

π -Facial Selectivity in Diels-Alder Cycloadditions

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Received May 18, 1999; revised July 9, 1999; accepted August 1, 2000

Diels-Alder reactions between π -facially differentiated dienes and/or π -facially differentiated dienophiles frequently proceed with remarkable π -facial selectivity. Experimental and theoretical studies have been undertaken in an effort to gain insight into the fundamental origins of this phenomenon. Reactions of interest in this connection include thermal [4 + 2] cycloadditions between (i) various dienophiles and cage-annulated 1,3-cyclohexadienes (*i.e.*, systems **1**, **4**, **6**, and **9**) and (ii) various dienes and cage-annulated dienophiles (*i.e.*, systems **1a**, **11a**, and **14**). The results of relevant molecular mechanics, semiempirical, and *ab initio* molecular orbital calculations generally are consistent with experiment.

Key words: π -facial selectivity, Diels-Alder cycloadditions.

INTRODUCTION

Cycloaddition reactions that take place between a *cisoid* conjugated diene and an alkene or alkyne (the dienophile), *i.e.*, »Diels-Alder reactions«,¹ are used routinely to synthesize organic compounds that contain six-membered rings. Reactions of this type often proceed regio- and stereoselectively, a feature that serves to enhance their appeal to synthetic organic chemists.

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The apparent insensitivity of the Diels-Alder reaction to the usual mechanistic probes (*e.g.*, substituent effects, solvent effects, stereochemical and kinetic studies) proved to be especially troublesome to early investigators who sought to elucidate the detailed mechanism of this important reaction.² Nevertheless, two general principles have been forwarded to account for the course of Diels-Alder reactions: (*i*) the »*cis* principle«,³ which requires that the stereochemical integrity of substituents in the diene and dienophile be maintained in the product, and (*ii*) the Alder-Stein »principle of maximum accumulation of unsaturation«,⁴ which has been invoked to explain why kinetically controlled Diels-Alder cycloadditions of cyclic dienes to substituted ethylenes (dienophiles) generally afford the corresponding *endo* cycloadduct.^{4,5} The *cis* principle is never violated in Diels-Alder cycloadditions; however, the Alder-Stein principle of maximum accumulation of unsaturation frequently is violated in situations where steric demands override the electronic considerations, termed »secondary orbital interactions«,⁶ that are thought to give rise to this phenomenon.

Herein, we highlight some recent results of experimental and theoretical studies of Diels-Alder reactions between π -facially differentiated dienes and/or π -facially differentiated dienophiles that have been performed in our laboratory and/or collaboratively with other research groups. Cycloaddition reactions of this type frequently have been observed to proceed with remarkable π -facial selectivity; our studies were undertaken in an effort to gain insight into the fundamental origins of this phenomenon.

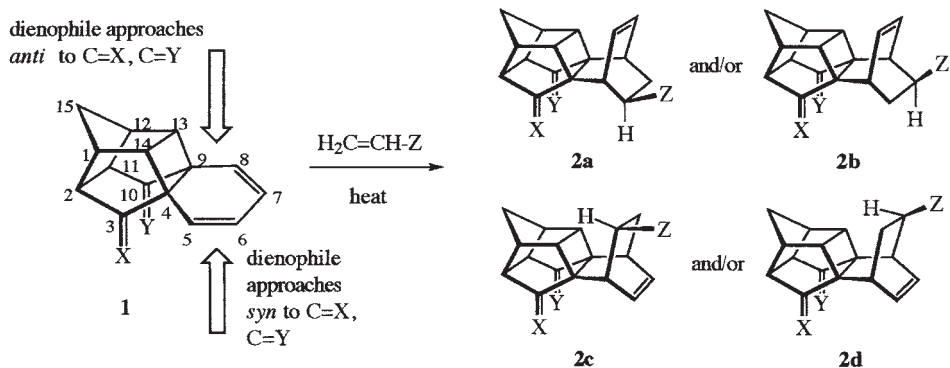
RESULTS AND DISCUSSION

Reactions of π -facially differentiated 1,3-cyclohexadienes with π -facially symmetric dienophiles

