

**MECHANISM AND STEREOCHEMICAL IMPLICATIONS
OF THE REACTION OF AN OXAZOLIUM-5-OXIDE WITH
1,2-DICYANOCYCLOBUTENE. AN AM1 STUDY†**

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Abstract - Oxazolium-5-oxide (**1**) cycloadds to 1,2-dicyanocyclobutene (**2**) to give the imino-acid (**3**) and the dihydroazepine (**4**). AM1 molecular orbital calculations were carried out on the reaction in order to rationalize the observed stereochemistry of **3** and to further elucidate the overall reaction mechanism leading to **3** and **4**.

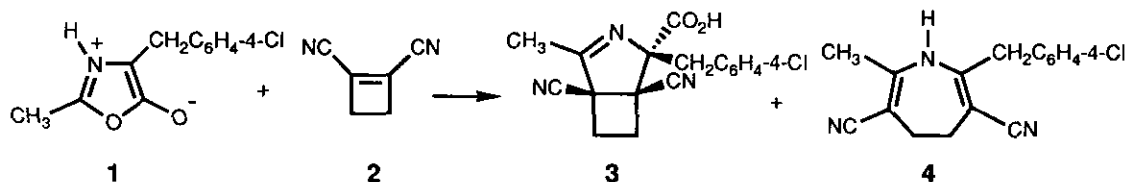
INTRODUCTION

Oxazolium-5-oxides are a class of mesoionic heterocyclic compounds which serve as masked azomethine ylides in 1,3-dipolar cycloaddition reactions.¹ When these species react with olefinic dipolarophiles, the resulting primary cycloadducts readily eliminate carbon dioxide to ultimately afford pyrrolines. Further reactions of the initially formed adduct usually result in the loss of stereochemical information concerning the cycloaddition. Padwa *et al.* isolated and characterized primary cycloadducts from the intramolecular cycloaddition of olefins with oxazolium-5-oxides.² Steric constraints on the transition states (TS) leading to expulsion of carbon dioxide from the cycloadducts are responsible for the stability of these products. The observed *exo* stereochemistry is also sterically imposed. Some intermolecular reactions of mesoionic heterocycles with alkenes have led to stable intermediates with established stereochemistry.³ Of note are the carboxylic acid derivatives isolated by Friedrichsen *et al.* which presumably arise *via* C–O bond cleavage of the primary adducts

†Dedicated to Professor Edward C. Taylor on the occasion of his 70th birthday

obtained from the cycloaddition of oxazolium-5-oxides with cyclohexenediones.⁴ These products exhibit high exo stereoselectivity.

Recently we reported the characterization of the imino-acid (**3**) and the dihydroazepine (**4**) obtained from the reaction of 2-methyl-4-(4-chlorophenyl)oxazolium-5-oxide (**1**, generated *in situ* by the cyclodehydration of 4-chlorophenylalanine with acetic anhydride) and 1,2-dicyanocyclobutene (**2**) and the single crystal X-ray analysis of the methyl ester of **3**.⁵ This provided structural confirmation and the exo stereochemical assignment for **3** (i. e., cyano groups are disposed exo to the carboxylate bridge) and thus the stereochemistry of the primary cycloadduct (**7**). Hplc analysis of the total crude product from the reaction of **1** and **2** revealed the presence of just two compounds, 80 % of **3** and 18 % of **4**. The cycloaddition step is highly stereoselective for the exo primary adduct (**7**). We report herein the results of an AM1⁶ molecular orbital study which aided in elucidating the mechanisms of the individual steps in the overall process and the stereochemical outcome of the cycloaddition.



COMPUTATIONAL PROCEDURES

All calculations were carried out on a CACheTM WorkSystem using the AM1 Hamiltonian⁶ as implemented in the MOPAC 6.10 program distributed by CAChe Scientific. All geometries were fully optimized and transition states were located either by the reaction coordinate¹⁵ or saddle¹⁶ method. They were refined by minimizing the gradient norm¹⁷ and characterized by calculating force constants.¹⁷ Table 1 gives the calculated enthalpies and entropies of formation for all of the ground state species and TSs discussed.

