Long-Range Heteroatom Effects. Remote Oxygen

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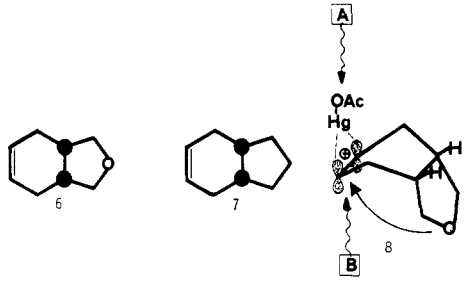
The ability of an oxygen atom, remote from the site of reaction, to influence the reactivity and stereochemistry of chemistry at the reaction site is reexamined by epoxidation and methoxymercuration studies on propellanes. Results from these studies, which compare a carbocyclic ring to a heterocyclic ring of nearly the same steric requirement, are compared to other models for which heteroatom effects have been suggested.

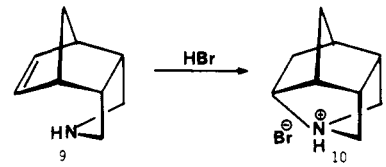
Participation by an oxygen atom to a reaction site remote from the heteroatom has been suggested by several groups.[1] Examples of the reactions studied and the general trends observed are summarized in Figure 1. We have maintained an interest in the question of how a heteroatom expressed its unique "heteroatom effects" in the structure and reactivity of nonaromatic heterocyclic molecules[2] and in this study question the importance of long-range electronic participation by oxygen. In one of our early studies we had noted that the competitive rate for oxymercuration of 6 was about 10 times faster than that for 7.[3] This



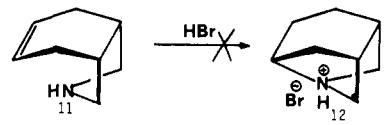
observation, although not expressing a dramatic rate increase,[4] when coupled with the observed stereochemistry of the major alcohol from the reaction, prompted us to suggest a remote oxygen participation as represented by 8 (see 3 for precedence).[1c]

An immediate problem surfaced in our attempt to ascribe the same kind of participation suggested for 3 to 8. Whereas reaction of 9 with HBr afforded the quaternary salt 10,[5] our similar treatment of 11 gave no internal quaternization.

Inspection of models suggested that the norbornyl system in 9 was considerably more "folded" than the similar general conformation of 11. Thus, it was possible, and certainly not without precedence, that attempts to model



(1)



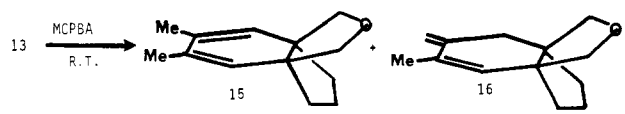
(2)

our interpretations on the norbornyl-type system were doomed to failure. It was necessary to seek another basis for examining whether the interactions proposed by 8 were reasonable.

Recognizing that the relative reactivities were not too different, we were concerned with the possibility that some of the rate data might be rationalized by a transmitted ring deformation resulting from C–O–C bond angles and bond lengths being different from the all-carbon analogue. Similarly, observed stereoselectivity might simply reflect lesser steric hinderance for attack via A (see 8) rather than B (hydrogen vs. methylene). The logical molecules to use as substrates to test this question appeared to be 13 and 14. *Both faces of the cyclohexene π system experience*

a five-membered ring; however, one also contains a heteroatom. Thus, these systems seemed to be unique models for separating steric from electronic effects. This manuscript reports the results of this study.

