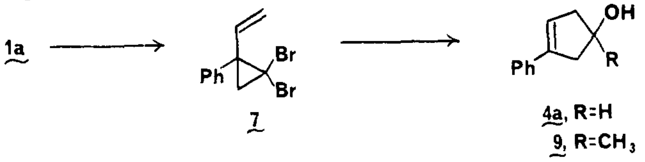
lizes readily available dibromocyclopropanes. Reaction of diene **1a** with 1 equiv of $CHBr_3$ and 1.2 equiv of KO-*t*-Bu in pentane (0–25 °C, 15 h) produced **7** in 73% yield.[7] This


1a **7** **4a**, R=H **9**, R=CH_3

dibromocyclopropane was converted to **4a** in one pot in 45% yield by sequential treatment in THF with (a) 1 equiv of *n*-butyllithium (−100 °C, 0.5 h), (b) 1 equiv of methanol (−100 to −78 °C, 2 h), (c) 2 equiv of *tert*-butyllithium (−78 °C, 2 h), and (d) anhydrous CO_2-free oxygen (−78 °C, slowly bubbled through reaction mixture for 2 h), followed by stirring at 25 °C for 2 h. The tertiary cyclopentenol **9** was produced (40% yield)[12] by substituting 1 equiv of methyl iodide[15] for methanol in the above procedure.

Several mechanisms may be postulated for the alkoxy-accelerated vinylcyclopropane rearrangement: (a) homolytic cyclopropane cleavage to a stabilized diradical intermediate (**10**), followed by internal coupling; (b) initial


10


11

heterolytic cleavage to an aldehyde (**11**), followed by aldol cyclization; (c) a concerted [1,3] sigmatropic rearrangement. Dramatic acceleration of [3,3][16] and [1,3][17] sigmatropic shifts by alkoxide substituents in other systems have been observed recently, although these rearrangements commonly involve the reaction of *potassium* alkoxides in highly dissociating media. Richey[18] has previously noted the accelerating effect of methoxyl and dimethylamino substituents on the thermal vinylcyclopropane rearrangement. Perhaps significant is the exclusive formation of the anti isomer **6**, as expected for a concerted reaction controlled by orbital symmetry[19] and subjacent orbital[20] effects.

Further studies are underway to clarify the mechanism of this rearrangement, to define the scope and limitations of the process, and to develop improved methodology for the synthesis of 2-vinylcyclopropanols.

Acknowledgment. This investigation was supported in part by a Pennwalt Corp. grant from the Research Corp.

Registry No. 1a, 2288-18-8; **1b**, 78-79-5; **1c**, 2495-32-1; **2a**, 72926-75-1; **2b**, 72926-76-2; **2c**, 72926-77-3; **3a**, 72938-30-8; **3c**, 72926-78-4; **4a**, 27856-20-8; **4b**, 72926-79-5; **4c**, 72926-80-8; **5**, 592-57-4; **6**, 694-70-2; **7**, 58189-55-2; **9**, 72926-81-9.

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Perturbed Pericyclic Reactions: Stereochemical Consequences of Heterosubstitution. A Qualitative Mechanistic Model Based on the Nonpreservation of Orbital Topology[1]

Summary: The CNDO/B potential energy surfaces for ring closure of 1- and 2-hetereosubstituted butadienes leads to results unexpected from a naive application of the Woodward–Hoffmann rules; however, the deviations are rationalizable in terms of nodal shifts within the highest occupied π molecular orbital of the dienoids as ring closure sets in.

