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STEREOSELECTIVITY IN THE REDUCTIVE CLEAVAGE OF VINYLCYCLOPROPANE

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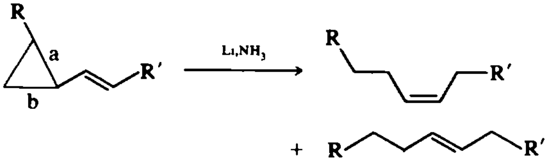
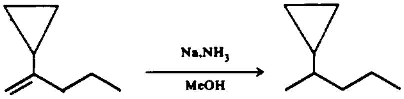
Abstract—Treatment of vinylcyclopropane (**6**) with lithium in liquid ammonia at 0° or 25° slowly effects reductive cleavage to afford a mixture of *cis*-2-pentene (**7**), *trans*-2-pentene (**8**), and 1-pentene (**9**). The major product is **7** and the ratio **7**:**8** is greater at 0° (4·5) than at 25° (3·2). Control experiments have established that the products are stable in lithium amide-liquid ammonia at 25°. In contrast, product ratios for cleavage of **6** with sodium in liquid ammonia at 0° or 25° are somewhat variable due to equilibration under the reaction conditions, and **8** is the major product at longer reaction times at 25°. It is suggested that the predominant *cis*-stereoselectivity is greatest in solvent-separated ion pair transition states.

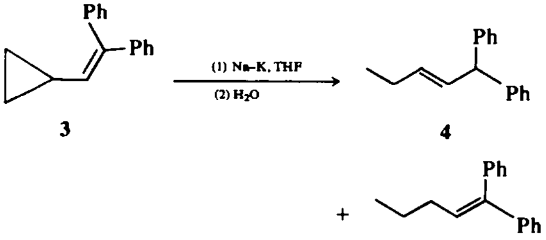
The problem of regioselectivity (the ratio of bond *a* opening to bond *b* opening) in the reductive cleavage of cyclopropyl rings conjugated with adjacent π systems has received a considerable amount of attention recently.[1,2] In contrast, the problem of *stereoselectivity* (the ratio of *cis* products to *trans* products[3] or the stereochemistry of protonation at the cleaved bond[2f]) is less well understood. Most reductive cleavages have been reported for systems in which double bond stereoselectivity is not possible. However, this problem was specifically considered in a recent study of the reductive opening of cyclopropyl ketones.[3] Our interest was focused on the comparison of the reactivity of these ketones with that of a closely related hydrocarbon, vinylcylopropane.



There are only a few examples of reductive cleavages of vinylcyclopropane derivatives in the literature. Orchin and coworkers reported that 2-cyclopropyl-1-pentene (**1**) was recovered unchanged on treatment with sodium in liquid ammonia at *ca* −33° for 4 h and that only 2-cyclopropylpentane (**2**) was obtained upon addition of methanol to the above reaction mixture.[4] Examples of successful reductive cleavages of vinylcyclopropane derivatives include the opening of spiro[2,4]hepta-4,6-dienes,[5] bullvalene,[6] and isobullvalene,[2a] but in each case the stereochemistry of the product is predetermined by the presence of a second carbocyclic ring. The single example of a cleavage in which the double bond is not incorporated into a ring is the opening of 1,1-diphenyl-2-cyclopropylethylene (**3**) with Na–K alloy in THF at room temperature to afford, upon quenching, a 3:2 mixture of *trans*-1,1-diphenyl-2-pentene (**4**) and 1,1-diphenyl-1-pentene (**5**).[7] However, it is not clear whether **4** is a product of thermodynamic or kinetic control.



1 **2**



3 **4** **5**

In the present paper we report the successful reductive opening of the parent compound, vinylcyclopropane (**6**), and present evidence for both kinetic and thermodynamic control of the stereochemistry of the product mixtures. We also consider the various factors which might be responsible for kinetic control of stereochemistry in the opening of **6**.

RESULTS

Treatment of vinylcyclopropane (**6**) with a 3·5-fold excess of sodium in liquid ammonia at *ca* −33° for 5 h gave less than 10% cleavage products. This is in accord with the experience of Orchin *et al* with **1**.[4] However, extensive cleavage of **6** occurs with Li or Na in liquid ammonia at 0° or 25° for periods of 1–9 h to afford **7**–**9** (Table 1).