Substituted hexacyclo[10.2.1.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]pentadecadienes (**1**) (Scheme 1) have been employed as the » π -facially differentiated 1,3-cyclohexadiene component«. Compounds of the type **1** are structurally rigid, contain π -facially differentiated 1,3-cyclohexadienes of known molecular geometry,⁷ and can be synthesized readily by using readily available and inexpensive starting materials.⁸⁻¹⁰

If the Alder-Stein principle is invoked, we can envision readily that any (or all) of four [4 + 2] cycloadducts potentially might result *via* the cycloaddition reaction shown in Scheme 1. Thus, the dienophile might approach **1** from either the *syn* or *anti* face of the π -system, and the C-Z bond in the cycloadduct might be either *proximal* or *distal* to the C=X bond in the resulting cycloadduct. In fact, Diels-Alder cycloadditions of **1** (X=Y=O) to mod-

erately reactive, π -facially symmetric dienophiles such as *p*-benzoquinone,^{11,12} methyl acrylate,¹¹ maleic anhydride,¹² and acrylonitrile¹² have been reported to proceed *via* predominant or even exclusive approach of the dienophile toward the *syn* π -face of the diene.

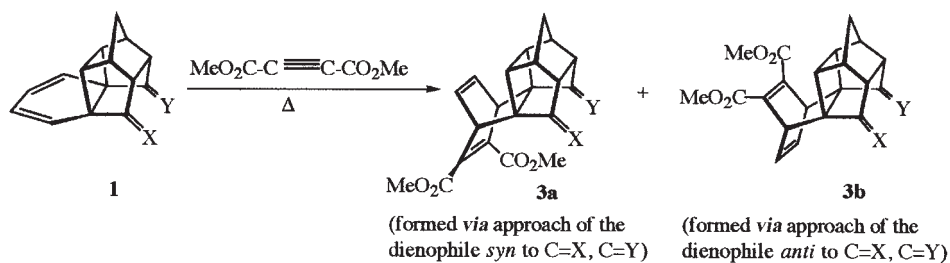


Scheme 1

More recently, ketone protecting groups (*e.g.*, ketals) have been demonstrated to function as stereodirectors of *syn/anti* π -facial diastereoselectivity in systems of the type **1**. This situation is illustrated by the data contained in Scheme 2 for Diels-Alder cycloaddition of **1a–1c** to DMAD.¹³

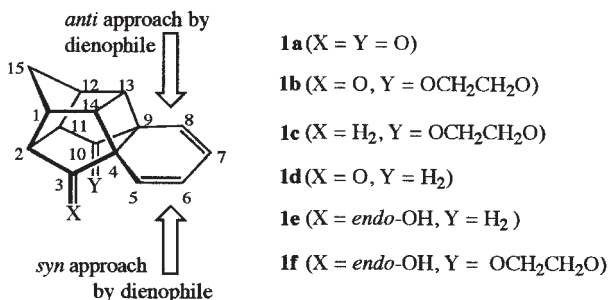
Diels-Alder cycloadditions of methyl acrylate (*i.e.*, R₂C=CR'Z where R = R' = H, Z = CO₂Me) to several unsymmetrically functionalized dienes of the type **1** (X ≠ Y) (*i.e.*, **1b–1f**, Scheme 3) have been studied.¹⁴ As noted in Scheme 1 (*vide supra*), in addition to *syn/anti* diastereoselectivity, the Z-group in the resulting [4 + 2] cycloadduct(s) may reside on a carbon atom that is either *proximal* or *distal* to the C=X functionality. In general, [4 + 2] cycloadditions of methyl acrylate to **1b–1f** were found to proceed with a high degree of *syn* π -facial diastereoselectivity but with only very modest *proximal/distal* regioselectivity.¹⁴

Fixed model MM2 transition state calculations¹⁵ have been performed for Diels-Alder cycloadditions of methyl acrylate to dienes **1b–1f**. In general, this approach accounts successfully for the observed π -facial diastereoselectivities. However, the results of semiempirical MO calculations on this system (AM1 Hamiltonian)¹⁶ show little variation in the energies of the diene HOMO and LUMO. Apparently, the difference between the magnitudes of the coefficients at the HOMO termini is insufficient to permit frontier orbital differentiation of regiochemistry.