Epoxidation studies have been used to examine electronic and steric effects,[7] and with 13 the added methyl makers were viewed as very useful for examining the stereochemistry of the products. Epoxidation of 13 using MCPBA proved to be very sluggish; after 1 h at 20 °C, GLC analysis (13% DEGS, 10 ft, $^1/_4$ in., 150 °C) showed only unreacted 13. At elevated temperature ($CHCl_3$ reflux, 90 min) two new products were obtained and all of 13 had been consumed. A combination of MS and NMR studies showed these products to be isomeric dienes, 15 and 16 (eq 3). Drieding models revealed the six-membered ring to



(3)

be far less rigid as the diene than as either the starting alkenes or the epoxide. Thus, the driving force for diene formation appears to rest in a relief of ring strain. The

(1) (a) Tarbell, D. S.; Hazen, J. R. *J. Am. Chem. Soc.* **1969**, *91*, 7657. Similar heteroatom effects have been observed in the sulfur series.[1e] Interestingly, the nitrogen series shows tremendous rate acceleration;[1f] however, ring fragmentation also occurs, suggesting a different mechanistic rationalization. (b) Paquette, L. A.; Begland, R. W.; Storm, I. C. *J. Am. Chem. Soc.* **1979**, *92*, 1971. (c) Wilder, P., Jr.; Drinnan, C. V. A. *J. Org. Chem.* **1964**, *39*, 414. The reactivity of 3 is only 2.5 times greate than the carbocyclic analogues. Comparing this reaction with the sulfur derivative[1g] (R. R. to carbon analogue = 752) the authors suggested, "Oxygen is less effective than sulfur as a neighboring group owing to its greater inducive rate-retarding effect, lower ability to donate electron pairs, and smaller size that decreases efficient overlap at a remote carbonium ion center". (d) Paquette, L. A.; Burson, R. L. *Tetrahedron* **1978**, *34*, 1307. (e) Ikegami, S.; Asai, T.; Tsuneoka, K.; Matsumura, S.; Akaboshi, S. *Ibid.* **1974**, *30*, 2087. (f) Ikegami, S.; Voji, K.; Akaboshi, S. *Ibid.* **1974**, *30*, 2077. (g) Wilder, P., Jr.; Gratz, R. F. *J. Org. Chem.* **1970**, *35*, 3295.

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(7) Rickborn, B.; Lwo, S. Y. *J. Org. Chem.* **1965**, *30*, 2212.

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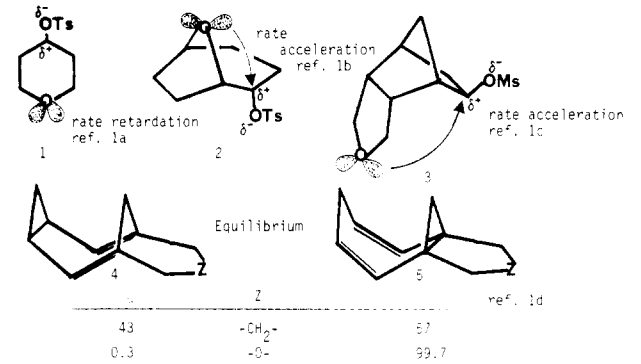
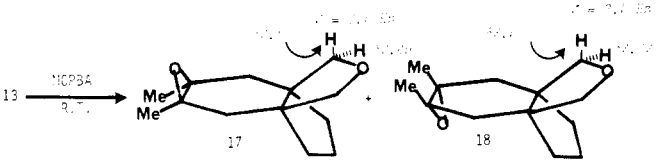


Figure 1. Representative examples of remote oxygen effects.

proton NMR assignments for these structures were very readily rationalized, particularly for the symmetrical **15**.

Since **13** is a highly symmetrical molecule, the protons on the tetrahydrofuranyl ring become very useful probes for any structural modifications of the parent structure. For **15**, the symmetry is maintained; however, the chemical shifts are moved slightly upfield. Two doublets are found, centered at 3.79 and 3.53 ppm (J = 10.0 Hz). For **16** the four protons experience different environments, and thus four doublets are seen for the THF protons: 3.77, 3.70 (J = 7.5 Hz) and 3.61, 3.58 (J = 2.5 Hz) ppm.

