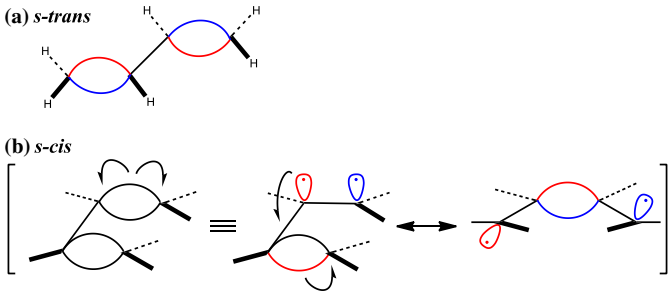

Fig. 4. Bent bond models of 1,3-butadiene.

What about planar *s-cis* 1,3-butadiene? Calculations support a quasi-planar geometry for the *s-cis* form, especially when participating in cycloaddition reactions.[15] The planarity of the *s-cis* structure seems at odds with the bent bond model because of eclipsing interactions at the central bond. However, its 1,4-diradicaloid resonance structure (i.e., a singlet, spin-paired formal

bond) alleviates the eclipsing strain. Consistent with our initial disclosure,[1] the radicals in the resonance structures shown in Fig. 4b are represented as partially pyramidalized centers. Thus, allylic radicals can properly delocalize via stereoelectronic alignment with their respective antiperiplanar bent bonds. Messmer's computational studies on the allyl radical showed that the bent bond model was favored over the σ/π model by 2.3 kcal/mol, using explicitly correlated ab initio VB wave functions, even with its geometry restricted to C_{2v} symmetry.[3k] A direct consequence of the antiperiplanar delocalization model is that the singlet diradicaloid geometry is trans as shown in Fig. 4b and 1,3-dienes may have relevant '1,4-diradicaloid character' that will be invoked during the analysis of their reactivity, regio- and stereoselectivity in the Diels–Alder reaction. The antiperiplanar delocalization in an allylic radical paints a picture that is somehow reminiscent of the frontier orbital symmetry of its SOMO while retaining tetrahedral character at the two termini.

The *s-cis* conformer of 1,3-butadiene is actually a saddle point and slight skewing of the structure leads to a local minimum that partly staggers the central C–C bond. Thus, the planar *s-cis* form must be more reactive than the skewed local minimum, and has greater diradicaloid character. Similar observations have been made for acrolein where the *s-trans* conformer is favored by ≈1.7 kcal/mol over the *s-cis* form but the latter may be more reactive as a Diels–Alder dienophile based on calculations.[16] Likewise, cyclopentadiene (planar) is known experimentally to be more reactive than 1,3-cyclohexadiene (skewed).[17,18] Recent theoretical findings by Hiberty on 1,3-dipolar cycloadditions show a direct correlation between barrier heights for the reactions and the weight of the diradical structures used to represent the 1,3-dipole component in their valence bond ab initio calculations.[19] Shaik also referred to the electronic distortion energy for diradical formation in the Diels–Alder reaction.[20] The estimation of singlet diradical character by experiment was not demonstrated until recently.[21]

2.2. Prototypical Diels–Alder reaction

As shown in Fig. 5, the reaction of 1,3-butadiene with a generic dienophile (represented here as any monosubstituted ethylene X–CH=CH_2) can be viewed as an initial interaction of diene **3** with dienophile **4** invoking their singlet diradicaloid resonance structure. For representational simplicity, partly pyramidalized radicals are drawn with single orbital lobes but one must assume the presence of a smaller lobe on the opposite side (as in an sp^3 hybrid for instance), which could participate in the proposed bond formation. Formation of cycloadduct **7** warrants that one radical inversion at the distal allylic center of intermediate structure **5** is necessary to reach transition state **6**. Radical inversions are typically rapid, low-barrier events, but we nevertheless assume that inversion in the specific case of the allylic radical is somewhat slower than for its alkyl counterpart because delocalization of the allyl radical with its antiperiplanar bent bond is disrupted during inversion. Such a radical inversion would lower the activation energy of the Diels–Alder reaction, establishing a six-electron ring current at the transition state. In other words, the transition state would have transient aromatic character; this is of course in agreement with Evans' proposal[22a,b] and strongly advocated later by Dewar.[22c] Overall, the model describes a concerted but asynchronous reaction where the formation of the first bond, involving the more reactive radicaloid center on both diene and dienophile, is somewhat more advanced than the second bond, consistent with the notion that the two incipient bonds have quite different bond lengths at the transition state.[15]

The addition of the dienophile is generally cis as the relative geometry of its substituents is retained in the cycloadduct (Alder–Stein rule[23]). This implies that the radical inversion necessary for forming the second bond is concurrent with the formation of the first bond. There are, of course, experimental examples in the literature where this is not the case; the reaction model in Fig. 5 readily accounts for these if one assumes that the interaction in **5** leads to the formation of a single bond leading to a true diradical intermediate in these unusual cases. In their critical survey of the Diels–Alder reaction, Sauer and Sustmann present several compelling cases for this two-step model.[24] Indeed, after the formation of the first bond, a diradical intermediate would result that could undergo bond rotation of the remaining dienophile C–C bond and, upon inversion of two radical centers, could recyclize to produce what corresponds to the *anti*-addition product. However, under normal circumstances, cyclization would take place via radical inversion to an aromatic transition state resulting in *syn*-addition but, in some cases where enthalpic impediments may be present, bond rotation could take place prior to ring closure to produce the *anti*-addition product.

After all, the notion that Diels–Alder reactions can take place through a diradicaloid mechanism has been suggested previously by both theoreticians and experimentalists[25] but, to the best of our knowledge, the reactive model shown in Fig. 5 invoking diradicaloid character of the diene and dienophile and radical inversion at the Diels–Alder transition state as a consequence of the bent bond model, is described here for the first time.