Sir: The idea implied by orbital symmetry conservation for analyzing the course of reactions, first proposed by Woodward and Hoffmann[2] and others,[3,4] has been expressed in a variety of ways.[5-18] The isomorphism has been demonstrated rigorously for a few of the cases[19] as well as extended to a hierarchy of symmetry rules.[20] The conceptual simplicity of the various methods coupled to their efficacious application to molecular systems containing no symmetry has had a profound effect on recent theoretical and experimental developments. Two of the currently more popular expressions of the orbital symmetry principle due to Dewar[5] and Zimmerman[6] postulate that molecules without symmetry survive the analysis because orbital topology is conserved across the potential energy surface for reaction.[21] Indeed, a wide variety of presumably concerted heterocyclic transformations have been rationalized as being consistent with this postulate. In the present contribution semiempirical MO calculations are presented to show that this is not necessarily the case for certain heteroelectrocyclic reactions which are isoelectronic with the butadiene/cyclobutene interconversion. One prediction of particular importance concerns the

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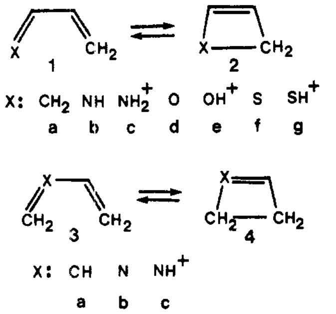
stereochemically dependent course of the reaction as a function of the heteroatom substitution site. Specifically, strong heteroasymmetry can remove the energetic distinction between conrotatory and disrotatory ring opening. A single determinant model for analyzing these and related rearrangements in terms of nodal properties of the key molecular orbitals is described.

Structures isoelectronic with butadiene/cyclobutene considered here are 1- and 2-heterosubstituted derivatives 1–4.



X: CH_2 NH NH_2^+ O OH^+ S SH^+

a b c d e f g

X: CH N NH^+

a b c

In all cases the ground-state end points have been fully geometry optimized with CNDO/B,[22] and in several instances with MINDO/3[23] and CNDO/2 as well. Reactions **1a–c**/**2a–c** were investigated (CNDO/B) both by a continuous deformation of end points into one another and by a partial geometry optimization of 9–17 of the intervening potential surface points. Reactions **1d–g**/**2d–g** were considered only by the former procedure and transformations **3b,c**/**4b,c** by the latter. The energy-optimized paths were constructed by regarding the internal heavy-atom angles as reaction coordinates. The stepwise potential surface behavior produced by MINDO parameterizations[24] and by extended basis set ab initio calculations[25] was mimicked by the CNDO/B surfaces constructed here.[26]

For each of the numerical reactions an MO correlation diagram was constructed. In accord with orbital symmetry rules and explicit calculations, the antisymmetric high-lying π_A MO of butadiene and **3b,c** are transformed into σ_{CC} and σ_{CC}^* for the conrotatory and disrotatory changes, respectively (cf. Figure 1a). For reactions **1c,e,g**/**2c,e,g** both stereochemical paths are accompanied by $\pi_A \rightarrow \pi_{CC}$ correlations as exemplified by Figure 1b, and thus both are genuine "allowed" processes. Closures of acrolein and thioacrolein (**1d,f**/**2d,f**) behave similarly, although it should be noted that the question of con vs. dis closure is not applicable here. Significantly, the conrotatory route of 1-azabutadiene involves a $\pi_A \rightarrow \sigma_{CC}$ interchange, whereas disrotation shows a $\pi_A \rightarrow \pi_{CC}$ correlation.[29,31]

