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Stereoselectivity in Diels−Alder Reactions of Diene-Substituted *N*-Alkoxycarbonyl-1,2-dihydropyridines

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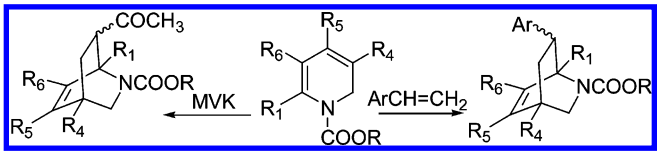

Diene substituent effects on the regiochemical and stereochemical outcomes of uncatalyzed Diels−Alder reactions of *N*-alkoxycarbonyl-1,2-dihydropyridines with both styrene and methyl vinyl ketone (MVK) were studied. Alkyl substitution on the diene in all cases examined resulted in a kinetic preference for 7-endo isomers (7-phenyl 51−96% exo and 7-acetyl 54−96% exo). For both dienophiles, the highest stereoselectivities (≥89% endo) were observed with 5-methyl or 6-methyl substituents in the dihydropyridine. Theoretical calculations of the energies of gas phase endo and exo transition states at the RHF/3-21G(*) predict that total entropy, ΔS_{total}, considerations favor endo cycloadducts for both dienophiles with DHP, while total energy considerations, $\Delta E^{\ddagger}_{o}$, favor endo cycloadducts for styrene and exo cycloadducts for MVK. At this level, favored *endo*-phenyl isomers are correctly predicted for styrene reactions, but the calculation of 7-acetyl exo or endo isomer dominance is diene-substituent-dependent for MVK reactions. The preference for endo addition of MVK to the parent, 5-methyl, and 6-methyl-DHPs was successfully predicted by calculations at the B3LYP/6-31G* theory level.

Introduction

The ease of synthesis of *N*-alkoxycarbonyl-1,2-dihydropyridines[1] (DHPs) and their ability to react with a variety of dienophilic reagents have led to their wide use as precursors of 2-azabicyclo[2.2.2]oct-5-enes. These structures have proven to be useful in the synthesis of a range of interesting and useful structures.[1−7] The regiochemistry for this thermal cycloaddition, at least for alkene-unsubstituted 1,2-dihydropyridines **1** reacting with monosubstituted dienophiles **2**, has the nitrogen atom near

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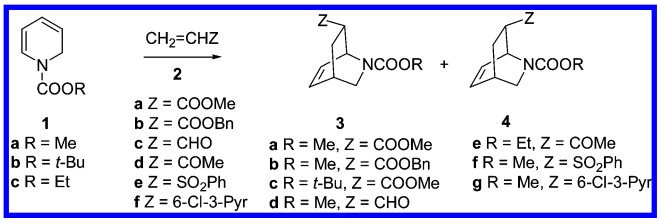
TABLE 1. Stereoselectivity for Thermal Cycloadditions of *N*-Alkoxycarbonyl-1,2-dihydropyridines (DHP) 1 with Monosubstituted Dienophiles 2 (CH_2 = CHZ)



1
a R = Me
b R = *t*-Bu
c R = Et

a Z = COOMe
b Z = COOBn
c Z = CHO
d Z = COMe
e Z = SO_2Ph
f Z = 6-Cl-3-Pyr

3
a R = Me, Z = COOMe
b R = Me, Z = COOBn
c R = *t*-Bu, Z = COOMe
d R = Me, Z = CHO

4
e R = Et, Z = COMe
f R = Me, Z = SO_2Ph
g R = Me, Z = 6-Cl-3-Pyr

entry	DHP	alkene	cycloadducts	R	Z	endo **3**/exo **4**	yield (%)
1	**1a**	**2a**	**3a** and **4a**	Me	COOMe	57:43	65[a]
2	**1a**	**2b**	**3b** and **4b**	Me	COOBn	67:33	39[b]
3	**1b**	**2a**	**3c** and **4c**	*t*-Bu	COOMe	50:50	*c*
4	**1a**	**2c**	**3d** and **4d**	Me	CHO	70:30	70[d]
5	**1c**	**2d**	**3e** and **4e**	Et	COMe	57:43	89[e]
6	**1a**	**2e**	**3f** (**4f**)	Me	SO_2Ph		28[f]
7	**1a**	**2f**	**3g** and **4g**	Me	Ar	79:21	44[g]

[a] Xylene, reflux, 120 h, refs 5b,7c. [b] Xylene, reflux, 15 h, ref 5b. [c] Toluene, reflux, no yield given, refs 6b,c. [d] Toluene, reflux, 28 h, ref 3c. [e] Neat, 50 °C, 5 days, ref 3c. [f] Toluene, reflux, 60 h, ratio undetermined, ref 9. [g] Ar = 6-chloro-3-pyridyl, decalin, reflux, 12 h, ref 4.

the C_7 dienophile substituent in the azabicycle. The stereochemical outcome for uncatalyzed cycloadditions is to generally give mixtures of products favoring endo isomers **3** in competition with exo isomers **4**. The results of representative cycloadditions are shown in Table 1. Stereochemical outcomes for methyl acrylate,[8] acrolein,[3c] and methyl vinyl ketone[3e] cycloadditions with dihydropyridines have been shown to be of kinetic origin.

Unlike the corresponding 1,3-cyclohexadiene that opposes a methylene group as a steric impediment to an exo-oriented dienophile substituent,[10] it might seem reasonable to anticipate that the lone pair of electrons on nitrogen and the *N*-acyl substituent might play a favorable role in facilitating formation of exo isomers. Indeed, for cycloadditions of *N*-methoxycarbonyl-1,2-dihydropyridine **1a** with methyl acrylate **2a** to give a 57:43 endo/exo ratio of isomers **3a**/**4a** in refluxing toluene (entry 1), it was postulated that the nitrogen atom of the dihydropyridine favorably interacts with the carbonyl of the ester and that the carbonyl of the carbamoyl group might electrostatically interact with the O atom of the ester carbonyl.[5b] This effect appears to be balanced by a decreased preference for exo isomers with an increase in size of the ester alkyl group (67:33 endo/exo **3b**/**4b** when R = Bn, entry 2). Inconsistent with the argument, an increased preference for exo adduct **4c** containing an *N*-Boc group has been reported, but without confirming experimental details.[6b,c] Nevertheless, the cycloaddition results with dihydropyridines **1** and alkyl acrylate **2a,b**, acrolein (**2c**), and MVK (**2d**) (entries 1−5) all indicate a greater kinetic preference for endo cycloadducts **3a**−**e** when compared to the near 1:1 equilibrium ratio of **3**/**4** isomers having ester[8] or aldehyde[3c] substitution and the 3:2 preference for *exo*-acetyl isomer **4e**.[3e] Phenylvinylsulfone (**2e**) addition to 1,2-dihydropyridine **1a** forms a cycloadduct of undetermined stereochemistry (entry 6).[9] During the development of synthetic approaches to homoepibatidines, we discovered that a vinylpyridine **2f** undergoes cycloaddition with 1,2-dihydropyridine to give a minor amount of exo cycloadduct **4g** (entry 7).[4]

Thermal cycloadditions have been extended to include diene-substituted 1,2-dihydropyridines **5** as well. In this regard, substituted 1,2-dihydropyridine reactions with *N*-phenylmaleimide[11] and the intramolecular cycloadditions of 2-(3-butenyl)-1,2-dihydropyridines have been carried out successfully with substituents at all diene positions.[7] Phenylvinylsulfone (**2e**) does not afford cycloadducts with 6-methyl-1,2-dihydropyridine, but gives 60−70% yields with 3-, 4-, or 5-methyldihydropyridines.[12]

Methyl vinyl ketone (**2d**) reacts with a 5-COOMe-1,2-dihydropyridine to afford a 21:4 mixture of endo/exo cycloadducts (25% yield).[7a] For methyl acrylate (**2a**), the regiochemical and stereochemical control exerted by diverse 3- and 5-substituents on the cycloadditions of 1,2-dihydropyridines are shown in Table 2.[8,13] A 3-methyl (entry 1) has little effect upon stereochemistry compared to the unsubstituted parent (Table 1, entry 1); both are about 6:4. A mixture of 3-ethyl and 5-ethyl dihydropyridines **5b**/**5c** reacts with methyl acrylate to give mixtures of stereoisomers of undetermined ratio (entry 2). The preference for endo isomers is altered by a bulky 5-trimethylsilyl group (entry 3), and there is now a 71:29 preference for *exo*-carbomethoxy in the cycloadduct **7d**. A 3-methoxy group on the DHP (entry 4) causes a reversal of favored regiochemistry. Since the methoxy group is a more powerful director than the *N*-alkoxycarbonyl group of the DHP, the exo cycloadduct **9** is now favored over the endo isomer **8**.[8] From these disparate results, it was clear at the outset of the present study that DHP substituents can have far reaching influences upon the regiochemistry and stereochemistry of cycloadditions.