The diradicaloid model readily explains substituent and directive effects in the Diels–Alder reaction, including the *ortho*/*para* rule.[25] In all cases, classical inductive, resonance, and steric effects can correctly assign the more reactive radicaloid center in both diene and dienophile, dictating, which bond will be more advanced at the transition state, and determining the regioselectivity of the reaction. For example, monosubstituted butadienes can be represented by resonance structures **8** and **11** (Fig. 6). The acrolein dienophile can also be represented as its diradicaloid resonance structure. The *ortho* and *para* products **10** and **13** are readily evident from the asynchronous diradicaloid transition states **9** and **12**, respectively, that emerge from combination of the more reactive radicaloid centers on both diene and dienophile. For diene **8**, the primary allylic radicaloid center is deemed more reactive than its secondary counterpart. For diene **11**, the radicaloid center nearest to the electron-donating R group is deemed more reactive. For acrolein, the radicaloid center farthest from the aldehyde carbonyl

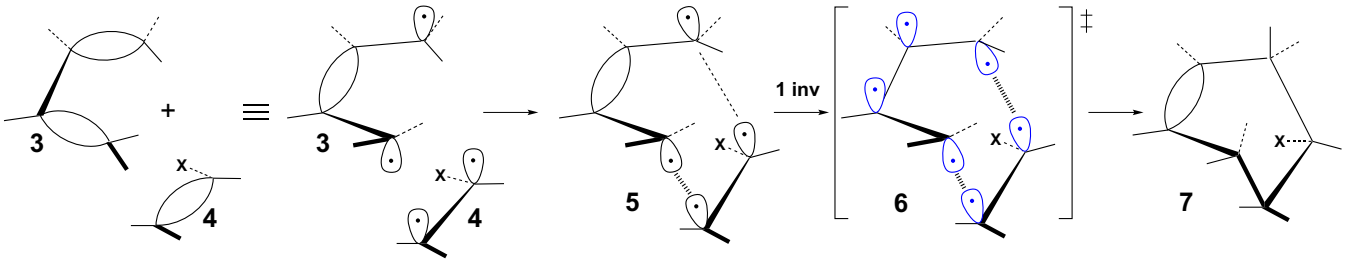

Fig. 5. Bent bond model for cycloaddition of *s-cis* 1,3-butadiene with a generic dienophile.

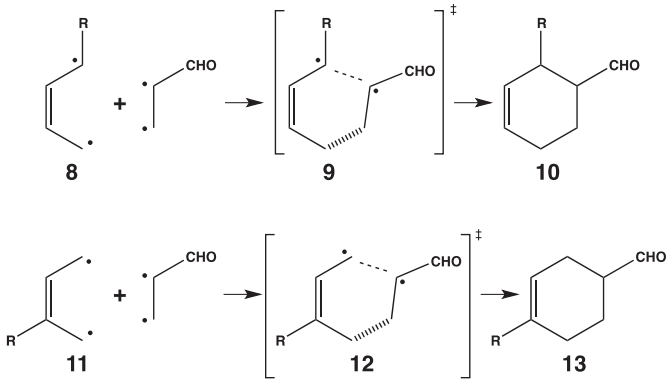

Fig. 6. Diradicaloid transition states and the *ortho*/*para* rule.

group is deemed more reactive. Consequently, transition states **9** and **11** correspond to their lowest-energy singlet diradicaloid (LESD) transition states.

As a recent example of how the LESD transition state can predict the outcome of the Diels–Alder reaction, it was reported that the methyl substituent in masked *ortho*-benzoquinones **14**/**15** affects the activation energy and asynchrony of the reaction (Fig. 7).[26] Indeed, cycloaddition of diene **14** with methyl vinyl ketone to form **17** is 15 times faster than for diene **15**. This agrees with the concept that the first bond formed at LESD transition state **16** is less sterically hindered for **14** (R=H) than for **15** ($R=CH_3$) and that the incipient radical in **16** next to R′ is tertiary when diene **14** is used. These experimental results were further supported by ab initio calculation, including the relative bond lengths at the transition state.

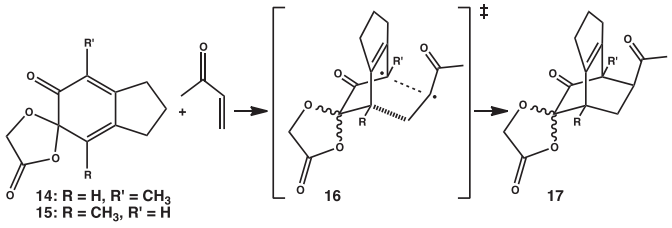

Fig. 7. Masked *ortho*-benzoquinones as Diels–Alder dienes.

2.3. Dimerization of cyclopentadiene

The bent bond model for the dimerization of cyclopentadiene can be considered next. The preferred *endo*-geometry for cycloaddition is usually attributed to some form of secondary orbital interactions at the transition state, although steric effects and other rationalizations[15,27,28] have also been put forth, and remains a subject of ongoing debate. Caramella's bis-pericyclic model based on DFT calculation has received much attention in recent years.[29] As shown in Fig. 8, the bent bond diene model dictates that for *endo*-cycloaddition, the approach of two identical cyclopentadiene diradicaloids **18** leads to orbital interactions as shown in **19**; the latter is C_2-symmetric in terms of both geometry and stereoelectronics. Radical inversion is now possible at two different sites leading to transition states **20** or **21** (i.e., corresponding to the Caramella transition state) to produce stereoelectronically identical cycloadducts **22** or **23**. So, for the dimerization of cyclopentadiene there exist two isoenergetic ways to form the second bond by radical inversion (i.e., at **c**/**f** in **20** and **a**/**d** in **21**) as the first bond is in the process of forming.

A similar analysis for the *exo*-dimerization of cyclopentadiene requires the approach of two diradicaloids of opposing chirality as in **24** (Fig. 9), resulting in only one possible transition state (i.e., **26**).

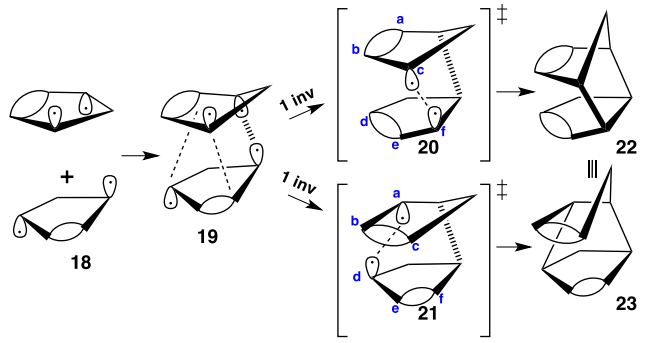

Fig. 8. *endo*-Dimerization of cyclopentadiene.

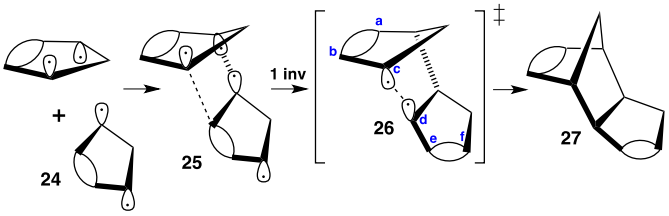

Fig. 9. *exo*-Dimerization of cyclopentadiene.

