

Chiral control of the Staudinger reaction

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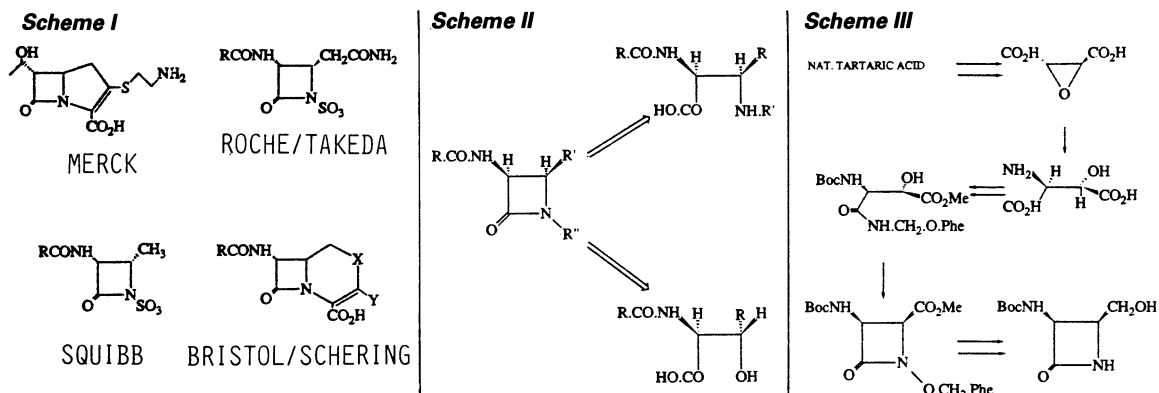
Abstract - A method is described for the chiral construction of β -lactams (and consequently other derivatives that use β -lactams as starting materials, e.g. amino sugars) in a versatile, high yielding, and predictable manner.

We have postulated a variation on the mechanism of the Staudinger reaction which explains the origins of the chiral induction in the reaction and using computational methods have been able to achieve a theoretical justification for our experimental observations.

Research into β -lactams has over the last 30 years resulted in many lifesaving antibiotics. This work is still continuing with unabated vigor, with periodic reinforcement from the discovery from natural sources of new and unexpected structural entities containing the β -ring. This has given the chemist a magnificent opportunity to practice his skills synthesizing structural variations of natural products and constructing molecules which are mosaics of structural groups derived from the various naturally occurring β -lactams. For example, in Scheme I several of these structures are shown. They have been selected to illustrate a particular aspect, i.e. they all contain a carbon-carbon bond of the C-4 position of the azetidinone (Scheme I).

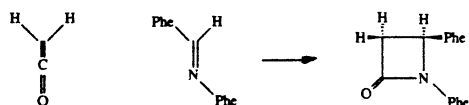
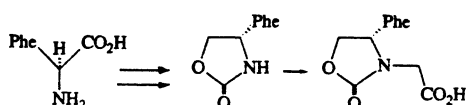
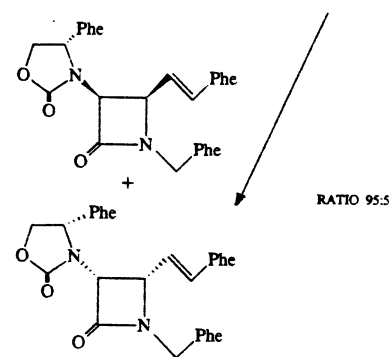
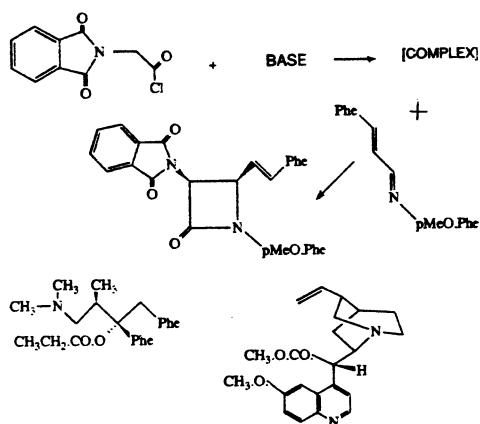
We have been interested for some time in developing synthetic methodology to generate this substitution in a facile and versatile manner. Furthermore, azetidinones are finding increasing application in the synthesis of more complex structures, e.g. amino-acids and amino sugars, and a successful solution of this goal could have significant application for the synthesis of these derivative structures.