When the present work was begun, there were no reports of styrene cycloadditions with 1,2-dihydropyridines **1**. We first explored the possibility of addition of a styrene **2f** to 1,2-dihydropyridine **1a** as a route to epibatidine homologues 6-aryl-2-azabicyclo[2.2.2]oct-7-enes **3g**/**4g**. When this cycloaddition was shown to be successful (Table 1, entry 7), we wanted to know more generally how alkyl groups on the DHP diene carbons might influence exo/endo stereochemical outcomes for reactions with styrenes. The results of this investigation are one subject of this paper. During the course of our studies, the investigation of substituent effects was extended to include DHP cycloadditions of methyl vinyl ketone (**2d**) and substituted 1,2-dihydropyridines. Attempts have also been made to assess our experimental results by theoretical means.

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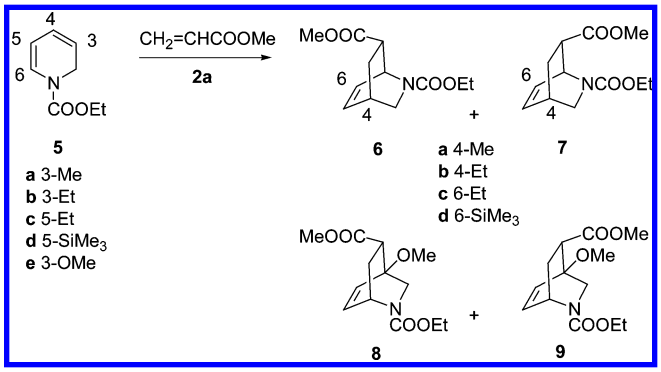
TABLE 2. Stereochemical and Regiochemical Results from Cycloadditions of Substituted Dihydropyridines 5 and Methyl Acrylate (2a)[a]



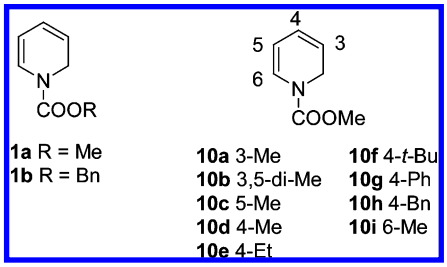
entry	1,2-DHP	R[b]	adduct(s)	R	endo/exo ratio	endo/exo equilibrium ratio	yield (%)
1	**5a**	3-Me	**6a**/**7a**	4-Me	60:40	1:1	70
2	**5b** +	3-Et	**6b**/**7b**	4-Et	*c*	*d*	65
	5c[c]	5-Et	**6c**/**7b**	6-Et	*c*	*d*	
3	**5d**	5-$SiMe_3$	**6d**/**7d**	6-$SiMe_3$	29:71	*d*	60
4	**5e**	3-OMe	**8**/**9**	4-OMe[e]	33:67	*d*	25

[a] Sealed tube, 120 °C, 48 h. See ref 8. [b] Other 3-isomers (R = SMe, Cl, $SiMe_3$, $SnMe_3$, $SnBu_3$, and COOMe) successfully reacted in 56−74% yields, but regiochemical and stereochemical ratios of cycloadducts **6**/**7** were not determined. [c] A mixture of unreported ratio. [d] Not determined. [e] Ester is at C_8.

Results and Discussion

Synthesis and Reaction of Substituted 1,2-Dihydropyridines. The requisite 1,2-dihydropyridines for the present study were prepared as described. *N*-Carbomethoxy-1,2-dihydropyridine (**1a**),[1b] *N*-benzyloxycarbonyl-1,2-dihydropyridine (**1b**),[2c] 4-methyl-*N*-carbomethoxy-1,2-dihydropyridine (**10d**),[14] and 4-phenyl-*N*-carbomethoxy-1,2-dihydropyridine[15] (**10g**) have been prepared previously. Other *N*-alkoxycarbonyl-1,2-dihydropyridines were prepared according to the reported procedure by Fowler,[1b] except for 5-methyl-*N*-carbomethoxy-1,2-dihydropyridine (**10c**).[2b] The reduction of pyridine and its analogues with sodium borohydride in the presence of methyl chloroformate normally gives a mixture of N-substituted 1,2- and 1,4-dihydropyridines. If the reaction temperature is controlled well below −70 °C, the formation of 1,4-DHP isomers is minimized and they can be removed by flash column chromatography. If the C_4 position of the pyridine ring is substituted, no 1,4-dihydropyridine derivatives were detected or isolated. The 2-picoline did not react readily with methyl chloroformate and sodium borohydride in methanol to give 6-methyl-1,2-DHP (**10i**) when the temperature was below −70 °C, but if the reaction temperature was raised to −50 °C, the reaction afforded **10i** in 14% yield along with unreacted 2-picoline. All 1,2-dihydropyridines were purified by the silica gel flash column chromatography under argon prior to use.

Diels−Alder Cycloadditions of DHPs with Styrenes 11a−c or Methyl Vinyl Ketone (2d). Identification and Analysis of Product Mixtures. The cycloadditions of DHPs with styrenes **11** were carried out with 3−5 equiv of the dienophile in refluxing decalin, boiling point 189−191 °C, under argon for 17−72 h. Decalin can be removed by passing the crude reaction mixtures through a silica gel flash column and then rinsing with an adequate amount of nonpolar solvent, such as cyclohexane. The cycloadditions of methyl vinyl ketone (**2d**) to DHPs were



best carried out on neat mixtures under argon containing 2.5-fold excess of MVK at 50−60 °C for 5−6 days. In order to obtain pure samples, the reaction mixtures were purified using a combination of techniques including repeated silica gel column chromatography, preparative TLC, medium-pressure reverse-phase column chromatography, and HPLC. The endo/exo stereoisomeric ratios were determined by ^{1}H NMR proton integrations, HPLC analyses, and/or column separations. Results from all three methods usually were consistent. For example, the ratio of **12a** and **13a** was 84:16 from ^{1}H NMR integrations of H_1 protons, 82:18 from HPLC analysis, and 84:16 from column separation.

The structure elucidations and peak assignments of 7-acetyl- and 7-aryl-2-carbomethoxy-2-azabicyclo[2.2.2]oct-5-enes were derived from combinations of ^{1}H NMR, ^{13}C NMR, ^{1}H−^{1}H 2D COSY, ^{1}H−^{13}C 2D COSY, and APT 1D NMR. The chemical shift of each proton of the 2-azabicyclo[2.2.2]oct-5-ene skeleton was assigned using decoupling experiments. The interconversion of two conformational isomers of the *N*-carbamate was restricted at ambient temperature, and two sets of peaks corresponding to two different conformers appeared in the ^{1}H NMR and ^{13}C NMR spectra. NMR experiments at high temperature (100 °C) were used in order to unambiguously identify the coupling patterns for the protons for the endo and exo stereoisomers.