The transition state geometries in the key computational study by Houk and Schleyer[15b] fit nicely with the diradicaloid model presented here. For example, the transition state for the *endo*-dimerization of cyclopentadiene shows very different lengths for the two incipient bonds (1.922, 2.910 Å), as predicted by transition states **20**/**21** en route to **22**/**23**. The C_2-symmetry at the transition state is also evident in **20**/**21**, with two different radical interactions for the *endo*-dimerization. The reaction model is fully compatible with the bis-pericyclic transition state model put forth by Caramella[29] and later studied by Houk.[27b]

The mechanism presented in Fig. 8 has obvious connection to the Cope rearrangement.[25a,†] As shown in Fig. 10, cycloadducts **28** and **28′** are directly interconvertible by Cope rearrangement if the bond cleavage is accompanied by a *double* radical inversion (i.e., via transition state **29**). At this juncture, we note that the activation energy for Cope rearrangement is known to be higher than for the corresponding Diels–Alder reaction; in our model, Cope rearrangement requires double radical inversion whereas Diels–Alder cycloaddition requires only one. The model is also consistent with the notion that the Cope transition state involves a six-electron cyclic process with aromatic character as originally proposed by Dewar.[22c] It is also interesting to note that the singlet diradical character of the transition state of the Cope rearrangement (and its aromatic character) was demonstrated by computational work.[30]

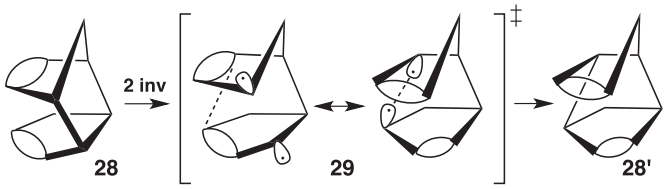

Fig. 10. Bent bond model for Cope rearrangement.

† In the classic Cope rearrangement reported by Woodward and Katz, α-1-hydroxydicyclopentadiene was shown to rearrange stereospecifically to *syn*-8-hydroxydicyclopentadiene *without* any apparent dissociation of the diene and dienophile moieties.[25a]

2.4. Thiele's acid

The LESD transition state model accounts for the formation of Thiele's acid **37**, a classic cycloadduct formed almost exclusively amongst 16 possible isomers from the cycloaddition between cyclopentadienecarboxylic acid tautomers (Fig. 11).[31] Representing the diene tautomers as 1,4-diradicaloid structures, the cross-conjugated tautomer **30** is assigned as the better diene (i.e., influence of electron-withdrawing E group and lesser steric hindrance at diene termini) and the linear-conjugated tautomer **31** is assigned as the better dienophile (i.e., more electron-withdrawing and less substituted olefin). For each diradical resonance structure, the more reactive center can be assigned based on proximity and conjugation to the E group (shown as asterisks in structures **32** and **33**), dictating, which bond will start to form first. Next, by considering the diradicaloid geometry in the reactants as in **34**, *endo*-approach of the reactants is shown in **35** leading to two different transition states **36** and **38** by allylic radical inversion. Transition state **36** yields Thiele's acid **37** while the alternate route involving transition state **38** leads to cycloadduct **39**, but implies ring closure between two stabilized tertiary radicals, producing two adjacent quaternary centers, which is not observed.

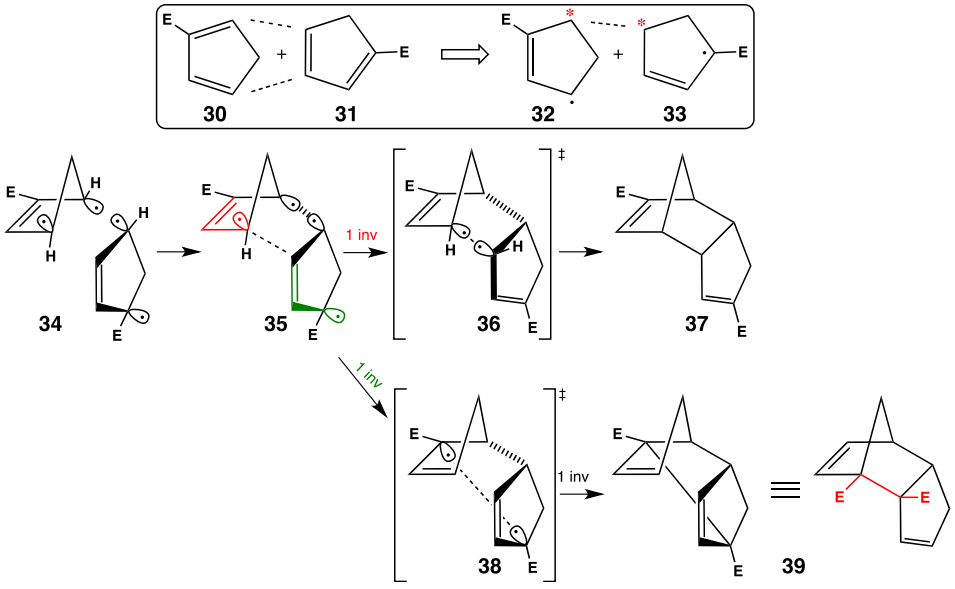

Fig. 11. Formation of Thiele's acid (E=CO_2H).

2.5. Dimerization of 1,3-butadiene

The analysis of 1,3-butadiene dimerization is similar to that of cyclopentadiene (Fig. 12) but also presents an opportunity to discuss the notion of secondary orbital interactions. Two identical diradicaloid *s-cis* 1,3-butadienes (**40**) can approach each other as in **41** leading to isoenergetic transition states **42**/**44** upon single radical inversions. The requirement for the dienophile to be *s-cis* is particularly noteworthy as it corresponds to the Salem–Houk model[15b,32] of *endo*-selectivity. By antiperiplanar delocalization of the allylic radicals into their opposing bent bond, the model predicts more important radical interaction between the diene and the terminal dienophile carbon (i.e., positions **a** and **d** in structure **44** and positions **c** and **f** in structure **42**) corresponding to the Salem–Houk model, than with the inner dienophile carbon (i.e., positions **b** and **e** in structure **42**/**44**) corresponding to the secondary orbital interactions of the Woodward–Katz model. As reported by Houk and Schleyer, Mulliken overlap population analysis[15b] revealed unfavorable overlap between **b** and **e** but favorable overlap between **a** and **d**, in agreement with the **42**←**41**→**44** interconversion model.

The coupling of cyclopentadiene with acrolein or acrylonitrile[33] as well as the dimerization of acrolein[34] can be analyzed in analogous manner.

