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HETERODIENOPHILES 9.[1] ON THE PREFERENCE FOR *EXO*-ORIENTATION IN ALDIMINE CYCLOADDITIONS

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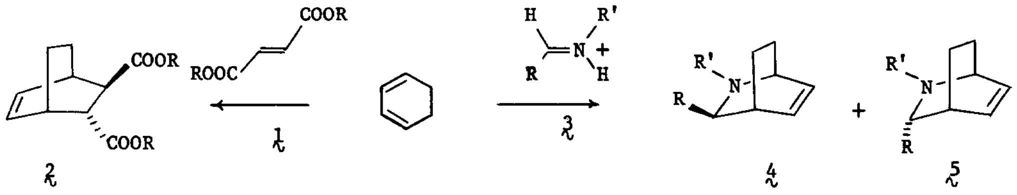
The synthetic utility of the Diels-Alder route to cyclic structures is enhanced by its remarkable stereoselectivity.[2] Notable among the several stereochemical aspects of this reaction are the "principle of *cis* addition" and the "Alder *endo*-rule." These are the general stereochemical rules governing kinetically controlled cycloadditions of 1,2-disubstituted olefins with dienes. While the "*cis* addition principle" can be related to the concertedness of Diels-Alder reactions, the basis for the "Alder *endo*-rule" is believed to be a combination of steric and polar effects combined with secondary orbital interactions.[2]

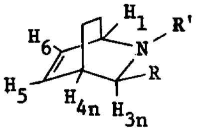
In order to enhance the utility of the Diels-Alder reaction as a route to stereoselectively substituted heterocycles,[3] we have been studying the limits of the Alder *endo*-rule as it applies to the cycloaddition of aldimines with cyclic dienes.[1] We here wish to report the first examples of substituent stereochemical preferences during the catalyzed cycloaddition of a diene with aldimines identically substituted on nitrogen and carbon.

If one considers cycloaddition of cyclohexa-1,3-diene with an *E*-1,2-disubstituted olefin **1**, the *cis* addition principle predicts the *trans* product **2**. Either carbalkoxyl group can be *endo* in **2** by virtue of the symmetry axis of olefin **1**. For cycloaddition of an *E*-aldimine **3**, R = R', the nitrogen atom destroys axial symmetry so either a C-3 *exo*-R **4** or *endo*-R **5** structure can form. If protonated E-imines **3** react with dienes via a transition state identical to an isoelectronic and sterically similar *E*-olefin, a nearly 50:50 *exo*/*endo* ratio of **4** and **5** can be predicted.



Aldimines **3** were generated by the action of boron trifluoride-ether in chloroform for 2-6 hr on N-carbalkoxy-2-methoxy glycinates **6**,[4] which were used in situ with cyclohexa-1,3-diene. Workup and molecular distillation (100-125°, 0.4mm) afforded in 25-35% yields mixtures of the C-3 exo and endo substituted adducts **4** and **5** (Table 1), purified by GLPC (5% SE-52 on Chromsorb G, 185°). The ratio of isomers **4**/**5** could be determined by proton NMR at ambient temperature by inspection of the olefinic region. The shift for proton H_5 of the C-3 endo-substituted isomer **5** at δ6.15 is upfield of the shifts for olefinic protons H_5 and H_6 of **4** and H_6 of **5** centered at δ6.46.[5] Isomer ratios as determined by NMR integration[6] are shown in Table 1.

Table 1. Kinetic[a] exo-Preferences in 3-Substituted N-Carboalkoxy-2-Azabicyclo[2.2.2]oct-5-enes **4** and **5** Formed Via Acid Catalyzed Addition of Aldimines **3** with Cyclohexa-1,3-diene.



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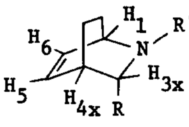

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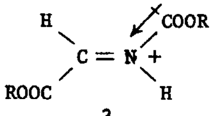
Adduct[b,c]	R'	R	Percentage **4** (C-3 exo-R)
I	COOMe	COOMe	73 ± 4
II	COOEt	COOEt	70 ± 4
III	COOMe	COOEt	70 ± 4
IV	COOEt	COOMe	65 ± 4
V[d]	$COOCH_2Ph$	COOMe	80
VI[e]	COOEt	COMe	67 ± 2
VII[e]	COOEt	Ph[f]	80 ± 2
VIII[e]	COOEt	$p\text{-}NO_2Ph$[f]	80 ± 2
IX[g]	COOEt	CCl_3	25 ± 3[h]
			38 ± 3[i]