A retrosynthetic analysis indicated that one approach would be the synthesis of either an α,β -diamino acid or a β -hydroxy α -amino acid with the stereochemistries as shown in Scheme II.



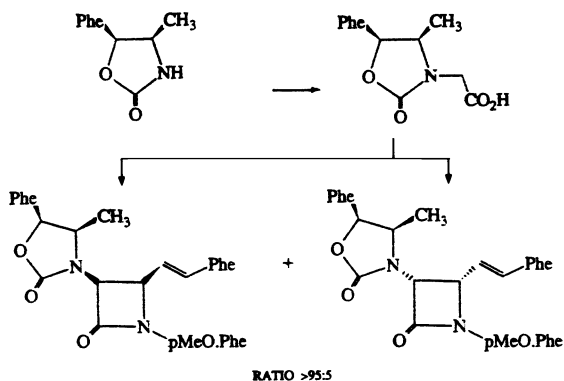
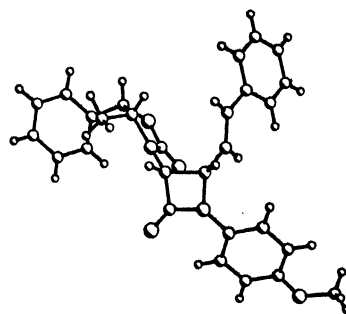
A collaboration with Dr. M. Miller (U. Notre Dame)¹ led to the required- β -hydroxy α -amino acid which was synthesized from R,R tartaric acid via the epoxy succinic acid (Scheme III). Although this approach resulted in a successful synthesis of the chiral 3-aminoazetidinone containing a C-4 carbon substituent, the method did not possess the ultimate simplicity of operation and versatility that we desired.

Our attention then turned to an investigation of the Staudinger reaction, the first reported method for the synthesis of a β -lactam ring². This reaction involved the 2+2 cycloaddition of a ketene and an imine (Scheme IV). The reaction has many advantages: it has been extensively studied for years, was exceedingly general in its functionality, and usually gave good yields. However it suffered from one major liability: its products were racemic. Our first approach to induce chirality into this reaction involved the use of a chiral base, e.g. propoxyphene and acetoxyquinidine (Scheme V), rationalizing that the acyl ammonium salt formed by reaction of the acetyl chloride and the base might itself then react with the imine to give a chiral acyliminium salt rather than proceed through a discrete

Scheme IV**Scheme VI****Scheme V**

ketene. Thus it might be possible to induce chirality into the initial acylation prior to final ring closure. The results were that only a 1:1 mixture could be observed, no induction was seen under a variety of conditions.

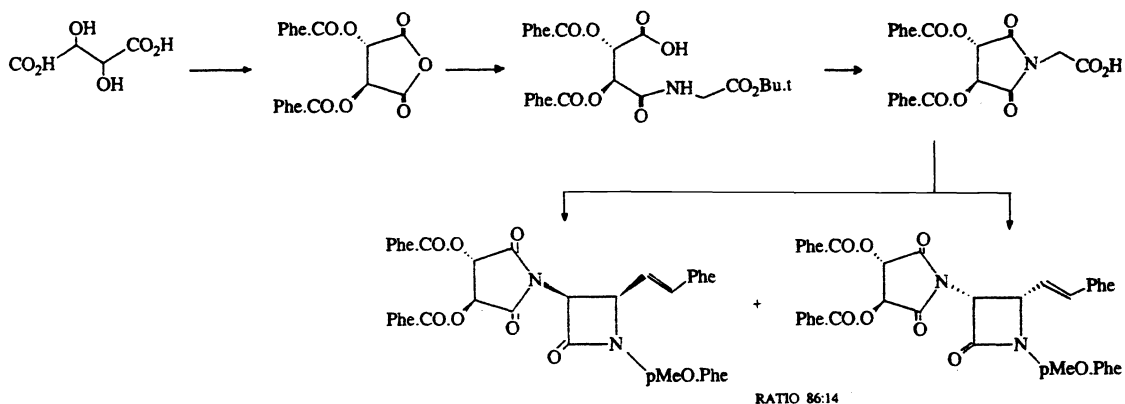
In discussions with Dr. D. Evans (Harvard Univ.), it was speculated on whether a chiral substituent in the amido portion of the ketene could induce chirality into the β -lactam ring. The Harvard group used a chiral auxiliary synthesized from L-phenylglycine and observed a 95:5 mixture of the two diastereomers (Scheme VI)³. The absolute configuration of the major product was proven by correlation with phenylalanine. We utilized the complementary chiral auxiliary prepared from norephedrine and found greater than 95% of one diastereomer (Scheme VII). The structure of this product was determined by X-ray crystallography⁴ to be that shown in Scheme VIII.