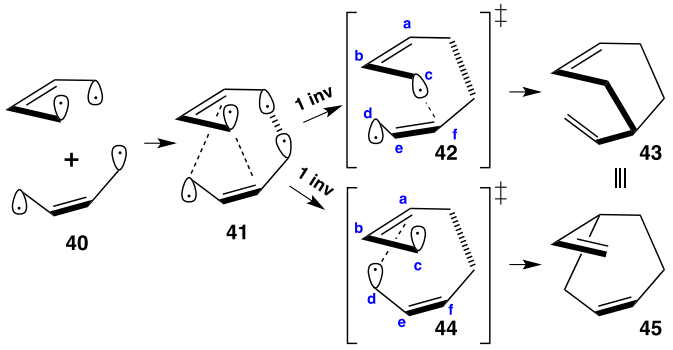

Fig. 12. Bent bond model for dimerization of *s-cis* 1,3-butadiene.

2.6. Furanone dienophiles

Ortuño reported that the thermal cycloaddition of 1,3-butadiene with furanones **56** (Fig. 13, X=OMe or Br) first produces 1,2-adducts **57a**/**57b**, which can then be converted to Diels–Alder adduct **58** *without* prior reversion to the initial reactants.[25e] The authors concluded that the reactions were taking place through a common diradical intermediate. In the bent bond model, the addition shown in **59** would first produce the highly delocalized diradical **60** by formation of one bond. Cyclobutane product **57a** can form via resonance structure **61** *without the need for radical inversion*. The formation of isomer **57b** would proceed by the analogous route **62**→**63**↔**64**→**57b**. Upon heating, cyclobutanes **57a**/**57b** could reform diradicals **61**/**64** and would converge to Diels–Alder racemate **58** after only one allylic radical inversion or without radical inversion by rotation of the butenyl chain. So why do furanones behave so differently as dienophiles compared to, say, 1,3-butadiene? The diene in furanone **56** is in a fixed *s-trans* geometry so neither the ring double bond nor the carbonyl group can

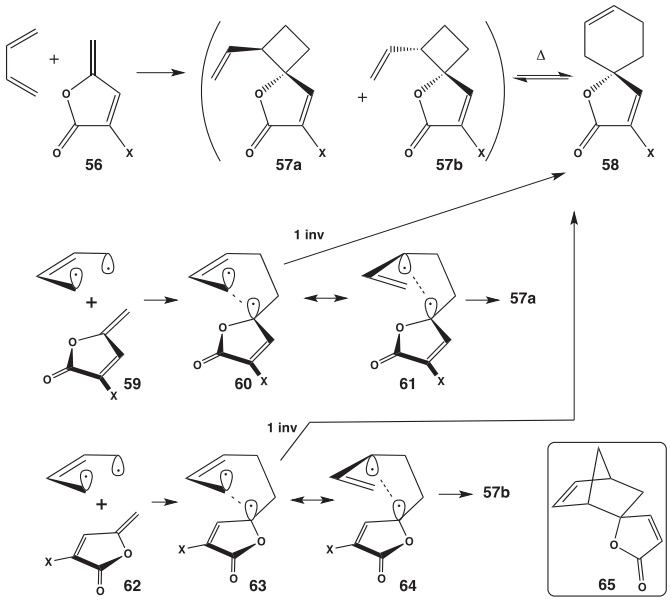

Fig. 13. Reaction of 1,3-butadiene with furanone **10**.

participate in a 'secondary' radical interaction with the diene, perhaps lessening its predisposition toward 4+2 addition. The dimerization of cyclohexadiene also behaves similarly.[17,18] In addition, it has been reported that furanone **56** (X=H) reacts with cyclopentadiene to yield a ~3:1 mixture of isomers in which *exo*-isomer **65** predominates.[35]

2.7. Substituent effects on facial selectivity

As noted by le Noble, "while the Woodward–Hoffmann rules in symmetry-allowed cases successfully specify whether these reactions occur suprafacially or antarafacially, they are silent about *which* faces will be presented for reaction".[36] Using the BBA hypothesis, the facial and regioselectivity as well as stereochemical outcome of Diels–Alder reactions involving functionalized dienes and dienophiles can be readily rationalized. Here are a series of key examples.

Ethylene approaches cyclopentadiene acetate **66** from the most crowded face, *syn* to the OAc group, giving product **67** (Fig. 14).[37] In

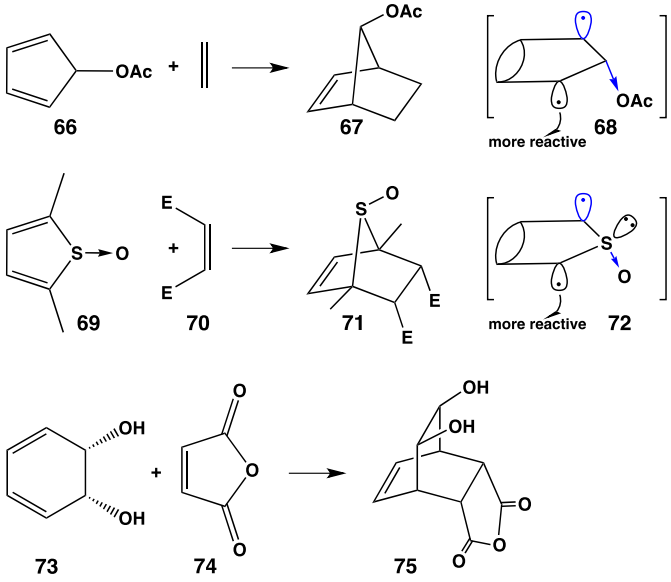

Fig. 14. Effect of diene substituents on Diels–Alder facial selectivity.

bent bond/singlet diradicaloid resonance structure **68**, one radical is antiperiplanar to the electron-withdrawing OAc group, and is stabilized by stereoelectronic alignment. Consequently, the radical *syn* to the OAc group reacts preferentially to give Diels–Alder cycloadduct **67**. A similar analysis for the reaction of diene **69** with dienophile **70** (E=ester) correctly predicts the formation of cycloadduct **71** via diradicaloid resonance structure **72**.[38] Likewise, the facial selectivity for the addition of maleic anhydride **74** to cyclohexadienediol **73**, which gives product **75**, can be rationalized by our simple model.[39]

Many other cases of facially perturbed dienes have been reported that are consistent with the above predictive model. For example, diene **76** reacts preferentially from its β-face whereas the opposite is observed for diene **77** (Fig. 15). Likewise, diene **78** undergoes cycloaddition *syn* to the OMe group.[40] In another interesting case reported by Valenta and Burnell,[41] diene **79** reacted preferentially from the α-face with a wide range of dienophiles. Some conjecture was made about potential hyperconjugative effects but it was concluded that steric effects accounted for the observed stereoselectivity based on MM2 calculations. We note that diene **79** displays two CH bonds (H_a) antiperiplanar to the β-spiro C–C bond whereas only one CH bond (H_b) is antiperiplanar to the α-spiro C–C bond; the bent bond/antiperiplanar hypothesis predicts electron enrichment of the bent bond on the α-face of the diene and formation of the observed cycloadduct isomer. The observed α-cycloadduct from **79** is actually higher in energy than the one resulting from β-attack (0.72 kcal/mol, AM1) so the preferred attack would occur from the more hindered face, assuming a late transition state.