(a) After four hrs in refluxing chloroform with 2-5% BF_3-etherate, 94/6 and 75/25 mixtures of **4**/**5** (Entry I) were unchanged. Longer reaction times or higher percentages of acid resulted in eventual decomposition of both exo and endo adducts; (b) Satisfactory analyses were obtained for all new compounds; (c) NMR ($CDCl_3$) shifts were identical within ± 0.05 δunits. $\delta H_1 = 4.76$; $\delta H_{3x} = 4.2$; $\delta H_{3n} = 3.83$; $\delta H_{4x} = 3.06$; $\delta H_{4n} = 2.92$; (d) ref. 3b; (e) ref. 5; (f) In reactions of E-olefins with cyclopentadiene phenyl prefers endo over carbomethoxy 56/44 and p-nitrophenyl prefers endo over carbomethoxy 72/28, Table VIII in ref. 2; (g) ref. 7; (h) BF_3 catalysis; (i) thermal.

In Table 1 aldimines **3** in which there are identical substituents on imine carbon and nitrogen (Entries I-II) indicate a kinetic preference for introduction of the substituent on carbon into the C-3 *exo* position. Modification of the alkoxy substituent on the ester or urethane (Entries III-V) has little effect on the stereochemical preference. These results are consistent with the reported preference[5] of aryl and acetyl for the C-3 *exo* orientation in reactions of aldimines **3** generated from alkylidenediurethanes (Entries VI-VIII). Only with the bulky trichloromethyl group (Entry IX) is a C-3 *endo* preference shown; however, this example is not for an N-protonated aldimine **3**, but for a thermal or boron trifluoride catalyzed reaction of the isolated aldimine.[7]

Assuming application of the Alder *endo*-rule to the reactions in Table 1, the enhanced preference for the substituent on aldimine carbon to occupy an *exo* orientation in the adduct **4** implies an enhanced preferance in protonated *E*-aldimines **3**[1,7-9] for the substituent on nitrogen to cycloadd via an *endo* orientation. One plausible explanation is that the inductive effect of the charged nitrogen atom in **3** makes the carbalkoxyl group adjacent to nitrogen more electron deficient than the carbalkoxyl group next to carbon.[8] Secondary orbital interactions between the diene and the aldimine substituent might favor interaction with the most electron poor carbalkoxyl group on nitrogen, thus leading preferentially with an *E*-aldimine to C-3 *exo*-carbalkoxy adducts **4**. This explanation is consistent with the strong *endo* prederence shown by acid coordinated substituents in the acid catalyzed Diels-Alder cycloaddition of olefins to dienes.[10a-d]



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Alternatively, the counter-ion associated with the iminium ion **3** may increase the effective steric bulk about the nitrogen substituent. For steric reasons the substituent on nitrogen would prefer the less hindered *endo* orientation. This would lead with an *E*-aldimine **3** to preferential C-3 *exo*-carbalkoxy adduct **4**. The invariance with leaving group of the C-3 *exo* substituent preference for Entry V, Table 1,[3b] when the aldimine **3** is generated from **6** or **7** appears to be inconsistent with this latter theory.[11]

$$\mathrm{PhCH_2OOCNH\underset{\displaystyle X}{\underset{|}{C}}HCOOCH_3}$$

6 X = OCH_3

7 X = $NHCOOCH_2Ph$

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2. J. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961).
3. See, for example; (a) K. Jankowski, *Tetrahedron Lett.*, 1976, 3309; (b) A. J. G. Baxter and A. B. Holmes, *J. Chem. Soc. Perkins I*, 1977, 2343.
4. E. Zoller and D. Ben-Ishai, *Tetrahedron*, **31**, 863 (1975). Amberlite IR-120(H^+) ion exchange resin was used in place of sulfuric acid. Yields of glycinate esters were 90-95%.
5. The upfield shift of H_5 in C-3 *endo*-aryl and *endo*-acetyl adducts **5** has been noted previously; G. Krow, R. Rodebaugh, R. Carmosin, W. Figures, H. Pannella, G. DeVicaris, and M. Grippi, *J. Amer. Chem. Soc.*, **95**, 5273 (1973).
6. Twice the integrated area of H_5 of the *endo* isomer **5** at δ6.15 was divided by the total olefinic area to obtain the fraction of **5** present in the mixture. Proton assignments were confirmed by decoupling.
7. G. Krow, C. Pyun, R. Rodebaugh, and J. Marakowski, *Tetrahedron*, **30**, 2977 (1974).
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11. Use of benzene solvent in place of chloroform has little effect on stereochemical preference for Entries I-VII, Table 1. See references 3b, 5.