THE CYCLOADDITION

The calculated lengths of the forming bonds of the exo (**5**) and endo (**6**) TSs indicate that the cycloaddition is a concerted but nonsynchronous process. The calculated ΔH^\ddagger for the reaction

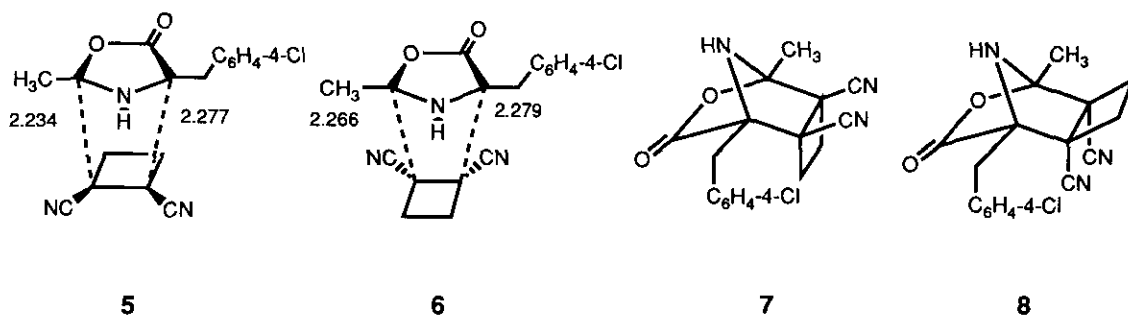
leading to the exo TS (5) is 23.40 kcal/mol while that leading to the endo (6) is 30.31 kcal/mol (all

Table 1. AM1 Calculated Heats of Formation (kcal/mol) and Entropies (e.u.) at 400° K

Compounds or TSs	ΔH_f	ΔS
1	-21.48	140.62
2	107.00	88.90
5	108.79	177.16
6	115.70	175.92
7	61.22	168.46
8	64.81	167.85
9	255.38	150.55
3	36.19	151.99
12	71.22	151.05
12 to 13 + CO ₂ TS	71.95	155.62
CO ₂	-79.83	54.52
13	132.50	143.95
13 to 4 TS	141.03	142.91
4	92.52	146.57
14	88.77	122.04
14 to 15 TS	116.01	121.03
15	76.43	124.72

activation parameters and ΔH_f^\ddagger 's are calculated at 400° K). These values ($\Delta\Delta H^\ddagger = 6.91$ kcal/mol) are in accord with our experimental observation of exo stereoselectivity in this cycloaddition.⁷ The calculated ΔS^\ddagger 's are -52.36 and -53.60 e. u. for the exo (5) and endo (6) TSs respectively, indicative of the usual highly ordered nature of cycloaddition TSs.⁹

What factors account for this 6.91 kcal/mol difference in the activation enthalpies and thus determine the stereoselective nature of this process? Calculation of the electron density isosurface



($0.01 e/A^3$) for both TSs using a CAChe™ WorkSystem provides qualitative evidence that steric factors are minimal in either TS. Inspection of appropriate frontier orbital coefficients afforded no clear distinction. Hehre and coworkers published a series of papers where they criticize frontier orbital theory and theories based on topological distinctions involving frontier orbitals as inadequate in all but very simple systems for explaining addition stereochemistry. They employed electrostatic potential calculations to rationalize the regio- and stereochemical course of a variety of addition reactions including the Diels-Alder reaction.¹⁰ In an attempt to explain our experimental results, we calculated the electrostatic potential isosurfaces (CAChe™) for both 5 and 6 at ± 0.03 atomic units (± 18.83 kcal/mol). Figures 1 and 2 show the electrostatic potentials of the *exo* and *endo* TSs respectively (the substituents are not shown for clarity). The light shaded surface is the -0.03 a.u. isopotential while the dark shaded surface is the 0.03 a.u. isopotential. Inspection of the surface in Figure 1 for the *exo* TS clearly shows attractive, stabilizing interactions between the exocyclic oxygen of the oxazolium ring and the methylene portion of the cyclobutene ring and between the CH–NH–CH portion of the oxazolium ring and the nitrile nitrogens. On the other hand, the surface in Figure 2 shows that repulsive, destabilizing interactions are evident in all regions of space in the *endo* TS. Thus we conclude that the interactions in the TS favoring the *exo* over the *endo* cycloadduct are predominately electrostatic in nature.¹¹ These same interactions are also reflected in the relative stabilities of the *exo* and *endo* cycloadducts (7 and 8 respectively); the former is more stable than the latter by 3.60 kcal/mol.

THE ELIMINATION OF CARBON DIOXIDE FROM THE EXQ CYCLOADDUCT (7)

In those examples which provide carboxylic acids, the elimination of CO₂ from the primary cycloadduct must be a stepwise process. The reaction conditions may also play a role in the

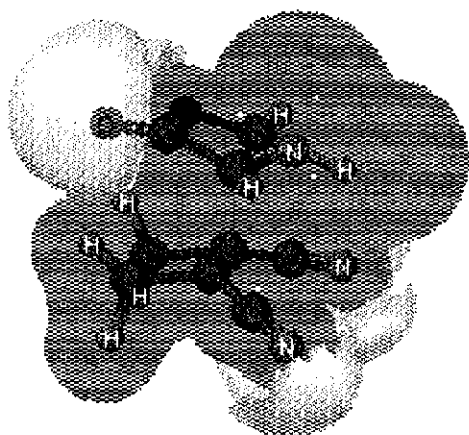


Figure 1. Electrostatic Isopotential Surface for the Exo TS (5)

