



Heterocyclic chemistry : unique role of heteroatoms in structure and reactivity  
by Changjoo Lee

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry

Montana State University

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Abstract:

To examine the influences of heteroatom and ring size of structures and reactivity in propellane series, propellanes are prepared using dianion ring annulation and Diels-Alder reaction.

A formal synthesis of maleimycin, an antibiotic natural product, was completed using, dianion chemistry and flash vacuum thermolysis (F.V.T.) conditions.

Under F.V.T. condition, 1,2-dicarbomethoxycyclopentene was prepared in nearly 100% yield. This is the key intermediate of cyclopentanoids such as antibiotic sarkomycin.

In a hydroboration study, the reactivities of propellanes are shown to depend on the HOMO energy and the atomic coefficient of olefin. Also, we see an interesting correlation between the reactivity and interatomic distance of heteroatom and the olefinic carbon atom, which is the steric control. And the stereoisomer ratio of electrophilic additions to olefins depend on the steric hinderance.

In a solvolysis study, the rate enhancement (1.6 times) was observed for the anti-tosylate of [10] relative to the syn-tosylate. Again, the big rate enhancement (70 times) was observed for the anti-tosylate of [30] relative to the syn-tosylate. This was interpreted to mean that the heteroatom does influence reactivity in these compounds. In examining the solvolysis of the different ring size and dioxo-propellane series, steric and transannular dipole effects were observed.

The major ions in the (EI) mass spectrum of [2] and propellanes have been determined and investigated. Mechanisms, illustrating the oxygen atom's role in the fragmentation process, have been proposed.

Stereospecific hydrogenation was observed in the catalytic hydrogenation of [112] and modest stereoselectivity, was observed in catalytic hydrogenation of [113] and [114].

HETEROCYCLIC CHEMISTRY-  
UNIQUE ROLE OF HETEROATOMS  
IN STRUCTURE AND REACTIVITY

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APPROVAL

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This thesis has been read by each member of the thesis committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

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To

My wife, parents and parents in law.

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## ABSTRACT

To examine the influences of heteroatom and ring size of structures and reactivity in propellane series, propellanes are prepared using dianion ring annulation and Diels-Alder reaction.

A formal synthesis of maleimycin, an antibiotic natural product, was completed using dianion chemistry and flash vacuum thermolysis (F.V.T.) conditions.

Under F.V.T. condition, 1,2-dicarbomethoxycyclopentene was prepared in nearly 100% yield. This is the key intermediate of cyclopentanoids such as antibiotic sarkomycin.

In a hydroboration study, the reactivities of propellanes are shown to depend on the HOMO energy and the atomic coefficient of olefin. Also, we see an interesting correlation between the reactivity and interatomic distance of heteroatom and the olefinic carbon atom, which is the steric control. And the stereoisomer ratio of electrophilic additions to olefins depend on the steric hinderance.

In a solvolysis study, the rate enhancement (1.6 times) was observed for the *anti*-tosylate of [10] relative to the *syn*-tosylate. Again, the big rate enhancement (70 times) was observed for the *anti*-tosylate of [30] relative to the *syn*-tosylate. This was interpreted to mean that the heteroatom does influence reactivity in these compounds. In examining the solvolysis of the different ring size and dioxo-propellane series, steric and transannular dipole effects were observed.

The major ions in the (EI) mass spectrum of [2] and propellanes have been determined and investigated. Mechanisms, illustrating the oxygen atom's role in the fragmentation process, have been proposed.

Stereospecific hydrogenation was observed in the catalytic hydrogenation of [112] and modest stereoselectivity was observed in catalytic hydrogenation of [113] and [114].

## CHAPTER 1

## INTRODUCTION

Neighboring Heteroatom Participation

Our lab has been interested in the unique role of heteroatoms in determining the structure and reactivity of heterocyclic compounds<sup>1,2,3</sup>.

In heteroatom containing molecules, the influence of the heteroatom on reactivity has been related to the degree in which it can stabilize positive charges, as interpreted through solvolysis reactions<sup>4</sup>. In some cases an oxygen atom has been shown to enhance reaction rates; while in other compounds, an oxygen has been shown to retard reactivity. Interpreting oxygen's effect in imparting reactivity on the molecule has been difficult because oxygen does not easily share its lone pair electrons in the stabilization of positive charges, a consequence of its high electronegativity. Yet, oxygen is very effective at stabilizing positive charge on an adjacent bonded carbon atom. As a result of these many differences, the various effects oxygen imparts on structure and reactivity are not completely understood.

Oxygen's influence is generally to be more subtle than that of nitrogen or sulfur, which have lower

electronegativities and more diffuse lone pair orbital. Often this subtle influence is reflected in small rate differences. Schleyer<sup>5</sup> suggests, however, "the detection of any rate enhancement due to anchimeric assistance, no matter how small, is indicative of strong (not weak!) participation by the neighboring group". We, and others, have tried to analyze the participation effects.