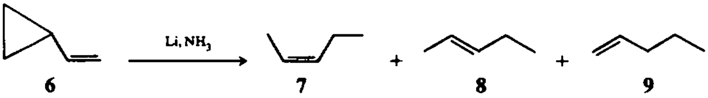


Table 1. Relative yields for the reductive cleavage of vinylcyclopropane (**6**) with lithium or sodium in liquid ammonia

Metal	Temp	Time	Relative Yield (%)[a,b] 7	8	9	Recovered **6** (%)
Li	0°	5 h	80	17	3	55
Li	0°	9 h	79	18	2	10
Li	25°	2 h	75	21	3	45
Li	25°	5 h	73	23	4	5
Na	0°	5 h	72	24	4	75
Na	0°	7 h	77	19	3	55
Na	25°	1 h	66	29	5	70
Na	25°	2 h	72	25	3	50
Na	25°	8 h	35	61	3	1

[a] Estimated to be better than ±2%.

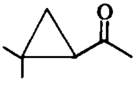
[b] In some runs a small (<1%) pentane peak was detected. This could arise by reduction of 1-pentene.

Control experiments have established that the material balance is >94% and that the products (**7**–**9**) are stable in lithium amide–liquid ammonia at 25°. In contrast, treatment of a 3 : 1 mixture of **7** and **8** with sodium amide in liquid ammonia at 25° effected at least partial equilibration of the pentenes, and a pentene mixture obtained in potassium amide–liquid ammonia (22% **7**, 76% **8**, and 1·4% **9**) is undoubtedly very close to the equilibrium ratio under these conditions.[8,9] These results and the poor reproducibility of the relative yields with sodium indicate that the latter cleavages are not governed as strictly by kinetic control as are the lithium cleavages.

DISCUSSION

It is of interest to compare the above results with those of Dauben and Wolf who determined, by trapping of the initially formed enolate ions, that cyclopropyl methyl ketone (**10**) is cleaved by Li in liquid ammonia at *ca* −33° largely *via* a cisoid conformation to afford *trans*-enol acetate **11** (82%) in preference to *cis*-enol acetate **12** (18%).[3]

Since it has been determined that the *cisoid* : *transoid* (or near-transoid) ratio in **10** is 80 : 20 ± 15% by electron diffraction[10] and 70 : 30 by NMR spectroscopy,[11] it was concluded that the cleavage ratios suggest little conformational change between the ground and transition states. Similar results were obtained for ketones **13** and **14**.[3] These workers made the reasonable suggestion that the parallel between ground state conformations and transition state populations may be due to a rapid electron-reductive process which allows little conformational change on going from the ground state to the transition state.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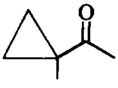
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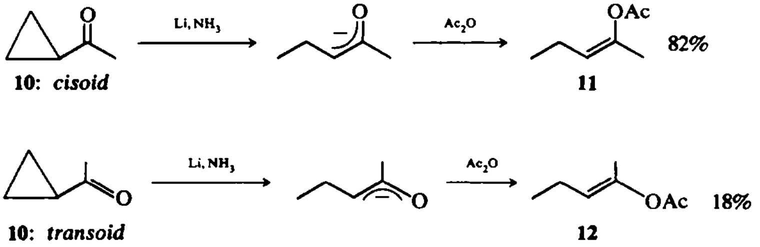
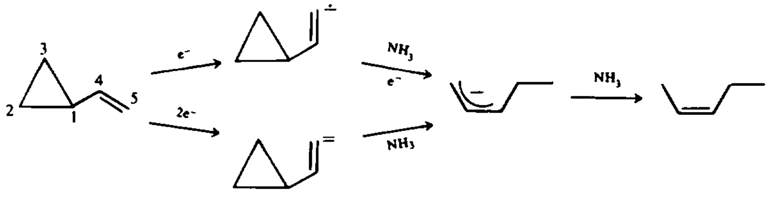
The *overall* reaction of **6** involves the addition of two electrons and two protons concomitant with cleavage of the cyclopropane ring. The actual opening could occur either at the radical anion or at the dianion stage (Scheme I), but this point is probably not critical to the present discussion since both electrons would be added to the same orbital. Nevertheless, we favor the former because the electrostatic repulsion appears to be excessive in the latter.