It was interesting to note that the ^{1}H NMR spectra of the 7-*endo*-aryl isomers did not clearly demonstrate two sets of signals after flash column chromatography purifications and therefore most peaks were broad, but if D_2O was added, the splitting pattern representing the two conformers was restored.

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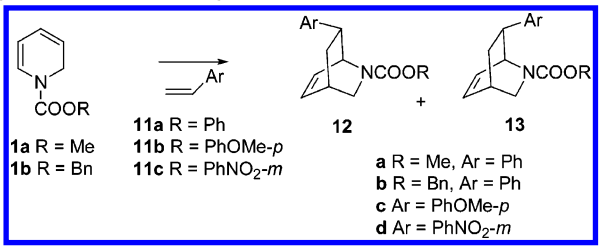
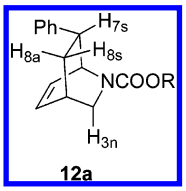
SCHEME 1. *N*-Alkoxycarbonyl-1,2-dihydropyridine Cycloadditions with Styrenes



The conformational isomers of 7-*exo*-aryl compounds always presented two distinct sets of peaks in the ^{1}H NMR spectra.

The structure of 7-*anti*-phenyl isomer **12a**, as determined by high-temperature ^{1}H NMR decoupling and ^{1}H−^{13}C 2D COSY experiments, is indicative of the method used for stereochemical assignments. There is a long-range W-plan coupling between H_{8a} and H_{3n} protons in a 2-azabicyclo[2.2.2]oct-5-ene system.[16] In the ^{1}H NMR spectrum of **12a**, the protons at δ 1.68 and 3.03 ppm are W-plan coupled with a coupling constant of 2.0 Hz. The multiplet at δ 1.68 ppm can thus be assigned to H_{8a}, and the multiplet at δ 3.03 ppm can be assigned to the H_{3n} proton. Further, there are coupling constants of 5.4 Hz for H_{8a} and the H_7 proton, and 9.6 Hz for H_{8s} and the H_7 proton. Therefore, the H_7 proton has the *cis* configuration to the H_{8s} proton (larger coupling) and the *trans* configuration to H_{8a}. Thus, the 7-phenyl group of **12a** has the endo configuration toward the 5,6-alkene.



Stereochemical Results for DHP/Styrene Cycloadditions. Styrene (**11a**) cycloadds to cyclohexa-1,3-diene under conditions of photoinitiation in the presence of an electron transfer catalyst to give a 10:1 endo/exo mixture in 13% yield, accompanied by large amounts of styrene polymer.[17a] The same reaction occurs electrochemically in 13−33% yield (19−30:1 endo/exo).[17b] Despite apparent difficulties, our goal was to see if styrenes could react with 1,2-dihydropyridines under thermal conditions (Scheme 1). The results for unsubstituted 1,2-dihydropyridines are in Table 3.

There were no significant differences observed in terms of regioselectivity and stereoselectivity between **12a**/**13a** and **12b**/**13b** as a result of changing the carbamate alkyl group from methyl to the potentially bulkier benzyl group (entries 1 and 2). The phenyl of the benzyl group can apparently avoid steric interaction with the styrene aryl group, and the stereochemistry did not change significantly when electron-rich 4-methoxystyrene (entry 3) or electron-poor 3-nitrostyrene (entry 4) was used in place of styrene as the dienophile to give **12c**/**13c** and **12d**/**13d**. All reactions gave a similar ratio of about 80:20 for the endo and exo products in similar yields (40 ± 11%).

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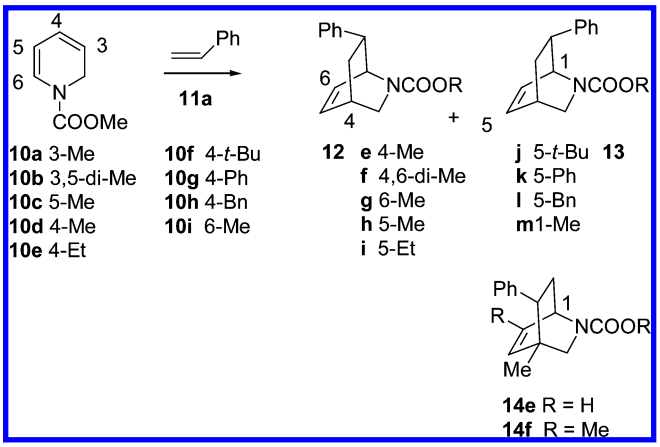
TABLE 3. Stereoselectivity for Cycloadditions of *N*-Alkoxycarbonyl-1,2-dihydropyridines with Styrenes[a]

		Substitutions			
entry	DHP	R	X	product ratio endo/exo	yield (%)[b]
1	**1a**	Me	Ph	84(**12a**)/16(**13a**)	32
2	**1b**	Bn	Ph	86(**12b**)/14(**13b**)	50
3	**1a**	Me	Ph-*p*-OMe	80(**12c**)/20(**13c**)	29
4	**1a**	Me	Ph-*m*-NO_2	79(**12d**)/21(**13d**)	30
5	**1a**	Me	6-Cl-3-pyridyl[c]	79(**3g**)/21(**4g**)	44

[a] Reactions were run in refluxing decalin. [b] Isolated yields. [c] See ref 4.

SCHEME 2. Substituted *N*-Alkoxycarbonyl-1,2-dihydropyridine/Styrene Additions



The Diels−Alder reactions of 1,2-DHPs and styrene have been performed at a very high temperature of 190 °C. The ratio of endo/exo products might result from either a kinetically controlled or thermodynamically controlled reaction. A kinetic study of the reaction of 1,2-DHP **1b** and styrene (entry 2) has shown that the product ratio remained between 90:10 (3 h) and 86:14 (24 h) endo/exo by HPLC during the 24 h course of the cycloaddition. Additionally, when *endo*-Ph **12b** (53 mg) was heated at reflux in decalin under argon for 48 h, 40 mg of pure *endo*-Ph **12b** was recovered after chromatography. The *exo*-Ph stereoisomer **13b** was not observed by ^{1}H NMR or HPLC analysis. Similarly, when *exo*-Ph isomer **13b** (55 mg) was heated at reflux in decalin for 24 h, 34 mg of **13b** was recovered after chromatographic purification. The *endo*-Ph stereoisomer **3a** was not detected. The endo/exo products are therefore derived from kinetically controlled Diels−Alder reactions. These results show that, while there may be some decomposition of cycloadducts over time, the stereoisomeric ratios are relatively invariant over time and the endo and exo stereoisomers are not interconverting.

We next turned our attention to the impact of alkyl substituents upon the endo/exo stereoselectivity, as shown in Scheme 2. The results are given in Table 4. The Diels−Alder cycloadditions of styrene with the parent (entry 1), the 3-methyl-1,2-DHP (entry 2), and 3,5-dimethyl-1,2-DHP (entry 3) afford similar endo/exo ratios of stereoisomers **12a**−**c**/**13a**−**c**; however, minor amounts of the 8-*endo*-phenyl regioisomers **14e** and **14f** were also isolated from reactions of the 3-methyl DHPs **10a,b**. This effect upon regiochemistry by the electron-releasing methyl group at C_3 is less significant than that observed for a 3-methoxyl group that was controlling for C_8 isomers with methyl acrylate/DHP cycloaddition (Table 2, entry 4).[8]

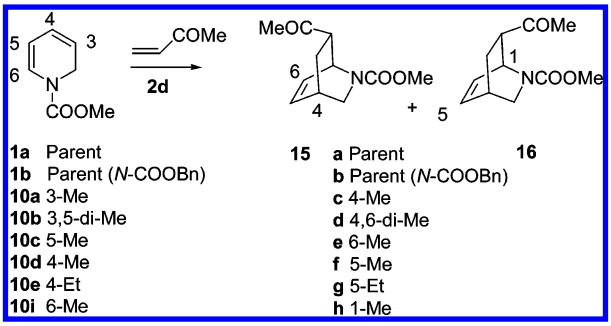
The lone 5-methyl substituent of DHP **10c** results in enhanced 89% endo selectivity in cycloadduct **12g** (entry 4). This result and that of the 3,5-dimethyl isomer (entry 3) are contrary to