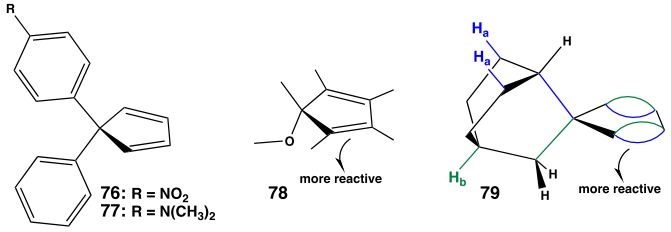

Fig. 15. Other facially perturbed dienes.

Transannular Diels–Alder (TADA) reactions can also be examined by the bent bond model. For example, using a TADA strategy for the total synthesis of the bioactive diterpene (+)-cassaine (Fig. 16), it was shown that triene **80** gave only the *trans-anti-cis* (TAC) cycloadduct **81**.[42] Of the two low-energy transition states, geometry **82** leads to the observed TAC product **81** whereas geometry **84** leads to an unobserved CAT product. In diradicaloid model **83** the electron-withdrawing OR group is antiperiplanar to the diene and is not expected to weaken appreciably the adjacent radical. However, in model **85** the OR group is antiperiplanar to the diene radical and is expected to deactivate the latter toward cycloaddition. Interestingly, in a similar macrocyclic series where OR was replaced by a methyl group, the TADA reaction was not stereoselective.

The influence of dienophile substituents on facial selectivity can also be accounted considering diradicaloid bent bond resonance structures. For example, reaction of cyclic enones **86** (Fig. 17, n=1,2) with 1,3-butadiene in the presence of $AlCl_3$ affords compounds **87** as the principal cycloadducts[43] where the diene added *syn* to the OTBS group of the dienophiles in contra-steric fashion. Bent bond resonance structures **88**↔**89**↔**90** readily explain the selectivity as the carbon radical in **88** would be more reactive than in **90**, the latter being deactivated by the antiperiplanar electron-withdrawing OTBS group.

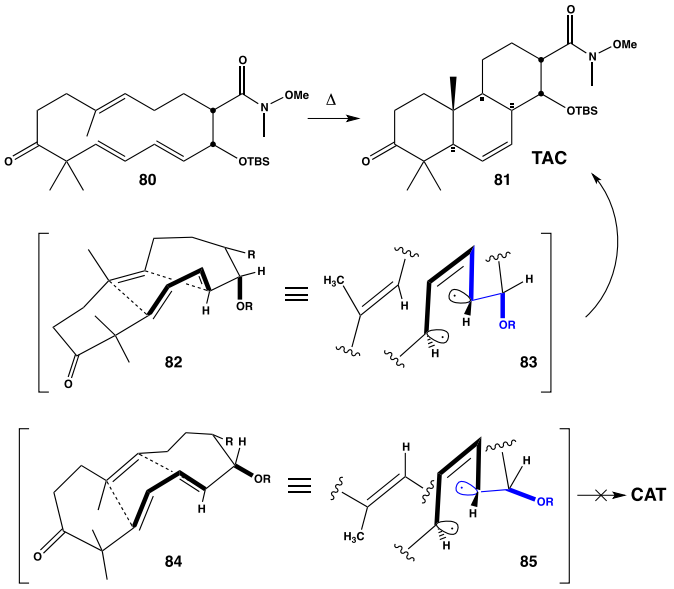

Fig. 16. Stereoselectivity in transannular Diels–Alder reactions.

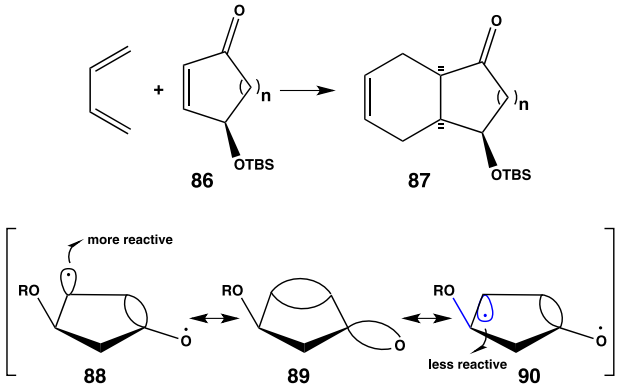

Fig. 17. Effect of dienophile substituents on Diels–Alder facial selectivity.

Cases where the same compound can serve as both diene and dienophile to produce Diels–Alder dimers provide yet another interesting testing ground for the BBA hypothesis. For example, cyclopentadiene epoxide **91** produces only dimer **93** out of four possible cycloadduct racemates (Fig. 18).[44] The facial selectivity can be readily accounted by the electron-withdrawing effect of the epoxide oxygen and, as shown in **94**, one of the radicals is roughly antiperiplanar to the epoxide C–O bond so the opposing radical would be more reactive. The asynchronous reaction model assumes LESD transition state **92** in which the more stable allylic diradicals recombine to form the second bond.

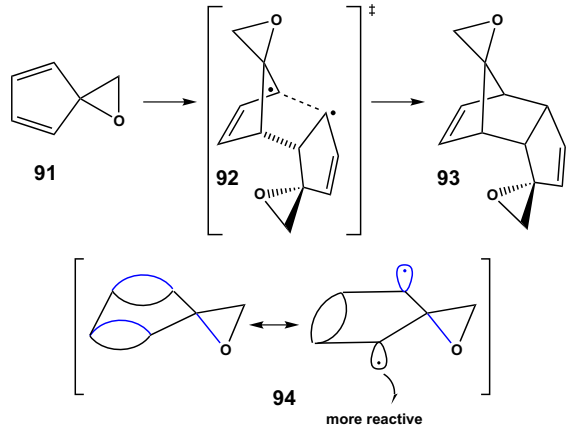

Fig. 18. Dimerization of epoxycyclopentadiene.