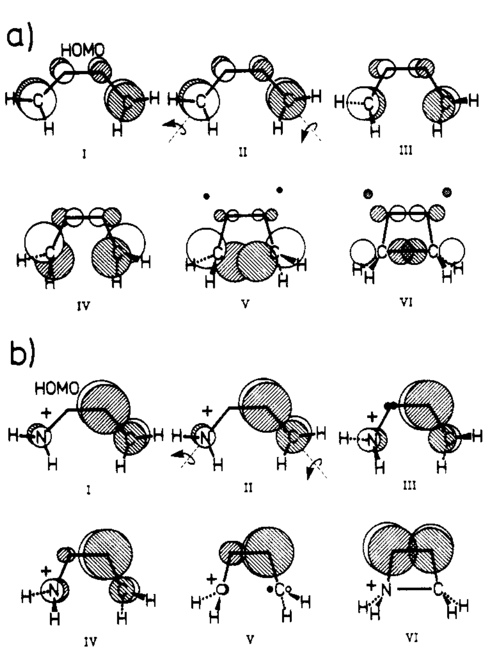


Figure 1. Deformation of the π HOMO of butadiene and the immonium salt **1c** as the diene is closed to the corresponding four-membered ring (CNDO/B). Circle diameters are proportional to the squares of the eigenfunction coefficients: (a) butadiene, a $\pi_A \rightarrow \sigma_{CC}$ correlation; (b) salt **1c**, a $\pi_A \rightarrow \pi_{CC}$ correlation.

Within single-determinant MO theory, the calculated transformations are nicely rationalized by considering the changes in nodal structure for π_A across the potential energy surface. Figure 2 depicts the CNDO/B π_A MO's for the heterodiene end points. With increasing electronegativity of the heteroperturbation and with replacement of the 2-position and then the 1-position, the node shifts continuously in the direction of the heteroatom. For N-protonated 1-azabutadiene, the node has in fact crossed C-2. The end-point nodal restructuring in response to heterosubstitution is manifested further as ring closure sets in. For simply substituted butadienes, 2-aza derivatives **3b,c**, and the 1-aza species **1b**, the orbital topology is preserved in the conrotatory transformation as the node moves about between positions 2 and 3, analogous to the symmetric parent (Figure 1a). A $\pi_A \rightarrow \sigma CC$ correlation results. The disrotatory closure of 1-azabutadiene and the reactions of **1d,f** involve a nodal shift across an atomic center as product is formed. Orbital topology is not conserved as a $\pi_A \rightarrow \pi_{CC}$ correlation takes place. The charged species **1c,e,g** utilize the same orbital deformation pattern, but in these cases the node already resides between positions 1 and 2 in the end-point structures. Figure 3 summarizes the nodal displacements.

The stereochemical consequence of a $\pi_A \rightarrow \pi_{CC}$ correlation can be appreciated by reference to Figure 1b. As

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(26) Energy barriers ($\Delta E^{\ddagger}$) for the incremental, unoptimized closure of cis dienes **1** to the four-membered ring **2** are as follows (X, $\Delta E^{\ddagger}$ in kcal/mol): CH_2, 55 (con) (vs. MINDO-3,[23,24b] 50; STO-3G,[27] 67; ab initio,[24b,25] 60; ab initio CI,[24b,25] 56); *endo*-NH, 45 (con), 48 (dis); NH_2^+, 27 (con), 29 (dis); O, 44; *endo*-OH^+, 29 (con, dis); S, 48; *endo*-SH^+, 36 (con), 37 (dis). As is usual for single-determinant calculations, the stability of the four-membered rings is overestimated, leading to an exothermic ring closure in most cases [X, ΔE_{reac} (**1** → **2**) in kcal/mol]: CH_2, −10 (vs. 0.5 to −20 kcal/mol by other methods[23,24a,27,28b] and +9 kcal/mol by experiment[28b]); *endo*-NH, −17; NH_2^+, −14; O, −28; *endo*-OH^+, −23; S, −2; *endo*-SH^+, 10 kcal/mol.

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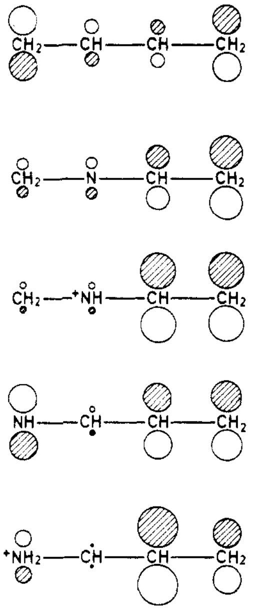

Figure 2. End point π_A MO's (CNDO/B) for the isoelectronic diene series **1a**, **3b**, **3c**, **1b** (exo), and **1c**. Circle diameters are proportional to the squares of the eigenfunction coefficients.