Scheme VII**Scheme VIII**

Both results were consistent in that a directing group α to the amide nitrogen, even a small group such as a methyl, has a profound effect, the S configuration giving the desired induction, the R configuration the undesired one.

One problem remaining was the removal of the chiral directing groups. Ideally it would be desirable to remove the auxiliary intact and recycle. One way to achieve this may be through an imide. We already know that imide protecting groups, e.g. phthalimide, gave excellent yields in the Staudinger reaction. The obvious imide to try was a tartramide. Based on analogy with our previous work, the desired tartaric derivative would be that prepared from the unnatural S,S tartaric acid. A key difference in this system would be that the chiral directing group(s) would be β to the amide and as a consequence of being further removed might be anticipated to have less of a chiral control.

Scheme IX



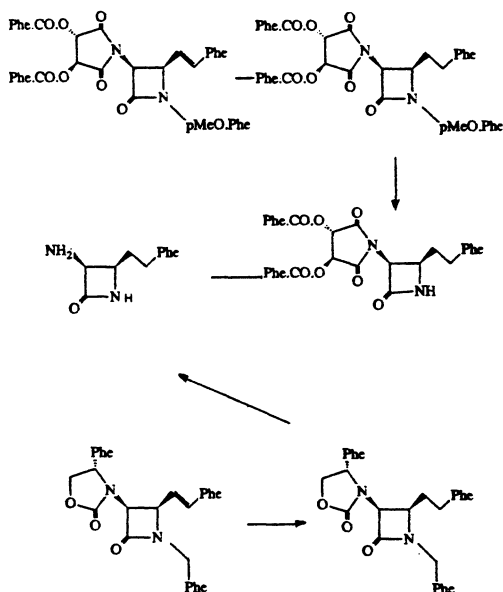
Synthesis of the auxiliary was accomplished from *S,S* dibenzoyl tartaric acid via the anhydride, opening with *t*-butyl glycinate to the amide and closure to the imide using thionyl chloride. Removal of the ester with trifluoroacetic acid gave the acid. Application of this chiral auxiliary gave two isomers in an 86:14 ratio. Transfer of the induction from the α to β position did indeed have an effect, especially when one considers that there were now two groups in the β position both operating in the same sense (Scheme IX).

The absolute stereochemistry of the major product was determined in the manner shown in Scheme X. Reduction of the double bond and removal of the *p*-methoxyphenyl group with ceric ammonium nitrate resulted in the azetidinone. This compound was also prepared by acylation of the previously described 3-amino-azetidinone and the corresponding *S,S* tartaric anhydride.