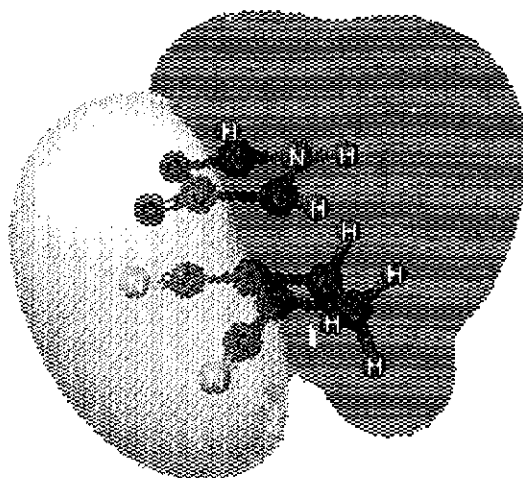
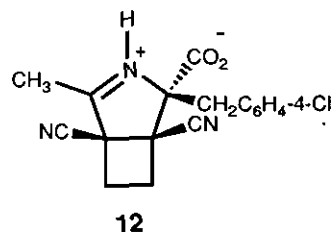
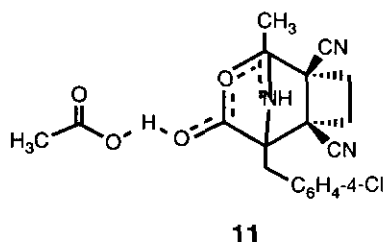
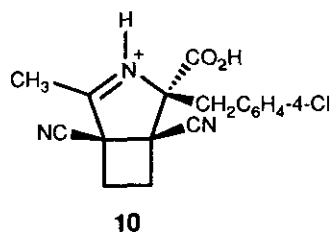
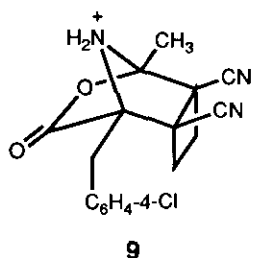


Figure 2. Electrostatic Isopotential Surface for the Endo TS (6)

mechanism of CO₂ elimination. In most cases as in ours, the mesoionic oxazole is generated *in situ* by the cyclodehydration of an amino acid or *N*-acylamino acid with acetic anhydride.^{1,5} The formation of acetic acid in these reactions provides the possibility of protonation of the cycloadducts. The calculated ΔH_f^\ddagger of the ammonium salt (9) is 255.38 kcal/mol. Attempts to calculate the ΔH_f^\ddagger for an intermediate which is protonated at the carbonyl oxygen did not lead to an energy minimum. Instead, C–O bond cleavage occurs to provide the iminium salt (10). Deprotonation of 10 affords the observed imino-acid (3). The same result is obtained when the ring oxygen is protonated. The AM1 calculations lead to the speculation that a possible TS for ring opening of 7 is 11. Thus, under the acidic reaction conditions, the zwitterionic intermediate (12) may not be involved in the formation of the imino-acid (3). Under neutral conditions (refluxing 3 in decalin) we isolated the dihydroazepine (4) in 70 % yield.⁵ Here we postulate that an equilibrium exists between the imino-acid (3) and the

zwitterion (12). Zwitterion (12) then gives the bicyclic azomethine ylide (AMY) (13) and CO₂ and ultimately the dihydroazepine (4). Of note is the calculated structure for zwitterion (12). The length of the sp³ carbon to carbonyl carbon bond is 1.66 Å. This anomalously long bond length is almost certainly an artifact of the AM1 semiempirical method and probably leads to an large overestimation of the energy of the zwitterionic species (12). All attempts to optimize the structure of the zwitterion

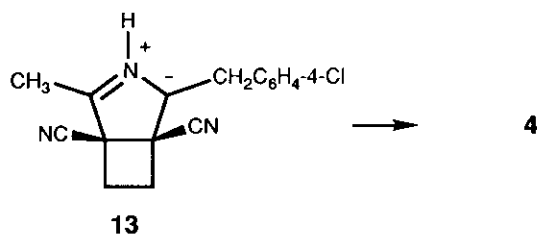


(12) by the PM3¹² and MNDO¹³ methods did not produce a minimum energy structure. These methods lead only to the AMY (13) and CO₂. We are currently investigating the structure and energy of zwitterions like 12 by ab initio MO methods.