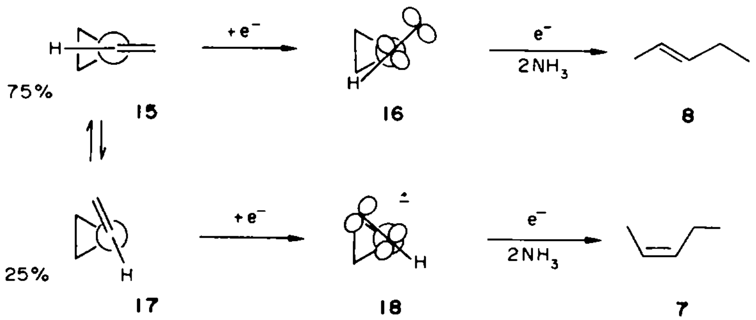
Since the transient allylic anion products are probably configurationally stable under the reac-



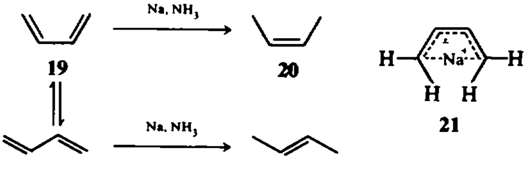


SCHEME I

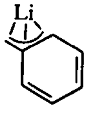
tion conditions,[12] the overall stereochemistry will be determined by the stereochemistry of the cleavage step. Conformations **15** and **17** would lead, by least motion considerations, to pentenes **8** and **7** *via* transition states **16** and **18**, respectively. However, despite the facts that (a) the s-*trans* conformation (**15**) has been found to predominate over the gauche conformation by a factor of about 3 : 1[13,14] and (b) formation of transition state **16** from **15** is favored over formation of **18** from **17** by a statistical factor of 2, *cis*-2-pentene (**7**) is formed about 4 times faster than its *trans* isomer (**8**). Thus, in contrast to the methyl cyclopropyl ketones,[3] it is clear that there is little relationship between preferred ground state and transition state conformations in the case of vinylcylopropane.



In considering reasons for this behavior, it is important to note that these results parallel those of Bauld, who found that reduction of 1,3-butadiene (**19**) by Na in ammonia afforded substantial quantities of *cis*-2-butene (**20**) (13% at −33° and 50% at −78°)[12] even though >98% of **19** exists in the s-*trans* conformation.[15] Bauld suggested that this selectivity arises from cation chelation, as in **21**.



Interestingly, recent x-ray crystallographic structure determinations of disolvated Li salts of delocalized carbanions (benzyl, triphenylmethyl, fluorenyl, and the dianion of naphthalene) have shown that Li prefers to form 3-center bonds with an allylic fragment, as in **22** or **23**.[16] The molecular orbitals of transition state **18** are also compatible with 3-center bonding of disolvated lithium (with C_1, C_4, and C_5). If this model adequately represents the structure of **18** it would not explain the observed stereoselectivity since three-center bonding of lithium can occur in either the s-*cis* (**18**) or the s-*trans* (**16**) transition state with more or less equal facility. In fact, the latter might actually be favored on steric grounds. Thus cation chelation probably does not provide an adequate explanation if the lithium cation is disolvated.



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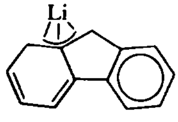

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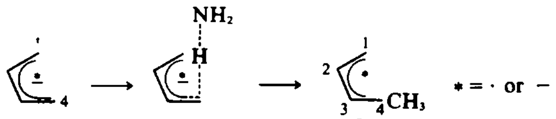
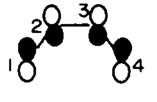
Three-center bonding of the π system with the cation is not expected if the latter is a trisolvated lithium atom. In this case the bonding site will probably be determined by σ bonding of a lithium sp^3 orbital to the atom of highest electron density in the transition state (probably C_5), in which case there would be no obvious preference for **16** or **18**, or by the minimum in the electrostatic potential in the carbanionic transition state.[16] The latter position is also expected for other alkali metals, such as sodium, and might conceivably explain a preference for **21** relative to the corresponding s-*trans* transition state.[12] Unfortunately, there is no conformational assignment available for the radical anion of butadiene[17] so this point cannot be confirmed or rejected at the present time.