Gratz and Wilder<sup>6</sup> have proposed the possibility of an intermediate of the type, [1], to account for the large (750 fold) rate increase of the endo-tricyclic sulfide relative to the carbon analog. This can be compared to the much smaller 2.52 rate increase of endo-tricyclic ether relative to the carbon analog. (Figure 1)

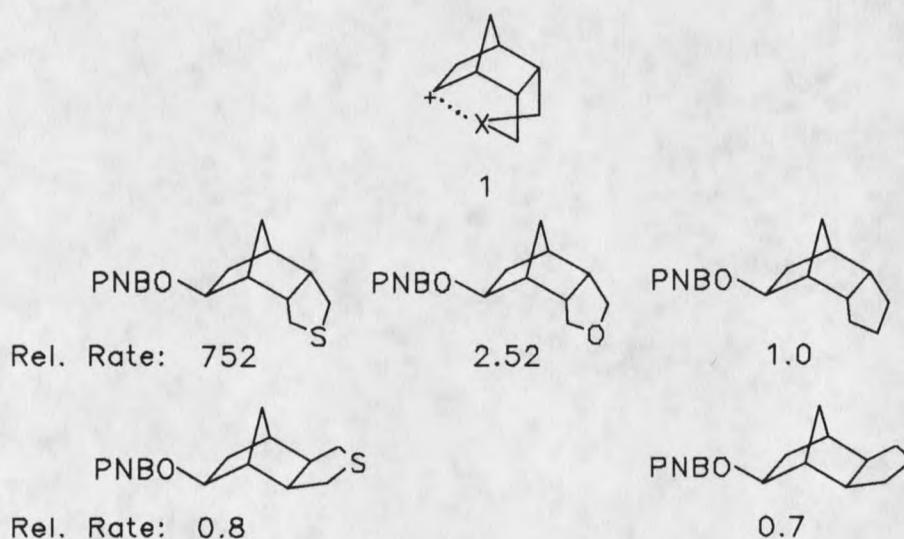
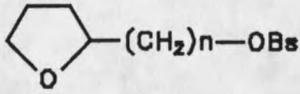


Figure 1. A Remote Heteroatom Participation.

Closson<sup>7</sup> also has found anchimeric assistance by the tetrahydrofuranyl group. This rate enhancement was shown to

be greater than that for the methoxy group, which in turn was far greater than the corresponding straight chain alkane (Table 1).

Table 1. Relative Rates of Solvolysis of p-Bromobenzene-sulfonates in Acetic Acid at 50°C.

<u>Compound</u>	<u>Relative Rate.</u>
	1
	657
	
n=1	13.1
n=2	26.3
n=3	1510
n=4	12400
n=5	1380

These systems are unlike the conformationally rigid norbornyl systems of Wilder, and greater conformational flexibility exists. As a result, oxygen is better able to stabilize positive charge through Neighboring Group Participation (NGP) (Figure 2).

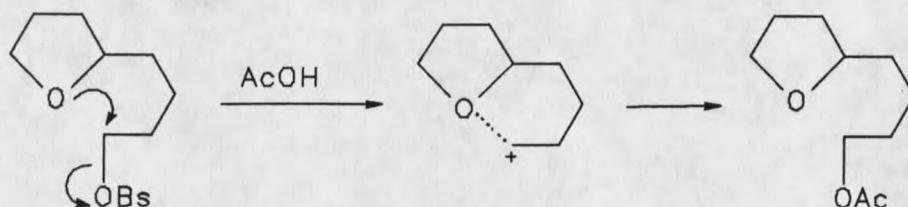


Figure 2. Oxygen Intermediate Stabilization.

Tarbell and Hazen<sup>8</sup> investigated the effects of oxygen on the rates of solvolysis of carbo- and heterocyclic brosylates. They observed the rates of solvolysis to be an order of magnitude slower than would be expected from a simple through-bond dipole effect of the oxygen (Figure 3). This information, coupled with the fact that the corresponding heterocyclic ketones had higher carbonyl stretching frequencies than their carbocyclic counterparts, led Tarbell and Hazen to conclude that they were dealing with a transannular dipole effect as illustrated in Figure 4.

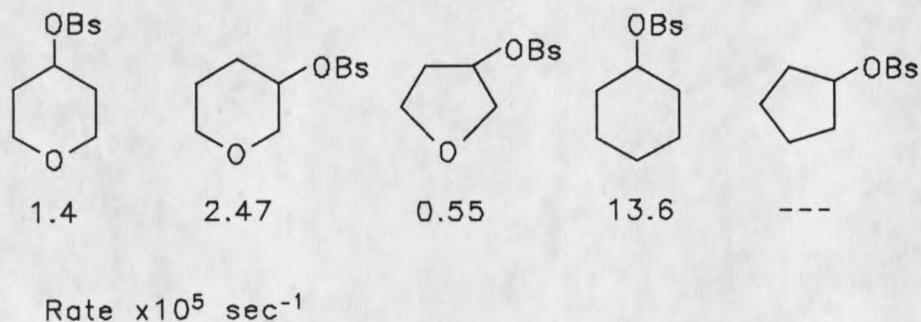


Figure 3. Solvolysis of Oxygen Heterocyclic Compounds.

































































































































































































































































































































































































































































