TABLE 4. Stereoselectivity for Cycloadditions of Alkyl-*N*-Methoxycarbonyl-1,2-dihydropyridines with Styrene[a]

entry	DHP	DHP Substitution 3	4	5	6	products endo/exo/regioisomer ratios	yield (%)[b]
1	**1a**	H	H	H	H	84(**12a**)/16(**13a**)	32
2	**10a**	Me	H	H	H	75(**12e**)/21(**13e**)/4(**14e**)	36
3	**10b**	Me	H	Me	H	78(**12f**)/8(**13f**)/14(**14f**)	52
4	**10c**	H	H	Me	H	89(**12g**)/11(**13g**)	38
5	**10d**	H	Me	H	H	55(**12h**)/45(**13h**)	47
6	**10e**	H	Et	H	H	62(**12i**)/38(**13i**)	53
7	**10f**	H	*t*-Bu	H	H	51(**12j**)/49(**13j**)[c]	22
8	**10g**	H	Ph	H	H	54(**12k**)/46(**13k**)[d]	30
9	**10h**	H	Bn	H	H	55(**12l**)/45(**13l**)[d]	29
10	**10i**	H	H	H	Me	96(**12m**)/4(**13m**)	45

[a] Reactions were run in refluxing decalin. [b] Isolated yields. [c] By NMR proton integration endo/exo = 55:45. [d] By NMR proton integration.

SCHEME 3. Cycloadditions of *N*-Alkoxycarbonyl-1,2-dihydropyridines with Methyl Vinyl Ketone



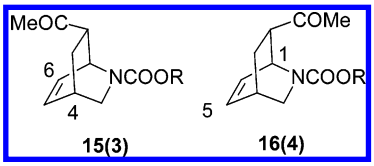
expectations for a possible adverse transition state steric interaction between a 5-methyl and the styrene phenyl.

The presence of a 4-alkyl or 4-aryl DHP substituent (entries 5−9) results in a surprising decrease in endo stereoisomer preference (51−62% endo) compared to substituents at other positions. Interestingly, the particular size of the substituents at the C_4 position of the 1,2-DHP **10d**−**h** is irrelevant to the endo/exo selectivity since all products from 4-substituted DHPs, even with the bulkier *tert*-butyl and phenyl, are in a very close range of preferences for endo adducts **12h**−**l** (55−62%).

The Diels−Alder cycloaddition of 6-methyl-1,2-DHP **10i** with styrene (entry 10) affords the *endo*-Ph stereoisomer **12m** as the dominating product with the endo/exo **12m**/**13m** ratio of 96:4. The methyl group has somehow either hindered approach of the styrene phenyl from the exo orientation or facilitated endo cycloadduct. Theoretical calculations were undertaken to gain insights on this issue (see below).

Stereochemical Results for DHP/MVK Cycloadditions. With a number of alkyl-1,2-DHPs in hand, we desired to see if methyl vinyl ketone cycloadditions would result in substituent stereochemical preferences similar to those observed with styrene. The reactions shown in Scheme 3 were carried out, and the results are in Table 5. Mariano[3e] reported the cycloaddition of *N*-ethoxycarbonyl-DHP **1c** with MVK as a neat thermal reaction at 55 °C. The result was a 4:3 endo/exo ratio of acetyl regioisomers **3e**/**4e** (entry 1). Upon base-catalyzed equilibration, a 2:3 mixture of these endo/exo isomers was observed. Our results at 50 °C by NMR analyses of mixtures prior to separation with both *N*-methoxycarbonyl-DHP (entry 2) and *N*-benzoxycarbonyl-DHP (entry 3) found slightly higher 70−74% preferences for *endo*-acetyl isomers **15a** and **15b**. The alkyl groups of the carbamates appear to be sufficiently distant from the reaction centers of the TSs so as not to be the determinative factor in controlling endo or exo product orientations.

TABLE 5. Stereoselectivity in the Cycloadditions of Alkyl-Substituted *N*-Alkoxycarbonyl-1,2-dihydropyridines with Methyl Vinyl Ketone (2d)[a]



entry	DHP	R	product substituent	products endo/exo isomer ratios	yield (%)[b]
1	**1c**	Et	parent	57(**3e**)/43(**4e**)	89[c]
2	**1a**	Me	parent	74(**15a**)/26(**16a**)	63
3	**1b**	Bn	parent	80(**15b**)/20(**16b**)[d]	73
4	**10a**	Me	4-Me	68(**15c**)/32(**16c**)[e]	51
5	**10b**	Me	4,6-di-Me	53(**15d**)/47(**16d**)[f]	27
6	**10c**	Me	6-Me	90(**15e**)/10(**16e**)	22
7	**10d**	Me	5-Me	60(**15f**)/40(**16f**)	81
8	**10e**	Me	5-Et	54(**15g**)/46(**16g**)	69[g]
9	**10i**	Me	1-Me	96(**15h**)/4(**16h**)	45

[a] Reactions were run neat at 55 °C, 5 days. [b] Isolated yields. [c] See Table 1, entry 5 and ref 3e, 50 °C, 6 days, neat. [d] NMR proton integration and HPLC endo/exo 70:30. [e] By NMR proton integration. [f] By NMR proton integration endo/exo 54:46. [g] Reaction was run neat at 50 °C, 6 days, neat.

The cycloadditions of MVK with 3-methyl-DHP **10a** (entry 4) and 3,5-dimethyl-1,2-DHP **10b** (entry 5) resulted in only modest preferences for endo isomers **15c** and **15d**. However, the 5-methyl-1,2-DHP (entry 6) showed a significant 90:10 preference for endo adduct **15e** versus exo adduct **16e**. The cycloaddition yields from the 5-methyl-DHPs **10b** and **10c** are quite low, however.

The 4-substituted 1,2-DHPs **10d** and **10e** (entries 7 and 8) did give higher yields of 7-*exo*-acetyl products; however, 7-*endo*-acetyl stereoisomers **15f** and **15g** are the stereochemically favored products by only a slight margin. The Diels−Alder cycloaddition of 6-methyl-1,2-DHP **10i** and MVK afforded 96:4 endo/exo products favoring **15h** (entry 9). This high preference for endo cycloadduct from the 6-methyl-DHP **10i** previously was noted for its cycloaddition with styrene to give cycloadduct **12m** (see Table 4, entry 10).

Mariano demonstrated that the cycloaddition between the parent 1,2-DHP **1c** and MVK gives a kinetically derived endo/exo **3e**/**4e** ratio of 4:3,[3e] but the equilibrium endo/exo ratio is 2:3. In order for us to show that alkyl-substituted DHPs also give kinetically controlled isomer ratios, stereoisomers **15g** and **16g** independently were subjected to the original reaction conditions and were heated to 55 °C for 1 week under argon. They also were heated at 105 °C for 24 h. No epimerization of the 7-acetyl group was detected by ^{1}H NMR in either case, and decomposition of adducts was minimal. When the temperature was raised to 130 °C for 2 days, endo cycloadduct **15g** was converted to a 65:35 mixture of **15g**/**16g** (35% recovery). Independently, the exo cycloadduct **16g** was epimerized to a 19:81 mixture of **15g**/**16g** (43% recovery). When epimerizations occur, they do so at higher temperatures than our 55 °C reaction temperature. Thus, the stereoselectivities of Diels−Alder reactions between 1,2-DHP and MVK are kinetically controlled.