Similarly, *o*-quinol **95** dimerizes to give **97** as the only stereoisomer (Fig. 19). In fact, racemic **95** gives only *S*–*S* and *R*–*R* dimers with no *S*–*R* or *R*–*S* cross-over.[45] This remarkable dimerization can be easily explained using LESD transition state model **96**. Regioselectivity is rationalized if the first bond forms via bimolecular combination of the most reactive radicals in the corresponding 1,4-diradicaloid resonance structures. Considering that cyclohexadienone **95** can be viewed as diradicaloid models **98**↔**99** and that the OH group deactivates any antiperiplanar radical (i.e., **98**), the regio- and stereo-selectivity are readily explained.

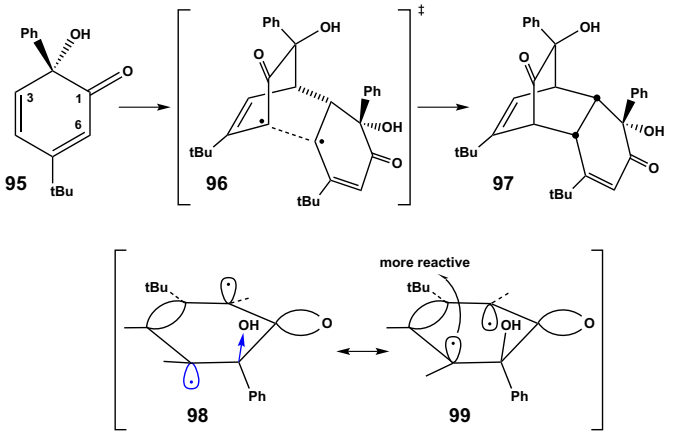

Fig. 19. Dimerization of *o*-quinol **95**.

The diradicaloid analysis of dienes presented herein can also be uniformly applied to a wide range of dienophile types. By simple assignment of the more reactive radicaloid center in the dienophile (i.e., in a singlet diradicaloid formal bond), we can determine, which dienophile position will begin to form a first cycloaddition bond with the preferred diene carbon, thereby determining the regioselectivity of the reaction.

The regioselectivity of addition of 2,4-diaryl-cyclopentadienone **101** as Diels–Alder dienophile is also readily accounted by considering its 1,4-diradicaloid character. As shown in Fig. 20, *o*-quinol enantiomer **100** was trapped with cyclopentadienone **101** to form cycloadduct **102** in near-quantitative yield.[46] Of the four possible sites on dienophile **101** that could form a bond with C3 of diene **100**, only its C5 position forms that particular bond. Viewing the dienophile as diradicaloid **103** restricts its reactivity to position C2 or C5, the latter corresponding to a more reactive radical center as the former is benzylic. Thus, the bent bond diradicaloid model predicts that cycloaddition involves a preliminary interaction between C5 of the dienophile and C3 of the *o*-quinol diene, followed by ring closure in accord with asynchronous LESD transition state model **104**.

For illustrative purposes, a range of other dienophiles are presented in Fig. 21 along with their predicted site of first attack in an asynchronous concerted Diels–Alder reaction with an unsymmetrical diene. A simple analysis of radical reactivity based on inductive effects and resonance is all that is required to account for the regioselectivity of the Diels–Alder reactions involving these dienophiles.

For example, Liao reported that dimethoxy *o*-benzoquinones **109** react as described in Fig. 22.[47] Note the opposite regioselectivity observed with dihydrofuran **106** and the related dehydro analogs **107**. These interesting results are completely predictable with our simple model.

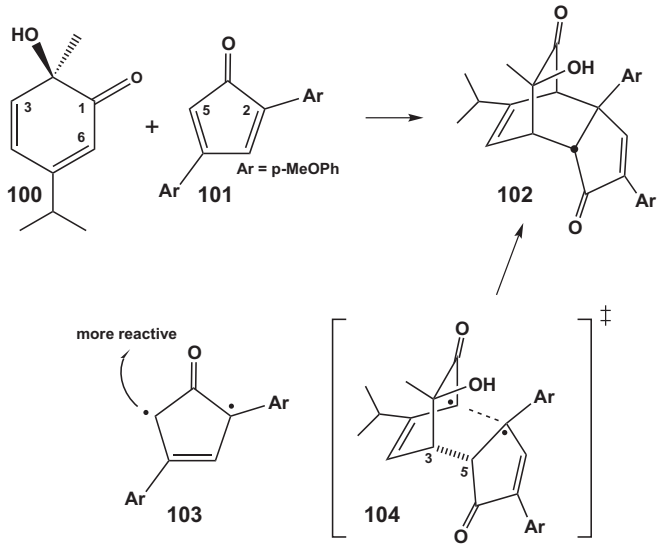

Fig. 20. Cycloaddition of *o*-quinol **100** with dienophile **101**.

diene **114**, and other dienes that have been extensively investigated with various unsymmetrical dienophiles, several of which are shown in Fig. 23.[51–54] Dienes **112** and **113** react uniformly such that the short bond in the transition state would involve their more reactive primary diradicaloid carbon (the secondary radical is inherently more stable and more sterically hindered). Likewise, all the dienophiles shown in Fig. 23 react uniformly through their most reactive radical (β to carbonyls as shown by the arrows) in

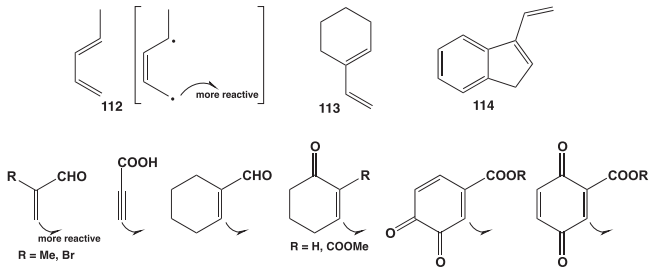

Fig. 23. Regioselectivity control with unsymmetrical dienes and dienophiles.