An alternate explanation for the stereoselectivity in butadiene and vinylcyclopropane focuses on nonbonded π-type overlap in the product-determining transition state. The exact transition state for the reduction of butadiene is unknown, but it obviously lies somewhere on the energy surface between the radical anion or dianion of butadiene (**24**) and the *cis*-methylallyl radical or anion (**26**). π-Overlap between C_1 and C_4 in ψ_3 of **24** (the orbital which the extra electron occupies; see **27**) is bonding; therefore the s-*cis* conformation of butadiene is stabilized relative to the s-*trans* conformation on going from the neutral molecule to the radical anion.[18] In addition, *cis*-alkyl-substituted carbanions such as **26** are known to be more stable than their *trans*-alkyl isomers,[19] possibly because of stabilization due to π overlap between C_1 and the group orbital of π symmetry on the Me group.[18] A combination of these interactions operating in transition state **25** may contribute significantly to the observed stereoselectivity. Furthermore, these considerations can readily be extended to **6** since the C_2-C_5 π interaction in the highest occupied MO of the radical anion of **6** (see **28**) is also bonding.


24 **25** **26**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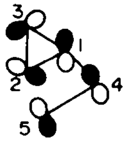
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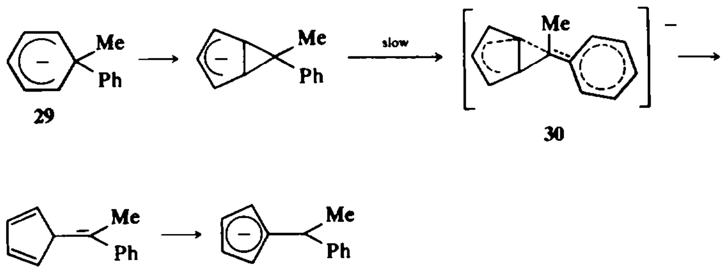
The temperature dependence of the product ratios may provide a clue as to the controlling factor in determining the stereoselectivity. The proportion of cis product increases on decreasing the temperature in both the reductive cleavage of vinylcyclopropane with Li in liquid ammonia and the reduction of butadiene with Na in liquid ammonia.[12] The former has been shown to occur with kinetic control and the latter (at −33° and below) probably does also. How can this temperature dependence be explained?

In ionic reactions such as these, the role of ion pairing must receive serious consideration. In previous work we were able to show that the slow step in the isomerization of **29** to **31** in liquid ammonia at 25° probably involves predominantly solvent-separated ion pairs in the lithium salt and contact ion pairs in the potassium and cesium salts.[20] Transition state **30** is a good model for transition state **18** (or **16**) except that the negative charge in the latter is more concentrated. It is therefore not unreasonable to expect a greater proportion of contact ion pairs with **18** than with **30** for the Li salts at 25°.[21] The proportion of solvent-separated ion pairs is known to increase as the temperature is decreased since the unfavorable entropy due to solvation of the counterion makes a smaller contribution to the free energy at lower temperatures.[21,22] Thus one possible explanation for the stereoselectivity in **6** is that the proportion of *cis* product (**7**) increases at 0° (relative to 25°) due to an increase in the proportion of solvent-separated ion pair transition states. If this were the case then one would have to conclude that there are factors other than direct counterion chelation which determine the stereochemistry of transition state **18**.

We have already noted that the predominant *cis*-stereoselectivity in the reductive cleavage of **6** may be related to the greater stability of *cis*-substituted allylic anions and related kinetic phenomena. These effects have been attributed to a variety of factors, including cation chelation,[12,23] dipole–dipole interactions,[19b,24] nonbonded π interactions,[18] ground state conformational preferences,[3,23e] and various other factors.[19c,25] While we cannot precisely define the predominant factors which determine the stereoselectivity in the case of **6**, we can firmly exclude ground state conformational preferences and express doubts about cation chelation. In our view, nonbonded π interactions provide an attractive but unproven explanation.

EXPERIMENTAL

General. IR spectra were recorded on a Perkin–Elmer model 337 grating spectrometer. Gas chromatographic analyses were performed on a Varian-Aerograph model 1200 flame ionization instrument equipped with 0·31 cm (0·125 in) columns, and connected with a Hewlett-


29 **30** **31**

Packard model 3370A integrator. Preparative separations were obtained on a Varian-Aerograph model A90-P3 instrument equipped with 0·63 cm (0·25 in) columns. Corrections were not made for response factors. The following columns (all of which were packed with acid-washed and silanized Chromosorb P) were employed: CW20M-1, 15% Carbowax 20M on 80–100 mesh Chromosorb P in 0·31 cm × 5m Cu tubing; CW20M-2, 15% Carbowax 20M on 80–100 mesh Chromosorb P in 0·63 cm × 3m Cu-tubing; DMS-1, 15% dimethylsulfolane on 80–100 mesh Chromosorb P in 0·31 cm × 3·1 m Cu-tubing; DMS-2, 25% dimethylsulfolane on 100–120 mesh Chromosorb P in 0·31 cm × 4·0 m Cu-tubing; DMS-3, 25% dimethylsulfolane on 100–120 mesh Chromosorb P in 0·63 cm × 3·1 m Cu-tubing.