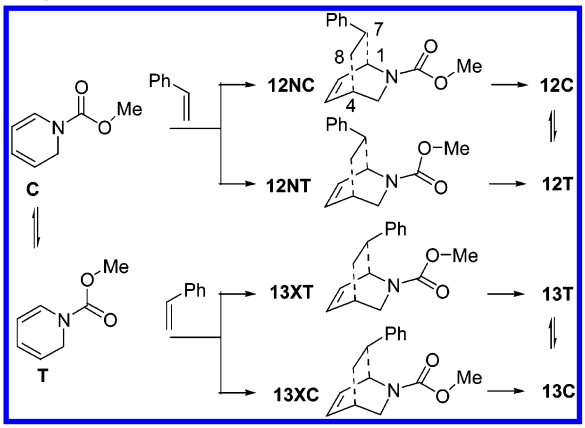
The stereochemical outcome for formation of cycloadducts **15a**/**16a** from MVK and 1,2-DHP **1a** was found to be solvent independent. As shown in Table 6, the highest cycloaddition

TABLE 6. Solvent Effects upon endo/exo 15a/16a Ratios for Reaction of MVK with *N*-Methoxycarbonyl-1,2-dihydropyridine (1a)

entry	conditions[a]	15a/16a endo/exo	yield (%)
1	neat	76:24	63
2	cyclohexane[b]	74:26	45[c]
3	dichloromethane[d]	79:21	35[c]
4	acetonitrile[e]	79:21	22[c]

[a] MVK/**1a** 5:1; 55 °C, 5 days. [b] Concentration of **1a** = 100 mg/mL. [c] The reaction did not go to completion. [d] Concentration of **1a** = 26 mg/mL. [e] Concentration of **1a** = 43 mg/mL.

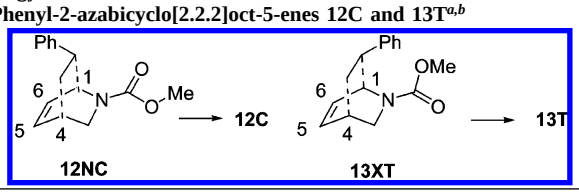
SCHEME 4. Major Cycloaddition Transition States for Azabicycles 12 and 13



yield was under neat conditions. All other reactions did not go to completion in 5 days.

Calculations of Styrene−DHP Cycloadditions. To gain insights into substituent influences upon the stereoselectivity of the styrene/DHP cycloadditions, ab initio calculations were performed. Four major possible transition states (TSs) were evaluated for cycloaddition reactions leading to azabicycles **12** and **13** (Scheme 4). These TS energies depend on the endo/exo (**N/X**) orientation of the styrene phenyl group and also on the conformational orientation of the carbamate carbonyl group as *s-cis* or *s-trans* (**C/T**) toward C_1 in the developing product azabicycle. In the general case, these TSs will be denoted as **12NC**, **12NT**, **13XT**, and **13XC**. The two cycloadducts and their major amide conformations, **12C**/**12T** and **13T**/**13C**, derive directly from these TSs by closing the partial bonds shown. The TS geometries were optimized at the RHF/3-21G(*) level, and each transition structure was confirmed by carrying out a frequency calculation to yield one and only one imaginary frequency. The vibration associated with the imaginary frequency was checked to correspond with a movement in the direction of the reaction coordinate. The results for the favored endo and exo TSs are listed in Table 7. The calculated $E^{\ddagger}_{elec}$ energy order (kcal/mol) of the TSs is **12NC** (0.00) < **12NT** (0.43) < **13XT** (2.0) < **13XC** (2.90). Single-point total energy calculations of the TSs were carried out at the RHF/6-31G* level. Both endo TSs are more stable than the exo TSs. The calculated energy difference between **12NC**, the more stable endo TS, and **13XT**, the more stable exo TS, is $E^{\ddagger}_{elec} = 2.0$ kcal/mol ($E^{\ddagger}_{o} = 1.7$ kcal/mol) in favor of the endo stereoselectivity. Thus, for further geometry optimizations and total energy minimizations of substituted 1,2-DHPs and styrene or its derivatives, the orientations of **12NC** and **13XT** were adopted as the preferred endo and exo TS geometries. These lead to **12C** and **13T** as endo and exo product geometries. The

TABLE 7. Calculated Transition State endo/exo (12NC/13XT) Energy Differences for Generation of 7-Phenyl-2-azabicyclo[2.2.2]oct-5-enes 12C and 13T[a,b]



entry	products	substituent	$\Delta E^{\ddagger}_{o}$[c]	ΔS_{total}[d]	$\Delta G^{\ddagger}_{T}$[c]	endo/exo **12**/**13** exptl (calcd)[e]
1	**12a/13a**	parent	−1.67	1.58	−2.30	84:16 (92:8)
2	**12b/13b**	parent[f]	−2.55	1.31	−2.89	86:14 (96:4)
3	**12c/13c**	Ph-*p*-OMe	−1.85	2.0	−2.67	80:20 (95:5)
4	**12d/13d**	Ph-*m*-NO_2	−3.30	0.44	−3.37	85:15 (97:3)
5	**12e/13e**	4-Me	−1.63	2.25	−2.57	78:22[g] (94:6)
6	**12f/13f**	4,6-di-Me	−1.49	1.6	−2.08	91:9[h] (91:9)
7	**12g/13g**	6-Me	−1.52	0.89	−1.76	96:4 (87:13)
8	**12h/13h**	5-Me	−1.00	1.31	−1.48	55:45 (83:17)
9	**12i/13i**	5-Et	−1.25	1.15	−1.67	62:38 (86:14)
10	**12j/13j**	5-*t*-Bu	−1.09	0.38	−1.10	55:45 (77:23)
11	**12k/13k**	5-Ph	−1.40	1.95	−2.22	54:46 (92:8)
12	**12l/13l**	5-Bn	−1.67	4.66	−3.83	55:45 (98:2)
13	**12m/13m**	1-Me	−3.29	3.02	−4.65	96:4 (99:1)

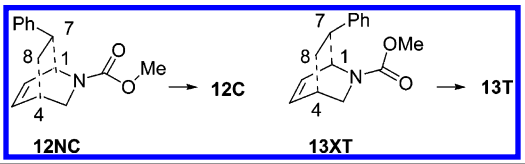
[a] Reaction of 1,2-DHPs and styrene. [b] Ab initio RHF/3-21G(*) ZPVE-corrected energies, $E^{\ddagger}_{o}$, of the cycloaddition transition states and free energy, $G^{\ddagger}$, values were calculated using Spartan'06 for Windows software. The *O*-methyl group of the carbamate preferred to be *syn* to carbonyl oxygen in all calculations. [c] In kcal/mol. [d] In cal/mol. [e] ($\Delta E^{\ddagger}_{o}$ or $\Delta G^{\ddagger}$) = ($E^{\ddagger}_{o}$ or $G^{\ddagger}$) **12NC** − ($E^{\ddagger}_{o}$ or $G^{\ddagger}$) **13XT** for all TSs leading to **12C** and **13T**. [f] *N*-COOBn analogue. [g] For the regioisomer, $\Delta E^{\ddagger}_{o}$ = ($E^{\ddagger}_{o}$) **12eC** − ($E^{\ddagger}_{o}$) **14eC** = −2.185; **12e**/**14e** 95:5 (92:8). [h] For the regioisomer, $\Delta E^{\ddagger}_{o}$ = ($E^{\ddagger}_{o}$) **12fC** − ($E^{\ddagger}_{o}$) **14fC** = −1.850; **12f**/**14f** 85:15 (88:12).

calculation results in Table 7 are qualitatively consistent with the experimentally determined endo isomer preferences and justify the level of sophistication of theory utilized.

The Table 7 calculations do overestimate the preference for the endo isomer in nearly all cases studied. The exception was the cycloaddition of styrene with 6-methyl-1,2-DHP **10i** to gave endo/exo adducts **12m/13m** (entry 7), for which there is a slightly smaller endo prediction than the experimental value. The largest deviations between experimental and observed isomer ratios are for the 5-substituted isomers **12h−l/13h−l** (entries 8−12) for which calculations consistently overestimate endo ratios by 22−43%. Calculations for the sterically crowded 1-Me derivative **12m**/**13m** (entry 13) capture the high endo preference. In light of the calculations for the MVK/DHP cycloadditions that follow (Table 9), it is notable that both transition state energy ($\Delta E^{\ddagger}_{o}$) and entropy (ΔS_{total}) calculations favor formation of endo isomers in all of the examples in Table 7.