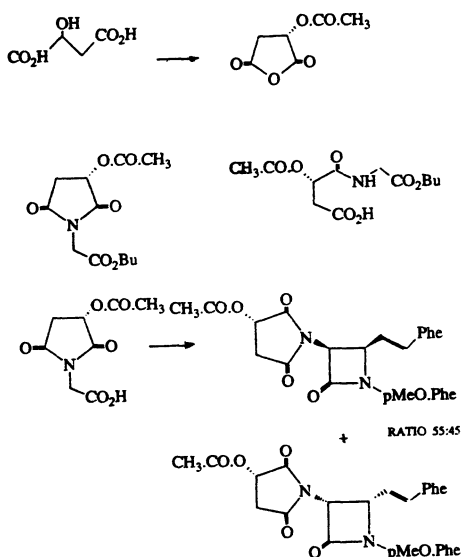
Similarly the dibenzyl derivative was prepared by alkylation of diethyl tartrate and hydrolysis to the diacid. Following the previous synthesis of the dibenzoyl derivative, the corresponding dibenzyl chiral auxiliary was synthesized. This chiral auxiliary also gave two isomers in the same ratio 86:14. The diacetoxy derivative, prepared in similar fashion from the diacetoxyanhydride gave two isomers in the ratio 70:30; thus, smaller directing groups had less control.

The effect of just one chiral directing group was shown by constructing the chiral auxiliary from malic acid (Scheme XI). Use of this chiral auxiliary gave two isomers in a 55:45 ratio.

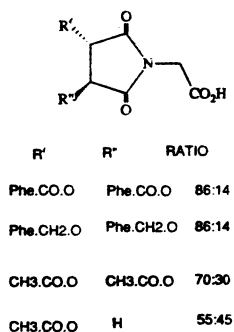
Scheme X



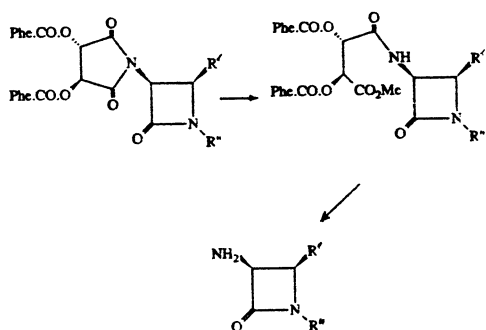
Scheme XI



Scheme XII



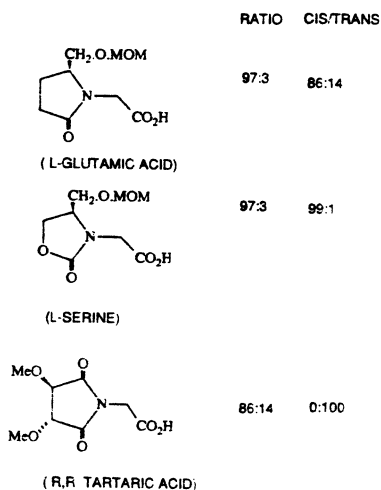
Scheme XIII



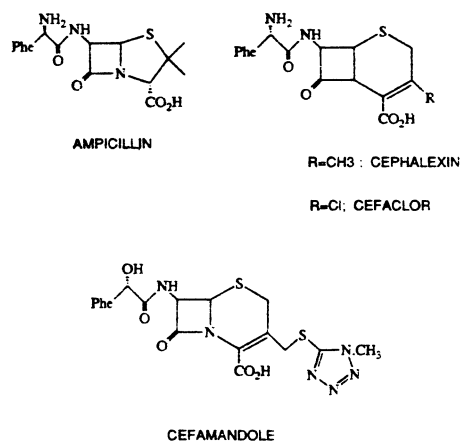
In summary, it appears that the dominant effect was steric, a large group being better than a small one, two groups better than one, and the closer to the amide nitrogen, the better (Scheme XII). However, one advantage of these tartaric systems was that they could be removed by opening the imide to the amide followed by application of the routine PCl_5 cleavage methodology (Scheme XIII). Our results were anticipated in the literature, or at least partially so⁵. The published results which are shown in Scheme XIV were somewhat different: The authors obtained a greater degree of induction from the dimethoxy tartaric acid than we would have anticipated from our results. More importantly, they only obtained the trans isomer from the reaction; we did not observe any trans isomer. This failure to control the stereo-chemistry of the reaction decreased its utility to a large extent.

These are several clinically useful antibiotics containing a chiral phenylglycine side chain and one with a chiral mandelic acid side chain (Scheme XV). Any new structural variations of the β -lactam theme will of necessity be evaluated with these important side chains; thus, perhaps we could use these side chains to induce the chirality in the Staudinger reaction.