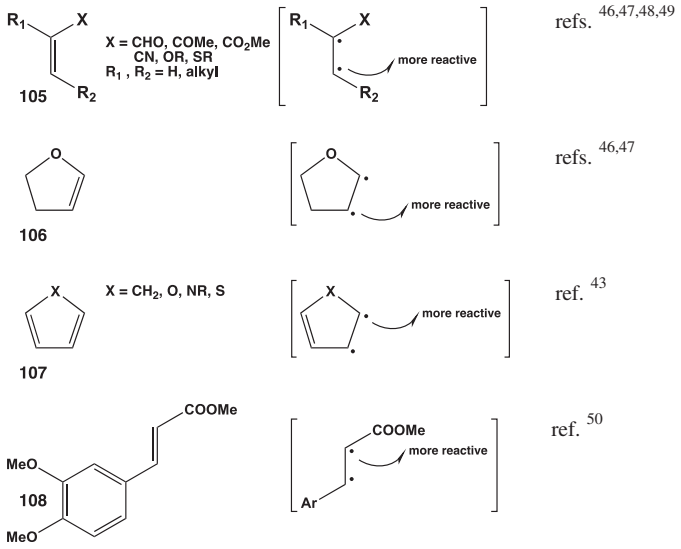

Fig. 21. Dienophile regioselectivities with unsymmetrical dienes such as *o*-quinones.[43,46–50]

As demonstrated earlier, our bent bond/diradicaloid model readily accounts for the regioselectivity of the Diels–Alder reaction with piperylene **112** (i.e., diradicaloid form **8**, Fig. 6). It also applies to dienes such as vinylcyclohexene **113** and the related aromatic

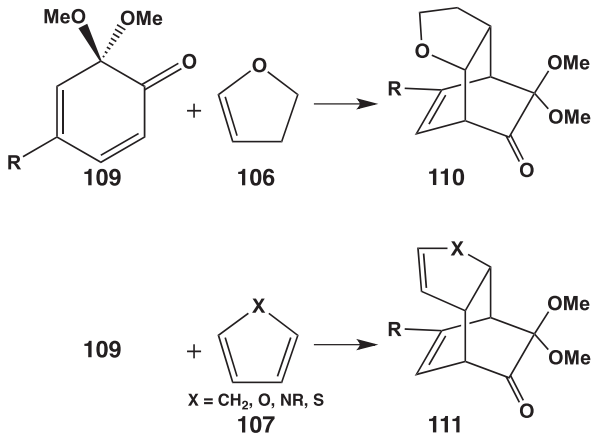

Fig. 22. Regioselectivity control with dihydrofuran and furan-type dienophiles.

forming the first bond with the dienes, and dictating regioselectivity.[51–55]

In the presence of Lewis acid catalysts, the observed reactivities and regioselectivities are simply increased because, as shown by Trost, the dienophiles become more reactive.[55f] For instance, a more powerful radical stabilizing substituent cleverly positioned can increase the diene reactivity.[55f] This is the case of OTBS vinylcyclohexene diene **116** (Fig. 24). When reacted with disubstituted acrylonitrile dienophile **115**, cycloadduct **117** is obtained, an intermediate used in Mander's total syntheses of the Galbulimima alkaloid GB13[56] and Himandrine.[57] Theodorakis used a similar strategy in his synthesis of (−)-Acanthoic acid.[58] In order to reverse the regioselectivity of a vinylcyclohexene derivative, a thiophenyl group was introduced in diene **118**, which reacted at −20 °C with methacrolein in the presence of $SnCl_4$ to produce the required tricycle **119** as the major isomer.

The aromatic diene **114** can now be examined (Fig. 25). To account for the preferred regioselectivity of this diene, the diradicaloid model must take into consideration the presence of the aromatic ring. In principle, a primary radical should be more reactive than a secondary one but the primary center in the diradicaloid view of **114** is directly conjugated with the ring, rendering

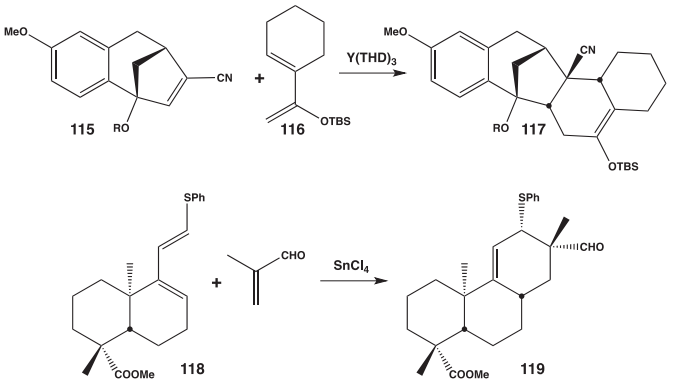

Fig. 24. Reversing Diels–Alder regioselectivity in natural products synthesis.

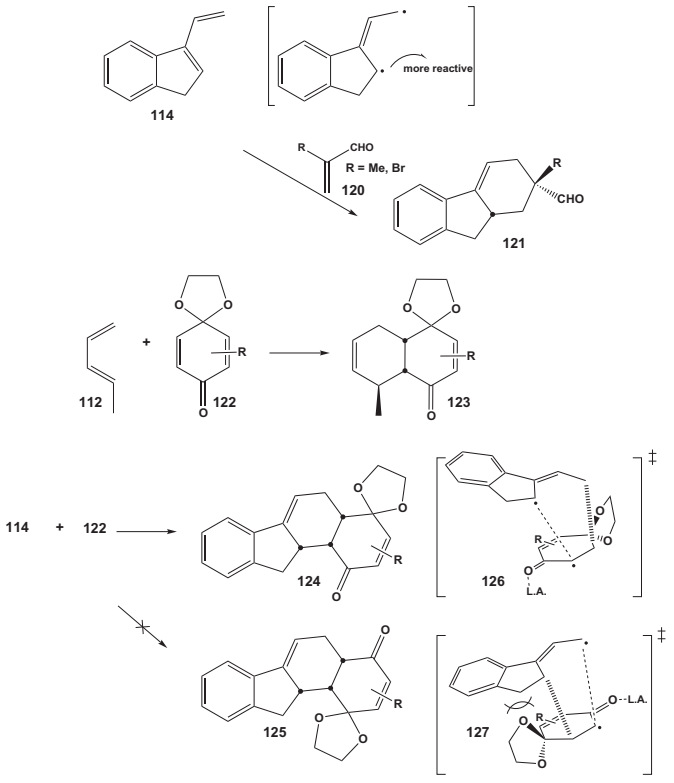

Fig. 25. Regioselectivity of cycloadditions with *p*-quinone monoketal **122**.

the secondary radical more reactive. Accordingly, the Lewis acid catalyzed cycloaddition of diene **114** with 2-methyl- or 2-bromoacrolein (**120**) gave tricyclic cycloadduct **121** in accord with the notion that the short bond in the LESD transition state occurs between the secondary ring radicaloid in **114** and the more reactive β-carbon of dienophiles **120**.[51,52,54]

Our model also accounts for results reported by Danishefsky on the Lewis acid catalyzed reaction of piperylene **112** with *p*-quinone monoketal **122** to give tetracycle isomer **123** (Fig. 25).[51] Piperylene **112** representing a 'normal' diene, we anticipate that the terminal radicaloid center is more reactive than its secondary counterpart and will react preferentially with one of the β-carbons of dienophiles **122**, and dictate the regiochemistry of the products obtained (**123**).