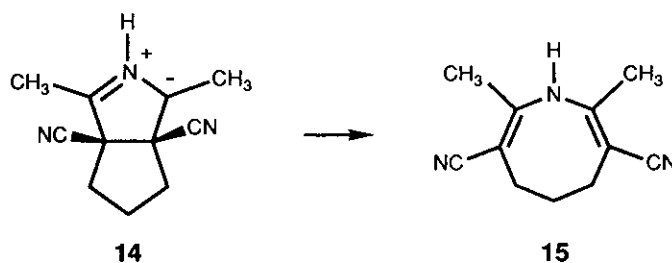
RING OPENING OF THE AMY 13 TO 2-(4-CHLOROBENZYL)-3,6-DICYANO-7-METHYL-4,5-DIHYDROAZEPINE (4)

The calculated ΔH^\ddagger for loss of CO₂ from the zwitterion (12) to provide the AMY 13 is 0.73 kcal/mol. This calculated low activation barrier is probably due to the overestimation of the energy of the zwitterion (12) as discussed above. Nevertheless, the AMY (13) is predicted to be a discrete intermediate in the reaction coordinate leading to 4, i. e., loss of CO₂ and ring opening are not in concert. Experimentally, AMYs have been trapped by dipolarophiles in the reaction of 2,4-diphenyloxazolium-5-oxide with olefins.¹⁴ The ring opening of 13 leading to the dihydroazepine (4) may be described as a 6 π -electrocyclic process. The calculated ΔH^\ddagger is 8.53 kcal/mol ($\Delta S^\ddagger = -1.04$

e.u.) and the reaction is highly exothermic ($\Delta\Delta H_f = 39.98$ kcal/mol, $\Delta\Delta S_f = 2.62$ e.u.). The length of the breaking C–C bond is 2.00 Å at the TS. What contribution does strain in the bicyclo[3.2.0] system make to the low value of the ΔH^\ddagger for ring opening? To answer this question, we compared bicyclo[3.2.0], [3.1.0] and [3.3.0] systems. Experimentally, cyclopropenes and cyclopropenones react with



mesoionic oxazoles to afford dihydropyridines and pyridones respectively; unlike the bicyclo[3.2.0] AMY, no intermediates were isolated.¹ Presumably the pyridine derivatives are formed by ring opening of the more highly strained bicyclo[3.1.0] AMY. In order to define the limit of ring size in the electrocyclic ring opening of bicyclic AMYs we calculated the ring opening of the bicyclo[3.3.0] AMY (**14**) (which would be derived from the reaction of 2,4-dimethyloxazolium-5-oxide with 1,2-dicyanocyclopentene) to the tetrahydroazocine (**15**). This too is an exothermic process ($\Delta\Delta H_f = 12.34$ kcal, $\Delta\Delta S_f = 2.68$ e.u.) but much less so than for the bicyclo[3.2.0] system. The calculated ΔH^\ddagger (27.24 kcal/mol), however, is 18.71 kcal/mol higher than the ring opening of the bicyclo[3.2.0] AMY and the length of the breaking bond is significantly longer (2.26 Å). Ring strain in **13** must serve to



increase the ground state energy relative to the TS for ring opening to **4** while the less strained **14** is much more stable toward ring opening to **15**. This relatively high ΔH^\ddagger for the conversion of **14** to **15** may lead to competing lower energy processes occurring such as pyrroline formation by proton transfer from nitrogen to carbon or trapping of **14** by external dipolarophiles. We are currently investigating the reaction of 1,2-dicyanocyclopentene and 1,2-dicyanocyclohexene with various

mesoionic oxazoles in our laboratories.

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7. Although the relative values of the enthalpies of activation leading to the *exo* and *endo* cycloadducts are in accord with our experimental findings, we believe that the absolute values are too large. Huisgen and coworkers experimentally determined ΔH^\ddagger 's for the reaction of 2,4-diphenyl-3-methyloxazolium-5-oxide with methyl acrylate, methyl methacrylate, styrene, methyl crotonate and ethyl undec-(10)-enate.⁸ They found that the cycloaddition step is rate determining with ΔH^\ddagger 's ranging from 10.7 – 14.2 kcal/mol.⁸ We calculated activation parameters for the cycloaddition of 2,4-diphenyl-3-methyloxazolium-5-oxide with each of the dipolarophiles mentioned above using the AM1 method. The calculated ΔH^\ddagger 's are in each case 8.3 – 12.4 kcal/mol higher than the experimental values with the exception of methyl acrylate which is 3.5 kcal/mol higher while the calculated ΔS^\ddagger 's are too negative by 21 – 23 e.u. The calculations were carried out for both *exo* regioisomeric TSs where little difference in the ΔH^\ddagger was found between the two. Thus the calculations suggest that these reactions are not regioselective. Unfortunately, the regiochemical information is lost because of the structural nature of the pyrroline products.
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Received, 7th December, 1992