Scheme XIV

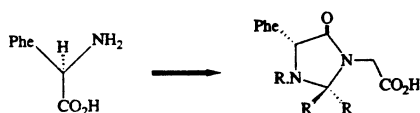


Scheme XV

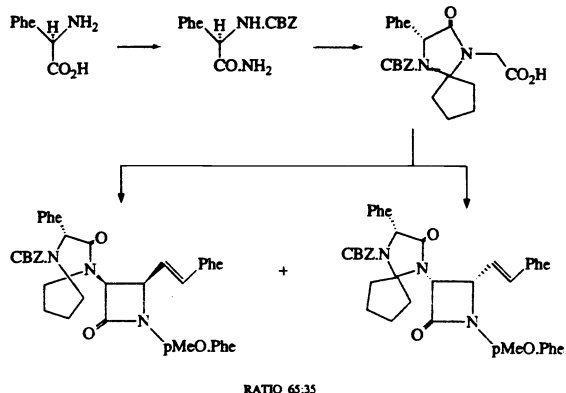


It would be necessary to convert the phenylglycine into a conformationally rigid ring structure to enable the phenyl group to exercise its maximum directing control. One such structure would be a five-membered imidazolone ring in which the phenyl directing ring would be at the β position (Scheme XVI).

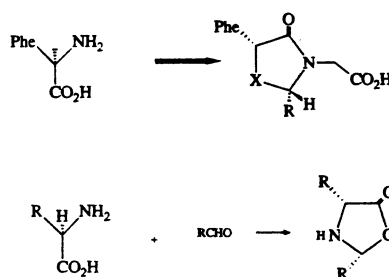
Scheme XVI



Scheme XVII



Scheme XVIII



Cyclization of the CBZ-amide derivative of D-phenylglycine with cyclopentanone under acidic conditions gave the imidazolone. Construction of the acid proceeded as described previously (Scheme XVII). Use of this acid in the 2+2 reaction gave two isomers in the ratio 65:35.

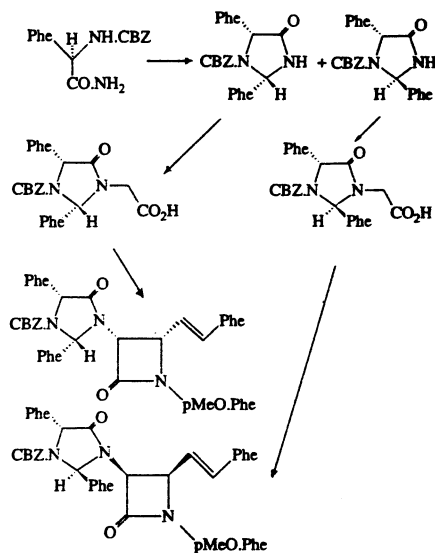
To overcome this liability, we needed to construct an imidazolone using an aldehyde instead of a ketone such that asymmetry was also induced at the center which would be now α to the amide nitrogen (Scheme XVIII).

This auxiliary should give a high degree of induction. The relationship of the α group must be trans to the phenyl group to result in the correct direction of induction.

Cyclization of the CBZ-amide with benzaldehyde under acidic conditions gave two isomeric imidazolones, in which the trans predominated in a 7:3 ratio. The stereochemical proof of the cis isomer was determined from the unusual NMR spectrum caused by rotational isomers. Coalescence to a greatly simplified spectrum could be achieved by raising temperature to 90°C⁶. Conversion of each isomer into its respective acetic acid followed by its use in the 2+2 addition resulted in only one isomer in each case. The trans isomer had both phenyl groups acting in concert and was anticipated to give a very high level of induction. The cis isomer had both groups operating in opposite senses, and it was interesting to note that the α directing group was dominant (Scheme XIX).

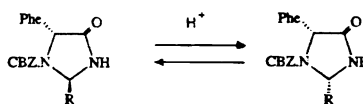
We have examined other aldehydes in an attempt to improve the trans/cis ratio in the imidazolone formations with the results shown in Scheme XX.