Compound	Product Ratio	
1a (X = Y = O)	55	45
1b (X = O, Y = OCH ₂ CH ₂ O)	17	83
1c (X = O, Y = OCH ₂ C(CH ₃) ₂ CH ₂ O)	18	82

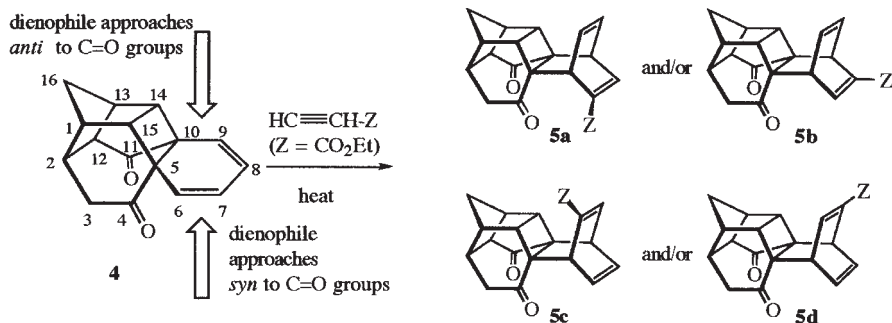
Scheme 2



Scheme 3

In addition, Diels-Alder cycloaddition of ethyl propiolate to another cage-annulated, π -facially differentiated 1,3-cyclohexadiene, *i.e.*, **4** (Scheme 4) has been studied.^{17a} In our hands, only two of four possible cycloadducts (*i.e.*, **5a–5d**, Scheme 4), were obtained (product ratio 60:40) upon workup of the reaction mixture after a toluene solution of **4** and ethyl propiolate had been refluxed for 5 days. The minor product of this reaction was demonstrated unequivocally to possess structure **5a** *via* application of X-ray crystallographic methods.^{17b} Despite numerous attempts, we were unable to obtain a satisfactory single crystal of the major reaction product; instead, the structure of this product was found to be **5b** *via* analysis of relevant one- and two-dimensional ¹H NMR and ¹³C NMR spectra.^{17c}

In an effort to gain insight into the various factors that might influence the relative energetics of the competing [4 + 2] cycloadditions in this system,



Scheme 4

semiempirical MO calculations were performed for the various possible modes of Diels-Alder cycloaddition of **4** to ethyl propiolate. Thus, semiempirical transition state optimizations for all systems were carried out at the AM1 level of theory¹⁶ as implemented in SPARTAN.¹⁸ Each transition structure afforded only one imaginary harmonic vibrational frequency that corresponds to the formation of new C–C bonds. Activation energies were estimated from RHF/3-21G single-point calculations performed on AM1-optimized geometries by using Gaussian 94.¹⁹

Interestingly, the AM1 computational results suggest that the ground state geometry of the diene moiety in **4** is not planar. Indeed, the computed torsion angle $\angle\text{C}(6)\text{--C}(7)\text{--C}(8)\text{--C}(9)$ in **4** deviates from planarity by 4.8° . The corresponding torsion angle obtained *via* X-ray structural analysis of **4** is 7.82° .²⁰ It seems likely that the geometric perturbation in **4** associated with nonplanarity of the diene system will have some influence on the observed regioselectivity and/or diastereoselectivity of Diels-Alder reactions that involve **4** as the diene component.

Frontier molecular orbital (FMO) analysis of diene **4** performed at the AM1 level of theory reveals no significant difference in the magnitude of the coefficients at the termini of the HOMO of this diene. Thus, FMO theory is not capable of rendering a clear prediction regarding *proximal/distal* regioselectivity in the case of Diels-Alder cycloaddition of ethyl propiolate to **4**.