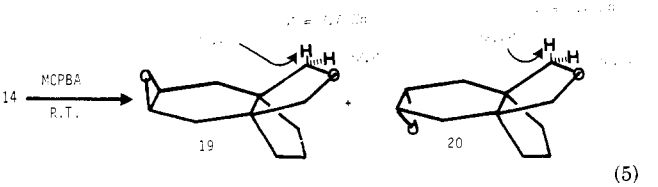
At 0 °C (for three days) the reaction with MCPBA produced the expected epoxides, **17** and **18**, in a ratio of 1:1 (eq 4). Here the highly symmetrical molecular



(4)

structure is maintained and is reflected in a simplified proton NMR spectrum for each product. Surprisingly, the methyl groups that we had designed into the molecules to help us in the structural assignments proved to be not too useful for this purpose. Again, however, the THF protons readily distinguished the two structures. Of particular interest is the sheilding of one of the THF protons by the *syn*-epoxide (see the Experimental Section for details).

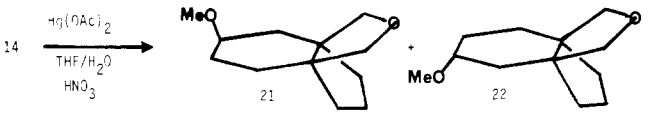
Epoxidation of **14**[6] gave essentially the same result; two epoxides (**19** and **20**) were obtained in the ratio of 53.1:46.9 (+/− 1.5), respectively (eq 5). Again, high-resolution proton NMR data readily distinguished the two symmetrical isomers.



(5)

These combined data suggest that compared to **6** very little selectivity is found in the epoxidation of **13** and **14** and speak very strongly against the earlier interpretation of stereoselectivity resulting from through space heteroatom interactions. It is more likely that the results were of steric origin, since with **6** the steric effects around the faces *are not equivalent*.

Recognizing that the nonionic nature of the epoxidation reaction might no allow for substantial heteroatom participation, we next examined the oxymercuration reaction. To our surprise, **14** proved to be resistant to oxymercuration under the same conditions that **6** reacted almost instantaneously. This suggested a strong steric retardation for this system. The influences of remote steric effects on the oxymercuration reaction have been well documented.[8] Under nitric acid catalysis,[9] we were able to successfully carry out the methoxymercuration of **14** in about 90% yield. After demercuration, GLC analysis demonstrated the existence of two products in essentially equal amounts, assigned structures **21** and **22** (eq 6). Structure determination was readily accomplished by proton NMR spectroscopy.



(6)

The structure assignments appeared, a priori, to be a major problem in these examples since the symmetry was lost. However, even for these examples, the THF protons held the key to identification. In he two isomeric methoxylated products, proton chemical shift differences are readily observed that help to determine the identity of the two products.

These data, in concert with those from the epoxidation studies, clearly establish the supremacy of simple steric effects in controlling the chemistry of reaction at the π bond for the propellanes used in this study. Furthermore, when comparing the results from these studies to those derived from **6**, one is led to the conclusion that the steric effects of the THF and the cyclopentane systems must be very similar. If this is true, we must still account for the greater reactivity of **6** compared to **7**. We suggest this to result from small skeletal deformations due to the differences in bond lengths and angles between the carbon and the oxygenated analogues. These deformations are transmitted through the skeleton and are thus responsible for the chemistry observed. This interpretation is consistent with our previous observations that **23** was about

four times more reactive than **24**, *even when it was structurally impossible for direct heteroatom participation*. Also, the results of Paquette,[1d] as shown in Figure 1, demonstrate how these deformations can be transmitted through a system and, when combined with our work, suggest that for oxygen having no direct participation the ideas of molecular distortion affecting both structure and reactivity must be given serious consideration.

In conclusion, the data from our study suggest that caution must be used when attributing small rate enhancements to through space oxygen participation, unless there are other data supporting the concept of participation. As we continue our search for the origins of heteroatom effects we shall examine other heteroatoms in the propellane skeleton.