Reductive cleavage of vinylcyclopropane. GLPC analysis (columns CW20M-1 and DMS-2 at 25°) of commercial vinylcyclopropane (Chemical Samples Co.) showed the major peak to constitute >98% of the total chromatogram peak area. Further purification was accomplished on passes through two columns, CW20M-2 and DMS-3 at 25°, prior to use. Since vinylcyclopropane suffered <10% reduction on treatment with a 3·5-fold excess of Na in liquid ammonia at *ca* −33° for 5 h, reduction was effected at higher temps. A heavy-walled Pyrex tube (1·3 × 18 cm) which narrowed to 0·6 × 5 cm at one end and could be sealed by a Teflon septum-type Swagelok fitting, was dried, immersed in a dry ice-acetone bath and charged with 4 ml of anhyd ammonia and 38·5 mg (5·6 mg at) of Li. The tube was then sealed and allowed to warm to room temp. The resulting blue soln was cooled to *ca* −78° and 70 μl (*ca* 0·7 mmol) of vinylcyclopropane was added. The tube was then warmed to room temp for 4 h, cooled again to *ca* −78°, and quenched with 50 μl of acetone followed by sat aq NH_4Cl. The mixture was then extracted with 0·5 ml heptane and analyzed by GLPC on column DMS-1 at 0°. The retention times of **7**, **8**, and **9** (relative values of 1·4 : 1·3 : 1) were identical to those of authentic samples. An IR spectrum of the major products (a 3 : 1 mixture of **7** and **8**), collected by GLPC on column CW20M-2 at 25°, was identical to that of an authentic mixture of the same composition. A small peak with the retention time of pentane (0·7) was also sometimes present.

A number of small-scale cleavages were effected in the same apparatus by syringing 8 μl (0·08 mmol) of vinylcyclopropane into a solution of 1·4 mg at of Li or Na in ammonia at 0° or 25° for various periods of time. Workup and GLPC analytical conditions were the same as above; the times, temp and product ratios are given in Table 1.

Control experiments. These reactions were performed with the same equipment described above for the analytical scale reductions.

(a) *Material balance.* Treatment of a 10 μl sample of a 43 : 57 mixture of cyclohexane and vinylcyclopropane with 19·3 mg (2·8 mg at) of Li in 3 ml of liquid ammonia at 25° for 6 h afforded (column DMS-1 at 0°) a mixture of 47% cyclohexane and 53% pentene isomers (**7**–**9**).

(b) *Base-promoted isomerization of pentenes.* Treatment of a 50 μl sample of a 78·5 : 21·5 mixture of *cis*- and *trans*-2-pentene with 128 mg (5·6 mg at) of lithium amide in 4 ml of liquid ammonia at 25° for 9 h afforded (column DMS-2 at 25°) a mixture of 78% **7**, 21% **8**, and 1·2% **9**. Reaction of a 25 μl sample of a 76·4 : 23·6 mixture of *cis*- and *trans*-2-pentene with 78 mg (2·0 mg at) of sodium amide in 4 ml of liquid ammonia at 25° for 1 h afforded (column DMS-2 at 25°) a mixture of 62% **7**, 33% **8**, and 5% **9**. Treatment of a 50 μl sample of a 96·1 : 3·9 mixture of *cis*- and *trans*-2-pentene with 78 mg (2·0 mg at) of sodium amide in 4 ml of liquid ammonia at 25° for 4 h afforded (column DMS-1 at 0°) a mixture of 48% **7**, 48% **8**, and 4% **9**. Treatment of a 50 μl sample of a 29·8 : 70·2 mixture of *cis*- and *trans*-2-pentene with 99 mg (1·8 mg at) of potassium amide in 4 ml of liquid ammonia at 25° for 6 h afforded (column DMS-1 at 0°) a mixture of 22% **7**, 76% **8**, and 1·4% **9**.

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