The results obtained *via* single-point calculations performed at the HF/3-21G level of theory by using AM1-optimized geometry provide additional insight into the nature of this cycloaddition process. The results of these calculations are shown in Figure 1. Here, it can be seen that there is a clear preference for transition state formation wherein ethyl propiolate (dienophile) approaches toward the *syn* face of diene **4** *vis-à-vis* that which might occur *via* corresponding approach of the dienophile upon the *anti* face

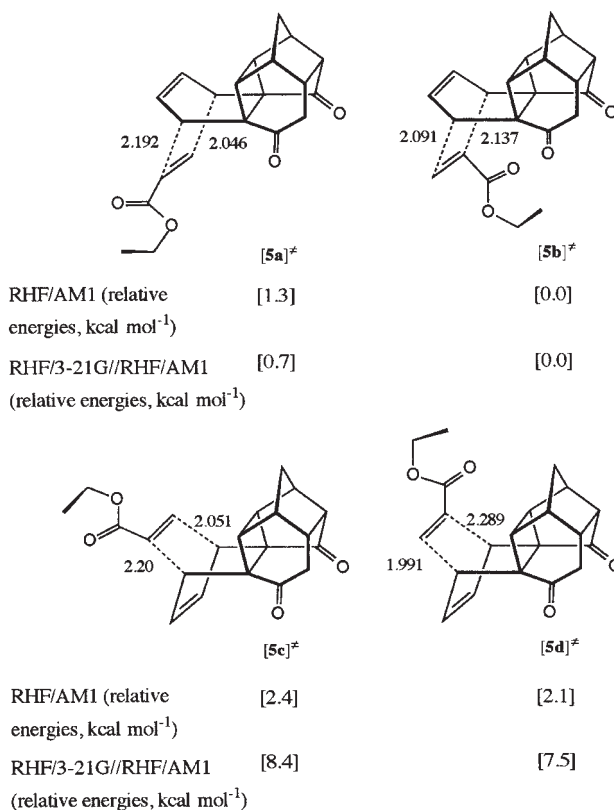
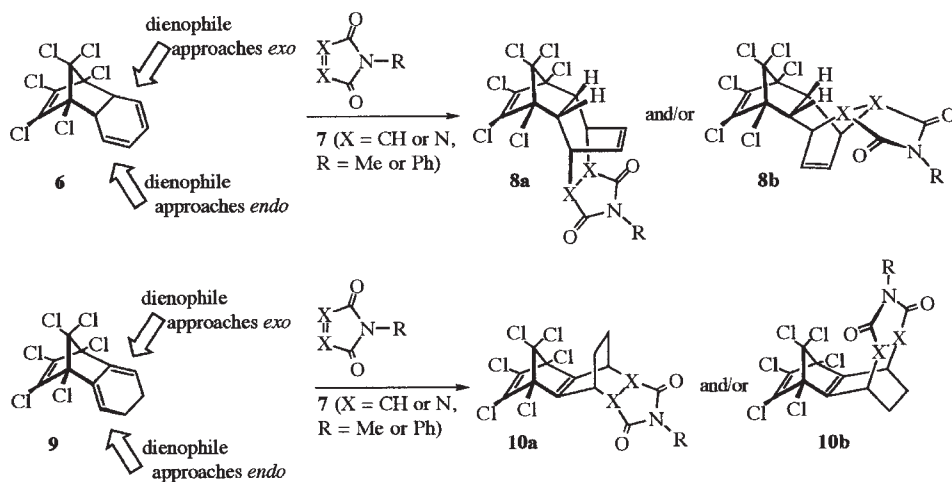


Figure 1. Results of transition state calculations for Diels-Alder cycloaddition of ethyl propiolate to **4**. Calculated bond lengths are in Å; relative transition state energies are given in kcal mol⁻¹.

of the diene. In addition, the calculated transition state energy for formation of **5b** (in which the CO₂Et substituent is *proximal* to the cyclopentanone ring) is *ca.* 0.7–1.3 kcal mol⁻¹ less than that for the corresponding transition state that leads to **5a**. Thus, in agreement with our experimental results for cycloaddition of ethyl propiolate to **4** (*vide supra*), the results of the transition state calculations shown in Figure 1 predict that **5b** should be the major product of this reaction.

