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RELATIVE DIELS-ALDER REACTIVITY OF 3-ALKYL-2-(3-BUTENYL)-1,2-DIHYDROPYRIDINES. INTERPLAY OF ELECTRONIC AND STERIC FACTORS RELATED TO THE 3-ALKYL GROUP.

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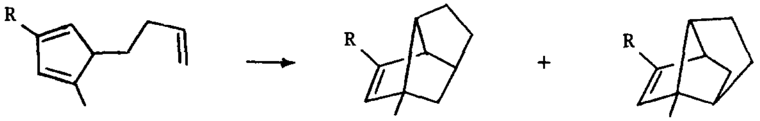
Summary: Steric effects have been found to predominate over Frontier Molecular Orbital (FMO) effects in controlling the relative rates of intramolecular cycloadditions of 3-R-substituted-2-(3-butenyl)1,2-dihydropyridines (DHP) in the series **4a-c** (R = H, Me, Et).

Snowden[1] has reported recently that intramolecular thermal (250°,benzene) cycloadditions of 5-(3-butenyl)-1-methylcyclopentadienes **1a** and **1b** afford primarily (3:1) the "meta" adducts **2a-b** rather than the ortho/para type adducts **3a-b**. The unusual "meta" regiochemistry of these cycloadditions, in full agreement with FMO theory,[2] was noted to be significant from a theoretical point of view. However, it can be seen that the observed "meta" orientational preference is also consistent with rate controlling steric interactions between a 1-methyl group and the proximal methylene of the 3-butenyl side chain; the steric and FMO effects are reinforcing.

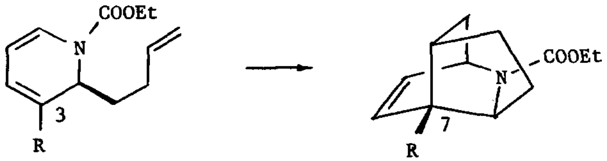


1 **2** **3**

(a) R = H; (b) R = $OSiMe_3$

During the course of our study of cycloaddition reactions of 1,2-DHP[3], we have prepared N-ethoxycarbonyl-2(3-butenyl)-1,2-DHP **4a**, along with its 3-methyl **4b**, and 3-ethyl **4c** homologs. Although the latter have the same vicinyl relationship of the alkyl and butenyl chains as found in structures **1a-b**, steric and FMO effects are <u>not</u> reinforcing for cycloadditions of **4b-c**. If electronic effects dominate the intramolecular cycloadditions of **4b-c**, the reaction rates should follow the order 3-Et>3-Me>3-H. A terminal alkyl group at C-3 is predicted by theory to raise the HOMO energy of the diene, thus lowering the HOMO/LUMO energy difference and facilitating the cycloaddition.[2] On the other hand, if steric interactions between the 3-alkyl and the proximal methylene of the 3-butenyl side chain inhibit attainment of the cycloaddition transi-

4a R = H
4b R = Me
4c R = Et



5a R = H
5b R = Me
5c R = Et

tion state, then the relative reaction rates for cycloaddition should be 3-H>3-Me>3-Et.

We wish to report evidence that with substrates 4b-c an alkyl substituent at C-3 exerts a *rate retarding* effect during intramolecular cycloaddition as expected if steric effects are dominating FMO effects. A reactivity order 4a>4b>4c has been determined by gas chromatographic analysis through three half-lives. The relative rate data are shown in Table 1.[4]

Table 1. Kinetic Data for Conversions of 4 to 5 in Decalin at 192°.

Reactant	IP (eV)[a]	λmax (nm)[b]	Product	k (hr^{-1})	t½ (hr)	($\Delta\Delta G^{\dagger}$) kcal/mol
4a Parent	8.1	298[c]	5a Parent	1.33 ± 0.02	0.52 ± 0.01	Standard (0.0)
4b 3-Me	7.7	295[d]	5b 7-Me	0.50 ± 0.01	1.40 ± 0.1	0.9
4c 3-Et	-	297[e]	5c 7-Et	0.25 ± 0.01	2.80 ± 0.1	1.5

(a) IP = ionization potential; (b) ultraviolet spectrum; (c) ε_{max} = 6100; (d) ε_{max} = 5500; (e) ε_{max} = 4900.

Further evidence that an electronic effect is not rate determinative has been obtained from ionization potential (IP) measurements obtained by photoelectron spectroscopy. As shown in Table 1, the IP of the parent 4a is 0.4 eV larger than the 3-methyl homolog 4b. Using this evidence alone, FMO theory predicts that 4b should cycloadd faster than 4a because of the lower HOMO/LUMO energy difference for 4b.

The ultraviolet spectra of 4a-c are informative, also. According to the rules formulated by Woodward,[5] an alkyl substituent attached to the parent diene shifts the absorption 5 nm toward the long wavelength region. The *reduction* in λ_{max} in going from the parent 4a to the 3-alkyl derivatives 4b-c suggests a greater degree of nonplanarity of the diene chromophores in the ground state conformers of the latter.[2b] This twisting is expected if a steric interaction between the 3-alkyl and the 2(3-butenyl) side chain is occurring. The cycloaddition transition states for 4b-c would exacerbate this interaction.

Cycloadditions of substrates 1a-b are in a class in which steric and FMO considerations are reinforcing; either effect might be dominant. In the cycloadditions of 4b-c we have shown a second class in which steric and FMO considerations are in opposition, and in which steric effects are dominant. An example from this second class in which FMO considerations are dominant might be the reactions of butadiene and 1-methylbutadiene with the polar dienophiles maleic anhydride or tetracyanoethylene; here rate enhancement is observed upon terminal alkyl substitution in the face of possibly repulsive steric interactions.[6]

References and Notes

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3. (a) Krow, G. R.; Carey, J. T.; Zacharias, D. E.; Knaus, E. E. J. Org. Chem. 1982, 47, 1989. (b) For the experimental procedure, see: Comins, D. L.; Abdullah, A. H.; Smith, R. K. Tetrahedron Lett., 1983, 2711. Our isolated yields of 5a-c were 81, 71, and 76%, respectively.
4. Satisfactory ^{1}H-NMR spectra, HRMS and/or elemental analysis data were obtained for 4a-c/5a-c.
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