The calculations of transition state bond distances demonstrate that both endo and exo TSs for the cycloaddition of styrene with DHPs are asynchronous (Table 8). The TSs for the 1-methyl-1,2-DHP **10i** to give **12m/13m** (entry 13) are the most asynchronous of the TSs. In the favored **12NC** TS for **12m** (Scheme 4), the newly forming C_1-C_7 bond (2.32 Å) is longer than that calculated for any other *endo*-phenyl **12NC** TS, and the C_4-C_8 bond (2.10 Å) is the shortest such TS bond. For the **13XT** TS for *exo*-phenyl isomer **13m**, the C_1-C_7 bond (2.43 Å) is again the longest such bond of the structures, and the C_4-C_8 bond (2.05 Å) is the shortest such bond. The 1-Me of the 1,2-DHP **10i** has hindered the approaching styrene but has not altered the regiochemical outcome. It can be noted that the

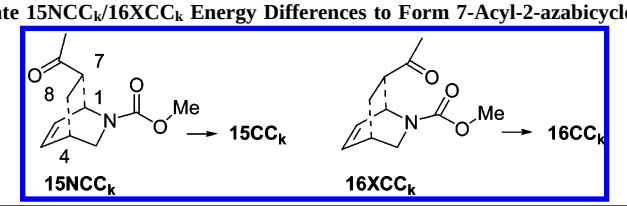
TABLE 8. Calculated Bond Lengths (Å) between Reacting Partners in the 12NC and 13XT TSs for Formation of 7-Phenyl-2-azabicyclo[2.2.2]oct-5-enes 12C and 13T[a]



			12NC[b]			13XT[b]		
entry	products	substituent	C_1-C_7	C_4-C_8	Δd (Å)	C_1-C_7	C_4-C_8	Δd (Å)
1	**12a/13a**	parent	2.268	2.130	0.138	2.325	2.115	0.210
2	**12b/13b**	parent[c]	2.268	2.132	0.136	2.332	2.113	0.219
3	**12c/13c**	Ph-*p*-OMe	2.264	2.133	0.131	2.318	2.116	0.202
4	**12d/13d**	Ph-*m*-NO_2	2.285	2.118	0.167	2.344	2.102	0.242
5	**12e/13e**	4-Me	2.259	2.130	0.129	2.316	2.116	0.200
6	**12f/13f**	4,6-di-Me	2.272	2.128	0.144	2.300	2.121	0.179
7	**12g/13g**	6-Me	2.279	2.117	0.162	2.312	2.127	0.185
8	**12h/13h**	5-Me	2.273	2.135	0.138	2.349	2.101	0.248
9	**12i/13i**	5-Et	2.271	2.133	0.138	2.338	2.105	0.233
10	**12j/13j**	5-*t*-Bu	2.273	2.155	0.118	2.347	2.128	0.219
11	**12k/13k**	5-Ph	2.296	2.118	0.178	2.365	2.089	0.276
12	**12l/13l**	5-Bn	2.285	2.139	0.146	2.340	2.114	0.226
13	**12m/13m**	1-Me	2.322	2.095	0.227	2.433	2.054	0.379

[a] Reaction of 1,2-DHPs and styrene calculated at RHF/3-21G(*) level. [b] Calculated TS bond distances (*d*) in angstroms. [c] *N*-COOBn analogue.

TABLE 9. Calculated Transition State $15NCC_k$/$16XCC_k$ Energy Differences to Form 7-Acyl-2-azabicyclo[2.2.2]oct-5-enes $15CC_k$ and $16CC_k$[a]



entry	products	substituent	$\Delta E^{\ddagger}_o$[c]	ΔS_{total}[d]	$\Delta G^{\ddagger}_T$[c]	endo/exo **15**/**16** exptl (calcd)
			RHF/3-21G(*)[b]			
1	**15a/16a**	parent	2.05	3.02	0.00	74:26 (50:50)
2	**15b/16b**[e]	parent[e]	1.58	3.34	0.40	70:30 (35:65)
3	**15c/16c**	4-Me	2.10	6.39	−0.12	71:29 (54:46)
4	**15d/16d**	4,6-di-Me	0.97	3.21	−0.08	53:47 (53:47)
5	**15e/16e**	6-Me	0.84	2.40	0.05	90:10 (48:52)
6	**15f/16f**	5-Me	1.62	5.38	−0.20	60:40 (58:42)
7	**15g/16g**	5-Et	0.59	4.16	−0.82	54:46 (78:22)
8	**15h/16h**	1-Me	2.16	5.28	0.39	96:4 (36:64)
			B3LYP/6-31G*[f]			
9	**15a/16a**	parent	2.47	4.97	−0.13	74:26 (55:45)
10	**15e/16e**	6-Me	0.13	5.26	−1.69	90:10 (93:7)
11	**15h/16h**	1-Me	1.37	6.80	−0.25	96:4 (60:40)

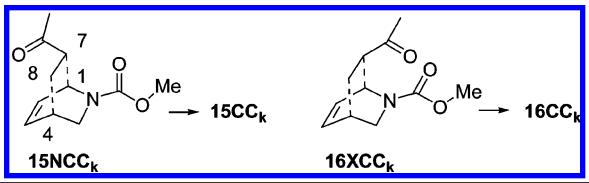
[a] Reaction of 1,2-DHPs and MVK. [b] Transition states were derived from RHF/3-21G(*). ZPVE-corrected energies $E^{\ddagger}_o$ of the cycloaddition transition states and $G^{\ddagger}$ values were calculated using Spartan'06 for Windows software. ($\Delta E^{\ddagger}_o$, ΔS_{total}, or $\Delta G^{\ddagger}$) = ($E^{\ddagger}_o$, S_{total}, or $G^{\ddagger}$) $\mathbf{15CC_k}$ − ($E^{\ddagger}_o$, S_{total}, or $G^{\ddagger}$) $\mathbf{16CC_k}$, respectively. $E^{\ddagger}_o$ was converted to $H^{\ddagger}_{total}$ by addition of H_{total} and RT (328.15 K). $G^{\ddagger} = H^{\ddagger}_{total} - TS_{total}$. The *O*-methyl group of the carbamate preferred to be *syn* to carbonyl oxygen in all calculations. [c] In kcal/mol. [d] In cal/mol. [e] *N*-COOBn analogue. [f] The same calculations as footnote b using TS: B3LYP/6-31G*-derived values.

12NC TSs leading to endo products **12C** are less asynchronous than the **13XT** TSs leading to exo adducts **13T** in all cases studied.

Calculations of MVK/DHP Cycloadditions. For the cycloaddition of *N*-methoxycarbonyl DHP with MVK, there are eight potentially important TSs. These depend on the approach of the 1,2-DHP with respect to the acetyl group (endo/exo or **N**/**X**), the orientation of the amide carbonyl (*s-cis* or *s-trans* toward C_1 of the cycloadduct, or **C**/**T**), and the conformational bias of the MVK (carbonyl *s-cis* or *s-trans* toward the methylene group of the cycloadduct, or $\mathbf{C_k}$/$\mathbf{T_k}$).