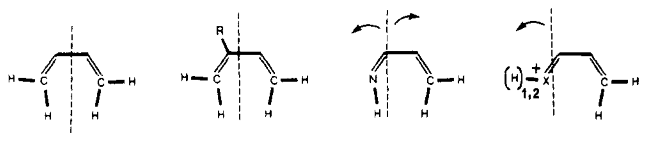

Figure 3. Nodal disposition for the HOMO of 1,3-dienes. The dotted lines represent the nodal positions for the planar ground states. The shift of the node as ring closure occurs is indicated by arrows. For 1-azabutadiene conrotation and disrotation cause opposite shifts, leading to $\pi_A \rightarrow \sigma$ and $\pi_A \rightarrow \pi_{CC}$ correlations, respectively. To the right, the subscripts in X^+–$(H)_{1,2}$ refer to OH^+/SH^+ and NH_2^+, respectively.

the node moves toward NH_2^+, the π MO follows behind, along the heavy-atom framework. In the transition state the atomic orbital contributions at the termini are very small by comparison with the corresponding butadiene transition state (cf. Figure 1a, IV and V). Consequently, whereas for the latter the termini direct the stereochemical outcome, for the former the key π-type MO is uninfluenced by the geometric disposition of the end atoms.

Accordingly, while cyclobutene and the 2-aza species **3b,c** exhibit a frontier-orbital crossing in their disrotatory openings characteristic of a relatively high-energy process, the highly unsymmetrical structures substituted in the 1-position, **1b,c,e,g**, yield a comparable energy barrier for both rotational motions.[26] The ease with which certain fused 2-azetines open by a disrotatory path may be supportive.[32] The role of substitution has yet to be unraveled, however, since counter examples are known.[32c] Further, an unsymmetrical 2-azapentadienyl anion delivers a 50:50 mixture of stereoisomeric ring-closed products in strong contrast to the behavior of the symmetrical 2,4-diaza species.[33]

Comparison of the preliminary calculated activation barriers reveals that substitution of the 1-carbon in butadiene by a heteratom causes a predicted drop of 7–11 kcal/mol in $\Delta E^{\ddagger}$ for ring closure. Protonation (**1c,e,g**/**2c,e,g**) augments the fall by 12–18 kcal/mol.[26] Experimentally, oxetes[34] and thietes[35] persistently ring open thermally at room temperature or below. In the former case, tetramethyloxetane has been shown to ring cleave with a nearly 10 kcal/mol lower energy expenditure than that in the corresponding cyclobutene.[34a] Likewise, destruction of the heterocyclic four-membered rings is found to be strongly acid catalyzed.[32b,34a,35a] Within the CNDO/B scheme, the $\Delta E^{\ddagger}$ differences do not appear to be a response to thermochemical factors,[33b,34a,36,37] but further work is needed to fully evaluate this point.

In conclusion, we note that molecular symmetry is a significant restriction, and relaxation of it may permit nodal shifts to occur within reaction-determining molecular orbitals on the slopes of the potential energy surface. Formally "forbidden" hydrocarbon processes can be expected to proceed by perfectly "allowed" pathways as unanticipated orbital correlations are utilized by the transforming molecules.[29,38] In such a circumstance orbital topology is not conserved, with the consequence that the orbital symmetry derived selection rules are inapplicable. Heterocycles amenable to formation and disruption by concerted ring-closure and ring-opening reactions, respectively, ought to be particularly susceptible to this analysis, exhibiting considerably enhanced rates and deviant stereochemical behavior relative to the all-carbon analogues. Furthermore, the mechanistic model outlined here should apply to perturbed pericyclic transformations of all types.[42]

Acknowledgment. I am grateful to the University of Copenhagen for generous provision of computer facilities, to Professor J. Michl (University of Utah) for stimulating

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discussions, and to Professor H. J. T. Bos (University of Utrecht) for access to unpublished results.