Scheme XIX



Scheme XX

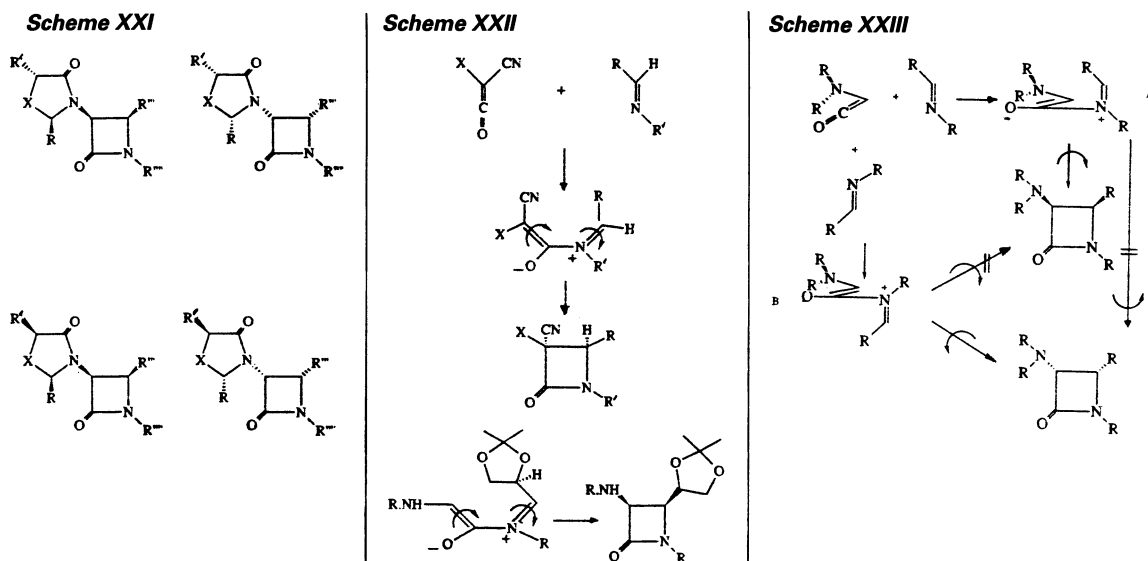
P	TRANS/CIS	K.CAL/MOL
Phenyl	70:30	11.4:12.56
2,6 Dichlorophenyl	0:100	15.43:18.39
1, Naphthyl	60:40	
4, Nitrophenyl	70:30	
4, Methoxyphenyl	90:10	



MM2^{7,8,9} calculations on the cis and trans isomers indicated that for the cases where R=phenyl and R=dichloro-phenyl, the trans isomer was more stable by about 1 and 3 kcal/mole, respectively. Thus, it appeared that the isomer ratios were the results of kinetic control. Indeed, treatment of the cis isomer with acid under the reaction conditions resulted in a 1:1 mixture of both isomers.

The overall result was one of a chirality transfer in which if the initial chiral group has the R stereochemistry, it has to transfer this chirality to the group in the 1,3 relationship in a trans relationship. This second group then transfers its chirality to the β -lactam ring resulting in the stereochemistry of the natural penicillins/cephalosporins. Alternatively, if the original group has the S configuration, transference in a cis manner to the second ring position would again give the desired β -lactam ring configuration (Scheme XXI).

Now one question we have not addressed so far is the mechanism of this reaction and the explanation for the high and now predictable chiral induction in the reaction. A recent publication has been devoted to the mechanism of the 2+2 reaction and concluded that the process was not concerted but first involved an acylation of the imine followed by a conrotatory bond formation to close the ring (Scheme XXII)¹⁰.