Using Spartan '06 for Windows software, the geometries of the eight transition states were optimized at the RHF/3-21G(*) level and single-point total energy calculations of the TSs were carried out at the RHF/6-31G* level. ZPVE-corrected energy differences were calculated for the lowest energy endo $\mathbf{15NCC_k}$ and exo $\mathbf{16XCC_k}$ TSs and products $\mathbf{15CC_k}$ and $\mathbf{16CC_k}$, formed by closing the partial bonds shown in Scheme 5. At this level of calculation, the minimum $\mathbf{16XCC_k}$ exo transition state, as measured by $\Delta E^{\ddagger}_{elec}$, is 2.05 kcal/mol *more* stable than the minimum $\mathbf{15NCC_k}$ endo transition state. Introduction of DHP substituents (Table 9) did not alter the preference for $\Delta E^{\ddagger}_{elec}$ of $\mathbf{16XCC_k}$ to be the minimum exo TS or for $\mathbf{15NCC_k}$ to be the minimum endo TS. In all cases, $\Delta E^{\ddagger}_{elec}$ of $\mathbf{16XCC_k}$ is the lowest energy TS. However, the endo isomers **15b**−**h** are experimen-

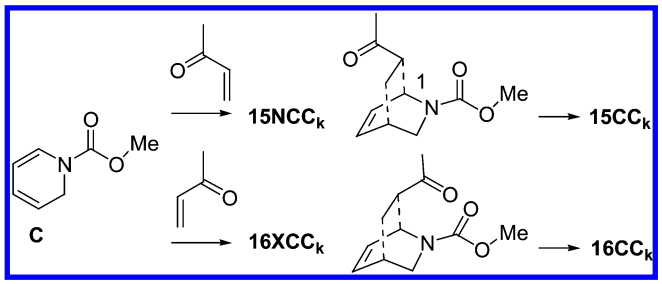
TABLE 10. Bond Lengths (Å) between Reacting Partners in the 15NCC$_k$ and 16XCC$_k$ TSs to Form 7-Acyl-2-azabicyclo[2.2.2]oct-5-enes 15CC$_k$ and 16CC$_k$[a]



			15NCC$_k$[b]			16XCC$_k$[b]		
entry	products	substituent	C_1-C_7	C_4-C_8	Δd (Å)	C_1-C_7	C_4-C_8	Δd (Å)
1	**15a/16a**	parent	2.354	2.061	0.293	2.544	2.01	0.534
2	**15b/16b**	parent[c]	2.352	2.063	0.289	2.525	2.018	0.507
3	**15c/16c**	4-Me	2.349	2.061	0.288	2.502	2.021	0.481
4	**15d/16d**	4,6-di-Me	2.370	2.047	0.323	2.487	2.024	0.463
5	**15e/16e**	6-Me	2.381	2.043	0.388	2.507	2.021	0.486
6	**15f/16f**	5-Me	2.382	2.043	0.339	2.635	1.978	0.657
7	**15g/16g**	5-Et	2.374	2.042	0.332	2.66	1.996	0.664
8	**15h/16h**	1-Me	2.480	1.984	0.496	2.845	1.933	0.912

[a] Cycloadditions of 1,2-DHPs and MVK at the RHF/3-21G(*) level. [b] Calculated TS bond distances (*d*) in angstroms. [c] *N*-COOBn analogue.

SCHEME 5. Favored Cycloaddition Transition States for Azabicycles 15 and 16



tally favored, so $\Delta E^{\ddagger}_{elec}$ values are inadequate to reproduce the observed endo preference for MVK/DHP cycloadditions.

To improve the analysis, the Spartan program was used to obtain H_{total} and S_{total}, the sums of translational, rotational, and vibrational enthalpies and entropies for the transition state structures. These were used to obtain the $\Delta G^{\ddagger}_T$ values from the $\Delta E^{\ddagger}_o$ values in Table 9. While the $\Delta G^{\ddagger}_T$ values do predict endo isomers to be favored for the 4-Me (entry 3) and 5-alkyl isomers (entries 4, 6, and 7), they still do not correctly predict endo isomers for the parents **15a,b** (entries 1 and 2), the 6-methyl derivative **15e** (entry 5), and the 1-methyl derivative **15h** (entry 8).

We next turned to the B3LYP/6-31G* theory level for transition state geometry optimization and energy calculations for entries 1, 5, and 8. At this higher level of theory, the calculated TSs leading to the parent **15a** (entry 9), 6-methyl **15e** (entry 10), and 1-methyl **15h** (entry 11) each now favor the **15NCC$_k$** TS leading to the observed endo cycloadduct isomers **15**, although only the 6-methyl isomer **15e** is quantitatively close to its observed endo preference. It is noteworthy for these calculated MVK cycloadditions that, while the transition state enthalpy contributions of **16XCC$_k$** favor formation of the exo isomers **16CC$_k$**, this factor is not product determinative: $G^{\ddagger} = H^{\ddagger}_{total} - TS_{total}$, and the greater total transition state entropy contribution of the **15NCC$_k$** transition states is dominant and accounts for the preferences for endo isomers **15CC$_k$**.

The calculations of transition state bond distances (Table 10) demonstrate that both endo and exo TSs for the cycloaddition of MVK with DHPs in Scheme 4 are asynchronous. The **15NCC$_k$** TSs leading to endo products **15CC$_k$** are less asynchronous than the **16XCC$_k$** TSs leading to exo adducts **16CC$_k$** for all cases studied. The most asynchronous TSs are for MVK reacting with 6-methyl DHP **10i** to give the 1-methyl isomers **15h/16h** (entry 8). Consistent with a steric effect, in the **15NCC$_k$** TS for **15h**, the newly forming C_1-C_7 bond (2.48 Å) is longer than that calculated for any other endo **15NCC$_k$** structure, and the C_4-C_8 bond (1.984 Å) is the shortest such TS bond. For the **16XCC$_k$** TS for exo isomer **16h**, the C_1-C_7 bond (2.845 Å) is again the longest such bond of the structures in Table 10, and the C_4-C_8 bond (1.933 Å) is the shortest such bond. These bond distances do not, however, explain the endo preference for the 1-Me isomer **15h**. The calculated thermodynamic parameters at two levels in Table 9 (entries 8 and 11) indicate that, although the **16XCC$_k$** TSs are favored by the activation energies, $E^{\ddagger}_o$, total entropy (S_{total}) considerations favor the **15NCC$_k$** TSs.

Conclusion

A series of 3-, 4-, 5-, and 6-substituted 1,2-dihydropyridines have been reacted with styrenes and methyl vinyl ketone to prepare 7-substituted-2-azabicyclo[2.2.2]hex-5-enes. There is a kinetic preference for 7-endo cycloadducts in all examples studied. Transition state energy calculations indicate that for styrene/DHP cycloadditions TS total energy $\Delta E^{\ddagger}_o$ and entropy ΔS_{total} factors both favor endo cycloadducts. Calculations of MVK/DHP cycloaddition transition states indicate that $\Delta E^{\ddagger}_o$ considerations favor exo cycloadducts, ΔS_{total} considerations favor endo cycloadducts, and the resultant free energy favors endo cycloaddition. The total entropy advantage for these endo cycloaddition transition states is relevant to the question of whether secondary orbital interactions, which would reduce rather than increase conformational freedom, are responsible for endo/exo selectivity preferences.[18]

Experimental Section

General Procedure for the Diels−Alder Cycloadditions between 1,2-DHPs and Styrene Derivatives. To the 1,2-DHP in a decalin solution was added 3−5 equiv of styrene. The mixture

(18) Garcia, J. I.; Mayoral, J. A.; Salvatella, L. *Acc. Chem. Res.* **2000**, *33*, 658−664.

was heated at reflux under argon for 24 h. After it was cooled to room temperature, the reaction mixture was loaded on a silica gel flash column and rinsed with cyclohexane to remove the high boiling decalin. The products were then eluted by flash column chromatography with a cyclohexane/EtOAc solution.