Experimental Section

Epoxidation of 13 at Elevated Temperature. To 100 mg (0.52 mmol) of **13** in ca 15 mL of $CHCl_3$ was added 100 mg of *m*-chloroperoxybenzoic acid dissolved in 5 mL of $CHCl_3$. The reaction was stirred at 20 °C for 1 h, after which time GLC analysis (10% DEGS on Chromsorb W-AW; 10 ft × $^1/_4$ in., 170 °C) showed only unreacted **13**. After the solution was heated to reflux for

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(9) Brown, W. H.; Wright, G. F. *J. Am. Chem.* **1940**, *62*, 1991.

1.5 h, the reaction was cooled to room temperature and allowed to stand overnight. The reaction mixture was worked up by rinsing the $CHCl_3$ solution with saturated $NaHCO_3$, followed by saturated brine. The $CHCl_3$ solution was then dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed by rotary evaporation to give 90 mg of a clear oil. GLC analysis showed that no starting material remained, and two new products in the approximate ratio of 1:1 were present. Samples of each were collected by GLC, and submitted to NMR analysis.

15: ^1H NMR (ppm from Me_4Si) 5.39 (s, 2 H), 3.79 (d, 2 H), 3.53 (d, 2 H), 1.83 (m, 2 H), 1.79 (s, 6 H), 1.65–1.32 (m, 4 H); MS, M^+ 190, 175, 145 (base), 131, 115, 105, 91.

17: ^1H NMR 5.45 (s, 1 H), 4.98 (br s, 1 H), 4.85 (d, 1 H), 3.77 (d, J = 7.5 Hz, 1 H), 3.70 (d, J = 7.5 Hz, 1 H), 3.61 (d, J = 2.5 Hz, 1 H), 3.58 (d, J = 2.5 Hz, 1 H), 2.39 (d, 1 H), 2.26 (d, 1 H), 1.87 (allylic doublet, 3 H), 1.80–1.55 (m, 6 H); MS, M^+ 190, 175, 158, 145 (base), 131, 117, 105, 91.

Epoxidation of 13 at 0 °C. To 20 mg of **13** in 15 mL of CH_2Cl_2 at 0 °C under N_2 was added 20 mg of MCPBA in 5 mL of the same solvent. The reaction mixture was stirred at 0 °C for about 72 h, after which time it was worked up as described above. GLC analysis demonstrated that all of the **13** had been consumed, and that only a trace of the dienes (**15** and **16**) were present. The major products (1:1) were collected by GLC and identified as the epoxides **18** and **19**.

17: ^1H NMR 3.69 (d, 2 H)8 3.27 (d, 2 H), 2.01 (d, 2 H), 1.88 (d, 2 H), 1.85 (m, 2 H), 1.55–1.30 (m, 4 H), 1.27 (s, 6 H); MS, M^+ 208, 193, 177, 163, 151, 145 (base), 135, 121, 109; HRMS calcd for $C_{13}H_{20}O_2$ 208.1463, found 208.1476.

18: ^1H NMR 3.73 (d, 2 H), 3.57 (d, 2 H), 1.96 (d, 2 H), 1.67 (d, 2 H), 1.70–1.40 (m, 6 H), 1.29 (s, 6 H); HRMS calcd for $C_{13}H_{20}O_2$ 208.1463, found 208.1443.

Epoxidation of 14. Treatment of 60 mg of **14** with 65 mg of MCPBA for 24 h at 20 °C in 20 mL of chloroform gave 66 mg (100%) of a clear liquid that was analyzed by GLC (10% DEGS, 10 ft × $^1/_8$ in., 180 °C), demonstrating the presence of two products (**19** and **20**) in the ratio of 53.1:46.9, respectively.