The combination of vinylindene diene **114** with *p*-quinone monoketal **122** leads to a very interesting result: the observed cycloadduct **124** has the opposite regiochemistry compared to cycloadduct **121**. The Danishefsky result may seem at odds with the diradicaloid model because we anticipated forming cycloadducts **125** from a preferred short bond interaction at the transition state between the secondary allylic radicaloid center in **114** and the more reactive β-carbon of dienophiles **122**. So why was product **124** obtained instead? We believe that severe steric interactions at the transition state are at play. Based on the diradicaloid model alone, the preferred transition state should correspond to geometry **127**. However, it suffers from severe steric repulsion between the ketal ring (i.e., a quaternary center) and the indene ring so it is reasonable to assume that transition state geometry **126** becomes the kinetically preferred route. The MMFF94x energies for products **124** and **125** (R=H) are 50.9 and 54.5 kcal/mol, respectively, in agreement with our model if one assumes late transition states. Finally, we note that such steric impediment is not present with piperylene **112** as diene and our model correctly predicts the formation of cycloadduct regioisomer **123**. These 'abnormal' reactions were investigated theoretically by Houk and co-workers. It was concluded that '*the reaction of (**114**) with (**122**) does not involve the reaction termini predicted by frontier MO theory, because the substitution terminus has the largest HOMO coefficient, but instead follows the model of electrostatic interactions*'.[53] Their theoretical calculations produced asymmetric transition states with the same short/long incipient bonds predicted by our simple model.

As a final case, we present an example from Valenta's steroid synthesis work where Lewis acid catalysis was used to control the regioselectivity of the Diels–Alder reaction.[59] As shown in Fig. 26, diene **128** reacted cleanly with dienophile **129** under $SnCl_4$ catalysis to produce regioisomer **130**; no other adduct could be found in a careful search of mother liquors and of chromatographic fractions. According to our model, the regioselectivity of diene **128** is akin to that of piperylene as opposed to that of vinylindene **114**. Indeed, the terminal diene position in **128** corresponds to the more reactive radicaloid center, and should form the short bond at the transition state (**131**). Likewise, dienophile **129** should react preferentially at its carbon α to the ketone (i.e., secondary radicaloid) under thermal conditions but, because of coordination of the ketone to $SnCl_4$, the tertiary carbon now becomes the more reactive center as shown in **131**. All in all, the exclusive production of cycloadduct **130** under these conditions is in complete agreement with the bent bond/diradicaloid model.

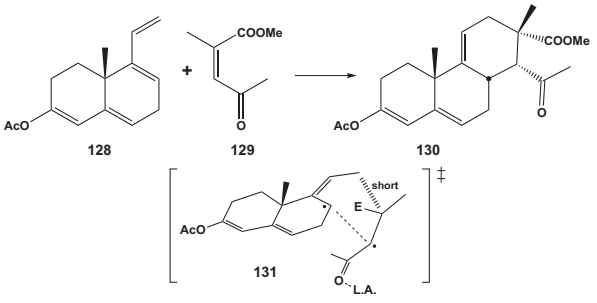

Fig. 26. Regioselectivity of cycloadditions with diene **128**.

2.8. Retro-Diels–Alder reaction

The bent bond model has some obvious implications for the course of the retro-Diels–Alder reaction. Based on the principle of microscopic reversibility, the reaction should normally proceed by the exact reverse of what was described herein, with asynchronous elongation of the two scissile bonds at the transition state. Interestingly, some experimental observations do suggest that, in some cases, the retro-Diels–Alder reaction may involve a diradicaloid intermediate prior to completely dissociating to the diene and dienophile end-products. For example, Berson reported that heating the *exo*-Diels–Alder cycloadduct from cyclopentadiene and acrylic dienophiles results in some stereo-randomization to the

endo-cycloadducts without complete dissociation to the diene/dienophile components.[25h,60] Interestingly, Berson reports several arguments against the diradical intermediate being in the triplet state; our model always assumes singlet 'formal-bond' diradicaloid states. A lack of cross-cycloaddition when the retro-Diels–Alder reaction is carried out in the presence of competing diene or dienophile traps lends further credence to the diradicaloid intermediate model. Finally, we note that Zewail's femtosecond reaction dynamics studies on the thermolysis of norbornene and norbornadiene support the presence of a non-concerted trajectory involving a diradicaloid transition state.[25d]

3. Conclusion

The bent bond/antiperiplanar hypothesis (BBA hypothesis) provides a qualitative yet novel theoretical model for understanding an ever-widening range of organic reactions and chemical observations, including now the Diels–Alder reaction. When applied to 1,3-dienes, the preference for staggering bonds in the bent bond model, implies that *s-cis* dienes must have important singlet 1,4-diradicaloid character rendering these highly reactive components of the Diels–Alder reaction. The antiperiplanar hypothesis also implies that allylic radicals have some inherent pyramidalization and delocalize in *anti*-fashion with their adjacent antiperiplanar bent bond.

Our analysis of the lowest-energy singlet diradicaloid (LESD) resonance structure of the diene and dienophile accounts for the regio- and stereoselectivity of the Diels–Alder reaction. The model implies that a radical inversion is required to provide aromatic character at the transition state, while accounting for the activation energy barrier of the reaction. The overall geometry of the transition state resulting from the above considerations is essentially in complete agreement with the recent ab initio work of Schleyer and Houk, as well as the Caramella bis-pericyclic model, and predicts, which of the two incipient transition state bonds will be shorter than the other.

The successful application of our simple model to predict the regio- and stereoselectivities of various Diels–Alder reactions, including so many cases involving facially perturbed dienes and dienophiles, does lead one to ponder its foundational concepts. The challenge here is that molecular orbital methods are inadequate to investigate the theoretical underpinnings of our model and robust quantitative valence bond methods for decent-sized organics were not available until recently. Nevertheless, this does not preclude one from advancing new ideas. Although this perspective may seem to some chemists like a throwback to '*a more innocent time, before the theory of orbital symmetry conservation*',[61] we are convinced that it will be highly useful to synthetic chemists due to its application simplicity and predictive nature.

Further applications of the bent bond/antiperiplanar model to other reactions, including sigmatropic rearrangements will be reported in subsequent disclosures.

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