Recently, the results of Diels-Alder cycloadditions of isomeric tricyclic dienes **6** and **9** (Scheme 5), each of which contains a π -facially differentiated 1,3-cyclohexadiene moiety, with symmetrical dienophiles of the type **7** [*i.e.*, MTAD, PTAD, and *N*-methylmaleimide (NMM)] have been reported.²¹ Interestingly, diene **9** proved to be noticeably less reactive than **6**. Furthermore, whereas **6** undergoes [4 + 2] cycloaddition to all three dienophiles *via* exclu-



Scheme 5

sive *exo* approach of the dienophile upon the diene, the corresponding cycloadditions of **9** to MTAD and PTAD each afford a mixture of cycloadducts wherein the major product results *via endo* approach of the dienophile upon diene **9**.

The results of semiempirical MO calculations (AM1 Hamiltonian)¹⁶ correctly predict that *exo* approach of MTAD, PTAD, and NMM is favored for their respective Diels-Alder reactions with diene **6**. By way of contrast, *endo* approach is favored for the corresponding reactions with diene **9**.²² Comparison of the AM1-calculated activation barriers for cycloaddition of each diene with NMM as dienophile fails to account for the observed sluggishness of both of these reactions *vis-à-vis* the corresponding [4 + 2] cycloadditions of these dienes to MTAD and to PTAD. Furthermore, the AM1-calculated transition structure for the Diels-Alder reaction of each diene **6** and **9** with both MTAD and PTAD is asynchronous, whereas the corresponding transition structures for [4 + 2] cycloadditions of these dienes to NMM are synchronous!²²

Improved agreement between theory and experiment was secured *via* application of *ab initio* computational methods to these systems. Thus, the results of theoretical calculations performed at the both the HF/3-21G* and B3LYP/6-31G* levels of theory account for both the observed π -facial diastereoselectivities and the observed relative reactivities of the various Diels-Alder cycloadditions of dienes **4** and **7** with MTAD, PTAD, and NMM.²¹

*Reactions of π -facially symmetric dienes with
 π -facially differentiated dienophiles*

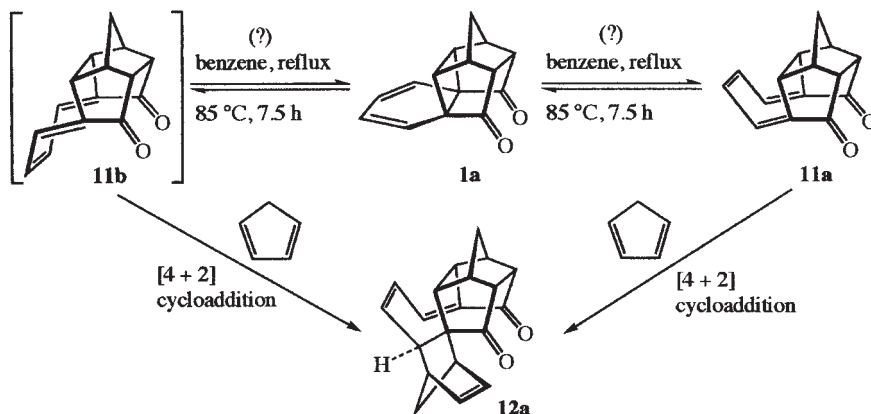
Interestingly, **1a** has been reported to suffer six-electron distrotatory electrocyclic ring-opening when refluxed in benzene solution.^{11,23} Thus, when **1a** is heated in the presence of excess cyclopentadiene, two [4 + 2] cycloadducts are obtained which correspond to 1:1 and 2:1 (diene:dienophile) cycloadducts, respectively. In each cycloaddition, ring-opened triene (*i.e.*, **11a** or **11b**) functions as a π -facially differentiated dienophile (see Scheme 6).²⁴

The Diels-Alder reaction shown in Scheme 6 that results in formation of a 1:1 Diels-Alder cycloadduct has been investigated computationally by considering two separate questions: (*i*) What is the direction of electrocyclic ring-opening of **1a** (*i.e.*, consider formation of **11a** vs. **11b**)? (*ii*) When the various possible modes of Diels-Alder cycloaddition of cyclopentadiene to the preferentially formed ring-opened triene are considered, which transition state is favored energetically?