19: ^1H NMR 3.66 (d, 2 H), 3.37 (d, 2 H), 3.14 (dd, 2 H), 2.10 (ddd, 2 H), 1.93 (dd, 2 H), 1.82 (m, 2 H), 1.65–1.45 (m, 4 H); MS, 180, 162, 149, 132, 117, 91, 79 (base); HRMS calcd for $C_{11}H_{16}O_2$ 180.1150, found 180.1163.

20: ^1H NMR 3.73 (d, 2 H), 3.57 (d, 2 H), 3.13 (dd, 2 H), 2.19 (ddd, 2 H), 1.77 (dd, 2 H), 1.70–1.40 (m, 6 H); MS, 180, 162, 149, 132, 117, 91, 79 (base); HRMS calcd for $C_{11}H_{16}O_2$ 180.1150, found 180.1155.

Oxymercuration of 14. To a magnetically stirred solution of 1 equiv (0.29 g) of $Hg(OAc)_2$ in 10 mL of MeOH was added 0.15 of **15**, followed by *one drop* of concentrated HNO_3. After stirring for 18 h, 1 equiv (48.6 mg) of NaOMe was added and the solution was stirred an additional hour. Then 0.5 M NaOH (5 mL) was added, followed by excess $NaBH_4$. The reaction was stirred briefly and then allowed to settle before being filtered through Celite. Removal of solvent afforded 0.17 g (95%) of a yellow liquid that by GLC (10 ft × $^1/_8$ in., 10% DEGS, 150 °C, 40 psi He) showed only two peaks in a 1:1 ratio.

21: ^1H NMR 3.75 (dd, 2 H), 3.68 (dd, 2 H), 3.32 (d, 3 H), 2.00–1.20 (m, 10 H); MS 196, 168, 166, 149, 137 (base); 119, 93, 91, 79; HRMS calcd for $C_{12}H_{20}O_2$ 196.1463, found 196,1456.

22: ^1H NMR 3.68 (dd, 2 H), 3.61 (dd, 2 H), 3.31 (s, 3 H), 2.00–1.10 (m, 10 H); MS, 196, 168, 166, 149, 119, 93, 91, 79; HRMS calcd for $C_{12}H_{20}O_2$ 196.1463, found 196.1466.

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Registry No. **13**, 88316-98-7; **14**, 15405-07-9; **15**, 91631-44-6; **16**, 91631-45-7; **17**, 91631-46-8; **18**, 91738-60-2; **19**, 91631-47-9; **20**, 91738-61-3; **21**, 91631-48-0; **22**, 91738-62-4.

^{15}N and ^{13}C NMR Study of *N*-Methyl-*N*-nitrosoaniline and Its Ring-Substituted Derivatives

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^{15}N and ^{13}C NMR spectra of *N*-nitroso-*N*-methylaniline and 15 meta and para ring-substituted derivatives have been measured. Complete assignments of all the atoms have been made. Correlations of the ring carbon-1, the amino nitrogen, the nitroso nitrogen, and the methyl carbon chemical shifts with substituent constants have been obtained. It is shown that the ring carbon shift is primarily influenced by π electron density at that position. The chemical shifts of the exocyclic atoms are explained in terms of the substituent effects on the resonance structure of the nitrosamino moiety. It is shown that the amino nitrogen is relatively invariant with substitution because its net hybridization (percent s character) remains relatively constant. The nitroso nitrogen shift correlates with Hammett σ constants with a positive slope, while the methyl carbon exhibits a small but negative correlation. This is explained in terms of increasing double bond character of the N–N bond as the substituents become more electron donating.

Introduction

NMR spectroscopy of heteroatoms has become a very important adjunct to more conventional proton and ^{13}C spectroscopy. The reason for this outburst of activity has been the development of pulsed high field multinuclear spectrometers which allow the observation of low sensitivity nuclei in natural abundance. The development of ^{15}N NMR spectroscopy as a widely used tool was pioneered by Roberts and his co-workers.[1] Most classes of nitrogen compounds have been examined during the past decade,

† LBI-Basic Research Program.
‡ PRI, Inc.

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