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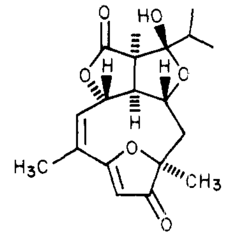
Chiral Models of the Furenone Moiety of Germacranolide Sesquiterpenes

Summary: A procedure is outlined for converting 2,3:5,6-di-*O*-isopropylidene-D-mannose (4, diacetone mannose), by a series of simple, efficient steps, into the unsaturated hydroxy esters **14** and **15**, which are then oxidized by Fetizon's reagent to afford the dienones **3a** and **3b**, these being analogues of the furenone system found in many germacranolide sesquiterpenes.

Sir: The plant metabolites known as the germacranolide sesquiterpenes are among some of the most intriguing natural products.[1] Many are of special interest because of their biological[2] and specifically antitumor[3] activity, and the majority possess structures which pose daunting challenges to the synthetic organic chemist. Eremanotholide A[3a] (**1**) and ciliarin[1e] (**2a**) and its recently isolated congener[1a] **2b** typically exemplify their structural complexity. The origin of their biological activity is still a matter of speculation. This is particularly so in relation to antitumor activity, since most members of the family possess α-methylene lactone and dienone functionalities, each[4] of which could conceivably act as an alkylating agent for terminating DNA synthesis, in the context of Kupchan's hypothesis.[5]



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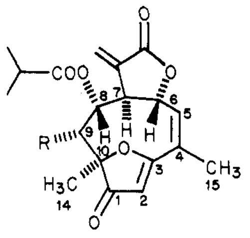

2a, R = H
b, R = OH

In spite of the foregoing there have been very few[6] reported synthetic ventures related to these substances. In order to acquaint ourselves with the idiosyncracies of such complex molecules, we have divided the molecules into upper and lower halves, noting that we thereby separate the two alkylating moieties. In this communication we describe the synthesis of a model of the lower half by a route which gives the material **3** in the chiral form that is congruent with most germacranolides.[7] Interestingly, the procedure can be adapted for preparing the enantiomer of **3** corresponding to the unnatural series.

For our approach the furenone **3** was viewed as a highly modified *C*-glycofuranoside, a class of sugar derivatives that has received much attention recently since they provide ready access to the pharmacologically important *C*-nucleosides.[8] It would obviously be judicious to introduce the angular methyl group at an early stage so as to avoid aromatization of the furan ring.

The model substance **3** is seen to have a two-carbon fragment at each end, one (C_8–C_9) being saturated and the other (C_4–C_{15}) unsaturated. One of these could conceivably be derived from the C_5–C_6 moiety of a hexofuranose, while the other could be elaborated from the anomeric center. For the latter objective 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**4**, diacetone mannose) seemed a logical choice since the anomeric center is not protected.

We therefore had two alternatives for proceeding from **4** to **3** (Scheme I). In pathway a, **4** → **5** → **6** → **3**, the anomeric center of **4** becomes the unsaturated "end" (C_3–C_4–C_{15}) of **3**, while the C_5–C_6 unit of **4** ends up as C_8–C_9 of **3**. In pathway b, **4** → **7** → **3**, the C_{10}–C_9–C_8 moiety of **3** is elaborated from the anomeric center of **4**, while the unsaturated "end" is derived from C_5–C_6. In either pathway, the addition of the two-carbon unit at the anomeric center could be carried out by means of tandem Wittig and Michael reactions developed by Moffatt and co-workers.[9] Actually these investigators had examined only aldoses, e.g., **4**, and an attractive feature is that the C_3 epimers of **5** produced could both be utilized since H-3 of **6** would be lost in going to **3**. These considerations would seem to recommend pathway a, but a further requirement would be the attachment of a methyl group at C_{10} of **5**. Although this has in fact been done by us in another study,[10] the difficulties encountered caused us to explore pathway b as shown in Scheme II.

Diacetone mannose **4** was oxidized with Collins reagent to the known[11] lactone **8** which upon treatment with methyllithium gave the β-D-ketose **9** as the exclusive product.[12,13] Attempts to react **9** with methyl (triphenyl-

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