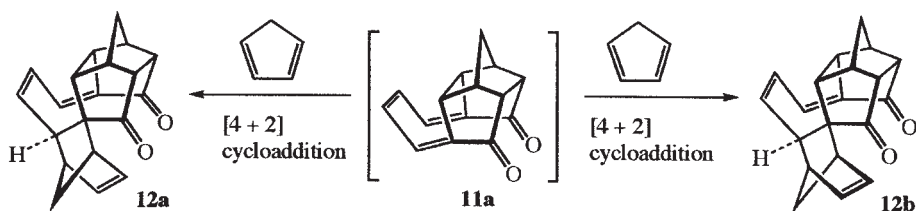
Initially, semiempirical MO calculations (AM1 Hamiltonian)¹⁶ were performed for thermal electrocyclic ring-opening of **1a** to the corresponding »Z,Z,Z-triene« (**11a**) and also for the corresponding process that leads to the »E,Z,E-triene« (*i.e.*, **11b**). Here, **11a** was found to be favored thermodynamically relative to **11b** by *ca.* 24 kcal mol⁻¹.²⁴ In addition, the results of these calculations suggest that the corresponding transition structure for electrocyclic ring opening of **1a** to **11a** is favored by *ca.* 22 kcal mol⁻¹ relative to the corresponding transition structure for electrocyclic ring opening of **1a** to **11b**.²⁴

Next, two possible modes of Diels-Alder cycloaddition of cyclopentadiene to **11a** were considered explicitly (*i.e.*, [4 + 2] cycloadditions that lead to the formation of either **12a** or **12b**, Scheme 7). The transition structure of each cycloaddition was located by using restricted Hartree-Fock (RHF) theory and by assuming a concerted reaction mechanism. For the reaction that affords **12a**, (ΔE^\ddagger)_{calcd(AM1)} = 31.3 kcal mol⁻¹ and (ΔE°)_{calcd(AM1)} = -15.1 kcal mol⁻¹. The corresponding values for the reaction that produces **12b** are: (ΔE^\ddagger)_{calcd(AM1)} = 33.7 kcal mol⁻¹ and (ΔE°)_{calcd(AM1)} = -13.4 kcal mol⁻¹. Thus, a clear thermodynamic and kinetic preference for formation of **12a** *vis-à-vis* **12b** is predicted by the results of these calculations; indeed, the veracity of this prediction has been demonstrated experimentally.²⁴

Interestingly, the course of Diels-Alder cycloaddition of either hexachlorocyclopentadiene or of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (**13a** or **13b** respectively) to **1a** was found to be strikingly different from that of the corresponding Diels-Alder cycloaddition of cyclopentadiene to this diene. Thus, in each case, when the reaction is performed in refluxing xylene solution, the substituted cyclopentadiene (»diene«) adds directly to



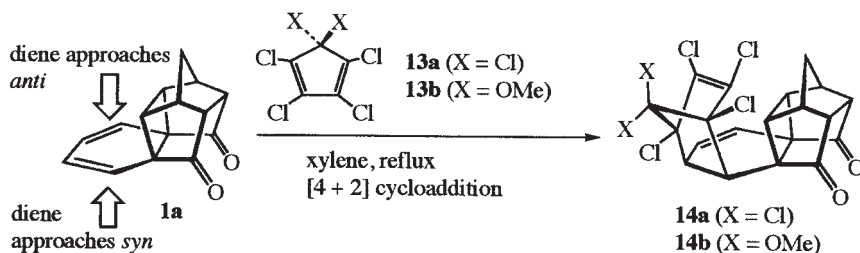
Scheme 6



Scheme 7

one of the C=C double bonds in **1a** (\gg dienophile \ll). In each case, a single [4 + 2] cycloadduct was formed (*i.e.*, **14a** and **14b**, respectively; see Scheme 8).²⁵ Recalling that electrocyclic ring opening of **1a** to **11a** has been shown previously to occur at (or possibly below) 85 °C (Scheme 6),^{11,23,24} it is particularly significant to note that neither reaction of **1a** with **13a** nor with **13b** affords any product that might have resulted *via* [4 + 2] cycloaddition of the diene to a C=C double bond in the tautomeric ring-opened triene (*i.e.*, **11a**).²⁵