Preparations of 7-*endo*-Phenyl-2-carbomethoxy-2-azabicyclo-[2.2.2]oct-5-ene (12a) and 7-*exo*-Phenyl-2-carbomethoxy-2-azabicyclo[2.2.2]oct-5-ene (13a). According to the general procedure, from DHP **1a** (1.08 g, 7.77 mmol) and styrene (3.88 g, 37.3 mmol) in decalin (10 mL) after 17 h under argon there was obtained a colorless oil (526 mg, 32%) of the mixed products **12a** and **13a**. The mixture, $R_f = 0.40$ (hexane/EtOAc 2:1), could not be separated by normal phase chromatography. From ^{1}H NMR integrations of the H_1 protons, the ratio of **12a** and **13a** was 84:16. The ratio of **12a** and **13a** was 82:18 if analyzed by HPLC, eluting with 35% acetonitrile aqueous solution. The retention times for **12a** and **13a** were 10.7 and 8.08 min, respectively. A sample of 112 mg of the mixture was loaded to a medium-pressure (60 psi), reversed-phase C18 column rinsed with 35% acetonitrile aqueous solution to give 84 mg of **12a** and 16 mg of **13a**. The ratio of **12a** and **13a** from separation was 84:16. For endo isomer **12a**: ^{1}H NMR ($CDCl_3$, 500 MHz, 75 °C) δ 1.68 (m, 1H, H_{8a}), 2.17 (ddd, J = 13.5, 9.5, 2.5 Hz, 1H, H_{8s}), 2.90 (br, 1H, H_4), 3.03 (dt, J = 10.0, 2.0 Hz, 1H, H_{3n}), 3.36 (dd, J = 10.0, 2.0 Hz, 1H, H_{3x}), 3.42 (m, 1H, H_7), 3.71 (s, 3H), 4.74 (br, 1H, H_1), 6.28 (t, J = 7.0 Hz, 1H, H_6), 6.55 (t, J = 7.0 Hz, 1H, H_5), 7.09−7.21 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.3, 31.5, 44.4, 46.7, 50.7, 52.3, 126.3, 128.1, 130.9, 134.8, 143.4, 155.5; HRMS *m*/*z* 243.1270, calcd for $C_{15}H_{17}NO_2$ 243.1260. For exo isomer **13a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.69 (m, 1H, H_{8s}), 1.92 (m, 1H, H_{8a}), 2.89 (m, 2H, H_7, H_4), 3.13 (dt and dt, J = 10.5, 2.7 Hz, 1H, H_{3n}), 3.34 and 3.60 (s and s, 3H), 3.41 and 3.51 (dd and dd, J = 10.5, 2.4 Hz, 1H, H_{3x}), 4.43, 4.45, 4.72 and 4.74 (br, 1H, H_1), 6.40−6.64 (m, 2H, H_5, H_6), 7.18−7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.2 and 30.0, 30.8 and 31.0, 44.6 and 45.4, 48.7 and 49.0, 50.6, 52.1 and 52.5, 126.5, 127.6 and 127.8, 128.5, 133.5, 134.1 and 134.3, 143.0 and 143.2, 156.3 and 156.6; HRMS *m*/*z* 266.1152, calcd for $C_{15}H_{17}NO_2$ Na (M + Na) 266.1156. DHP **1a** (0.5 g, 3.6 mmol) and styrene (0.82 mL, 7.2 mmol) in xylene (50 mL) did not form cycloadduct **12a**/**13a** after heating to reflux for 2 h with 600 W microwave irradiation.

General Procedure for the Diels−Alder Cycloadditions between 1,2-DHPs and Methyl Vinyl Ketone (MVK). Preparation of 7-*endo*-Acetyl-2-carbomethoxy-2-azabicyclo[2.2.2]oct-5-ene (15a) and 7-*exo*-Acetyl-2-carbomethoxy-2-azabicyclo[2.2.2]-oct-5-ene (16a). A. Neat Conditions. A mixture of MVK (0.908 g, 13.0 mmol) and DHP (**1a**) (0.361 g, 2.6 mmol) was heated to 55 °C and stirred under argon for 5 days. The reaction mixture was purified repeatedly by flash column chromatography (cyclohexane/EtOAc 5:1) to give a 74:26 ratio of **15a** (251 mg) and **16a** (89 mg) with an overall yield of 63%. The isomer ratio was 76:24 from ^{1}H NMR integrations of the H_5 and H_6 protons of the crude product mixture. For endo isomer **15a**, $R_f = 0.50$ (cyclohexane/EtOAc 1:1): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.68−1.85 (m, 2H, H_{8s} and H_{8a}), 2.16 (m, 3H), 2.84 (br, 1H, H_4), 2.95 (m, 1H, H_{3n}), 3.11 (m, 1H, H_7), 3.26 (d, J = 9.9 Hz, 1H, H_{3x}), 3.70 (s, 3H), 4.98 and 5.17 (br and br, 1H, H_1), 6.29 (m, 1H, H_6), 6.40 (m, 1H, H_5); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 24.7 and 25.5, 28.2 and 28.3, 30.6 and 30.9, 46.8 and 47.0, 47.0 and 47.2, 52.4, 52.4 and 52.8, 130.0, 135.1, 155.3 and 155.9, 206.2 and 206.5; HRMS *m*/*z* 232.0941, calcd for $C_{11}H_{15}NO_3Na$ (M + Na) 232.0950. For the exo isomer **16a**, $R_f = 0.54$ (cyclohexane/EtOAc 1:1): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.33 (m, 1H, H_{8a}), 2.17 (m, 1H, H_{8s}), 2.23 and 2.30 (s and s, 3H), 2.67 (m, 1H, H_7), 2.75 (m, 1H, H_4), 3.93 (dt and dt, J = 9.9, 2.7 Hz, 1H, H_{3n}), 3.26 (dd, J = 9.9, 2.1 Hz, 1H, H_{3x}), 3.61 and 3.64 (s and s, 3H), 4.94 and 5.13 (m and m, 1H, H_1), 6.42−6.53 (m, 2H, H_5, H_6); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 23.3, 28.4 and 28.7, 30.1 and 30.3, 47.1 and 47.5, 47.6 and 47.9, 52.3, 52.5, 131.6 and 132.0, 135.5 and 135.6, 155.3 and 156.3, 206.5 and 207.2; HRMS *m*/*z* 232.0940, calcd for $C_{11}H_{15}NO_3Na$ (M + Na) 232.0950. **B. In Cyclohexane.** A solution of MVK (1.0 g, 14.3 mmol) and DHP **1a** (0.401 g, 2.9 mmol) in cyclohexane (4 mL) was heated to 55 °C and stirred under argon for 5 days. The reaction was 87% complete by ^{1}H NMR. Purification afforded 271 mg of the mixture of **15a**/**16a** (45%) in a ratio of 74:26 by ^{1}H NMR integrations of H_5 and H_6 protons. **C. In CH_2Cl_2.** In a sealed vial purged with argon, the solution of MVK (0.339 g, 4.8 mmol) and DHP **1a** (132 mg, 0.95 mmol) in CH_2Cl_2 (5 mL) was heated to 55 °C and stirred for 5 days. The reaction was only 55% complete by ^{1}H NMR. Purification gave 70 mg (35%) of a mixture of **15a**/**16a** in a 79:21 ratio by from ^{1}H NMR integrations of H_5 and H_6 protons. **D. In CH_3CN.** In a sealed vial purged with argon, the solution of MVK (0.339 g, 4.8 mmol) and DHP **1a** (132 mg, 0.95 mmol) in acetonitrile (3 mL) was heated to 55 °C and stirred for 5 days. The reaction was 58% complete by ^{1}H NMR integrations. Purification gave 29 mg (22%) of a 79:21 mixture of **15a**/**16a** by ^{1}H NMR integrations of H_5 and H_6 protons.

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Supporting Information Available: Experimental procedures and spectroscopic data for 1,2-dihydropyridines **1a,b**, **10a−c,e,f,h,i**, and cycloadducts **12b−m**/**13b−m**, **14e,f**, and **15b−j**/**16b−j**, as well as copies of ^{1}H NMR and ^{13}C NMR for these compounds, X-ray data for **15d**, Spartan-derived RHF/6-31G* energies for all cycloadducts, RHF/3-21G(*) calculations for energies of all cycloaddition transition states, and B3LYP/6-31G* calculations for transition states **12a**/**13a** and **15a,e,h**/**16a,e,h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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