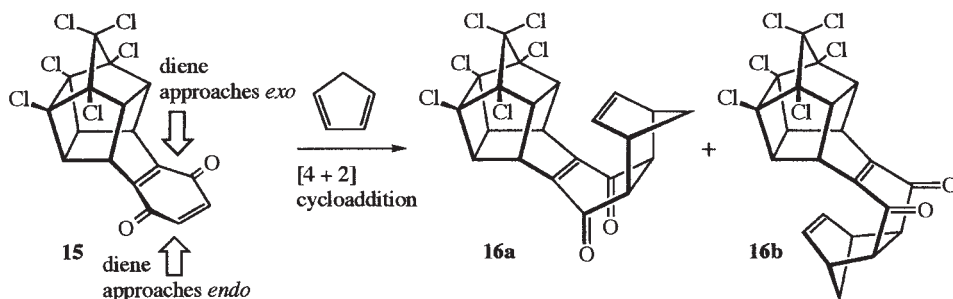
The relative energetics of four modes of Diels-Alder cycloaddition of **13a** to **1a** were investigated computationally: (i) *endo,anti* addition; (ii) *exo,anti* addition; (iii) *endo,syn* addition; (iv) *exo,syn* addition. The results of AM1 calculations¹⁶ reveal that among the four transition states considered, that which leads to **14a** is more energetically favorable than any of the alternative transition structures by at least 3 kcal mol⁻¹.²⁵ Furthermore, **14a** is favored thermodynamically relative to the other three possible Diels-Alder cycloadducts by 2.3–11.5 kcal mol⁻¹.²⁵ The results of our analysis of HOMO-LUMO interactions were consistent with expectations for an inverse elec-



Scheme 8

tron demand Diels-Alder reaction.²⁶ Finally, the results of MMX calculations²⁷ suggest that steric effects exert relatively little effect upon the course of the Diels-Alder reaction between **1a** and **13a**.

Finally, Diels-Alder cycloaddition of cyclopentadiene to a π -facially differentiated *p*-benzoquinone (*i.e.*, **15**, Scheme 9) has been reported²⁸ to afford a mixture of two [4 + 2] cycloadducts (*i.e.*, **16a** and **16b**; product ratio: **16a** : **16b** = 1 : 1.5). However, transition structures for the respective cycloaddition processes that lead to the formation of these two products have not been investigated computationally.



Scheme 9

SUMMARY AND CONCLUSIONS

Diels-Alder reactions between (*i*) various dienophiles and cage-annulated 1,3-cyclohexadienes (*i.e.*, systems **1**, **4**, **6**, and **9**) and (*ii*) various dienes and cage-annulated dienophiles (*i.e.*, systems **1a**, **11a**, and **15**) have been investigated. The results of relevant molecular mechanics, semiempirical, and

ab initio molecular orbital calculations generally are consistent with experiment and provide insight into the detailed mechanism of each of the reactions that has been investigated experimentally.

Acknowledgments. – A. P. M. thanks the Robert A. Welch Foundation (Grant B-0963) and the Office of Naval Research (Grants N00014-92-J-1362, N00014-94-1-1039, N00014-96-1-1279, and N00014-98-1-0478) for financial support of the experimental and theoretical studies reported herein. J. M. C. gratefully acknowledges grants from the New Zealand Lotteries Board and from the New Zealand Government Marsden Fund.

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SAŽETAK

π -facijalna selektivnost u Diels-Alderovim cikloadicijama

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Diels-Alderove reakcije između različitih π -facijalnih diena i π -facijalnih dienofila često se odvijaju sa znantnom π -facijalnom selektivnošću. U ovome radu provedena su eksperimentalna i teorijska istraživanja da bi se dobio detaljniji uvid u ovu pojavu. Proučavane reakcije bile su termičke [4+2] cikloadicije između (i) različitih dienofila i 1,3-cikloheksadiena prstenom vezanih na kavez (na primjer spojevi **1**, **4**, **6** i **9**) te (ii) različitih diena i dienofila prstenom vezanih na kavez (na primjer spojevi **1a**, **11a** i **14**). Teorijski proračuni dobiveni molekulskom mehanikom, semiempirijskim i *ab initio* računima u skladu su s eksperimentalnim rezultatima.