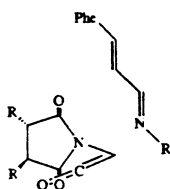
The Roche workers¹¹ who discovered the induction of the glyceraldehyde acetonide imine have postulated that the induction was a result of a preferential direction of rotation of this initial planar complex. Using these arguments it was not obvious why the chiral auxiliaries employed in our work have given such high induction, as the inducing group was directed away from the other substituents in the planar transition state. However, on consideration of the geometry of the transition state, it may be more appropriate to postulate an orthogonal approach. This approach could occur from either the α or β faces, and as such, these two intermediates A, B were the two chiral isomers (Scheme XXIII). These would then undergo a conrotatory bond closure with concomitant assumption of planarity. Transition state A could only give the β -lactam with both protons α , and vice versa. Thus, the origin of chirality occurred at the acylation of the imine, not on the direction of rotation, and was controlled sterically by the asymmetry of the substituent groups on the nitrogen.

This was illustrated in Scheme XXIV when the approach of the imine was directed to approach from the β -face due to the interaction with the R group on the α -face.

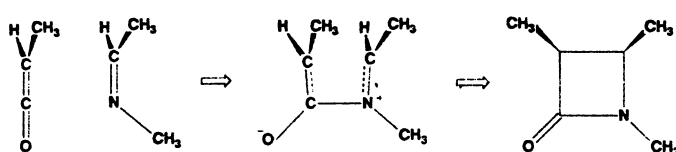
We have attempted to explore theoretically the structures of the reactants, transition species, and the product of the reaction. Through a better understanding of the transition intermediates and especially the transition state(s), some rational choices could be made about the most propitious substituents for asymmetric induction.

The approach we have taken was to use the MNDO semiempirical molecular orbital method¹² to deduce energy minimized structures. The MNDO method represented a good compromise between accuracy and computing speed^{13,14} and has been used in numerous molecular modeling^{15,16} studies, including formation of amide bonds¹⁷ and several electrocyclic reaction

Scheme XXIV



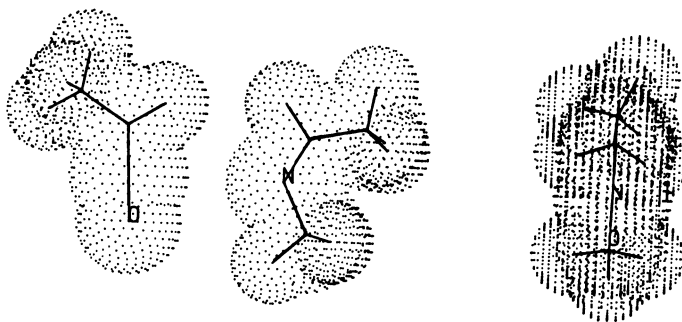
Scheme XXV



mechanisms¹⁸⁻²¹. The computational experiments were performed with the MOPAC computer program²² running on a VAX 11/785. Graphical depiction of the computational results were prepared with the SYBYL molecular modeling system^{23,24}.

The molecular modeling calculations were done on the simple mono-methyl substituted ketene and the N-methyl-2-methyl-imine (Scheme XXV). These were minimal structures that would represent the chiral reaction centers. The two reactants were initially optimized in a coplanar arrangement with 4.0 Å separating the α carbon of the ketene and the nitrogen of the Schiff base. This geometry of the reactants is shown in two orthogonal views (Scheme XXVI). The dots represent the approximate van der Waals shape of the molecules.

Scheme XXVI

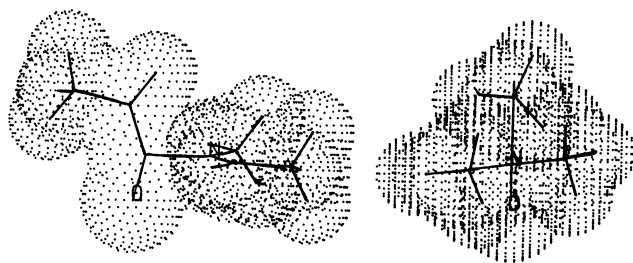


Similar to the description of the ketene molecular orbitals given in a recent review²⁵, the HOMO in the ketene reactant has out-of-plane $2p\pi$ character distributed over C=C=O. The LUMO has in-plane $2p\pi$ character localized on only C=O. From the nature of the LUMO, one might expect some preference on an in-plane electrophilic attack on the ketene. However, steric effects from the substituents on the ketene would probably overwhelm these orbital guidelines at short intermolecular distances.

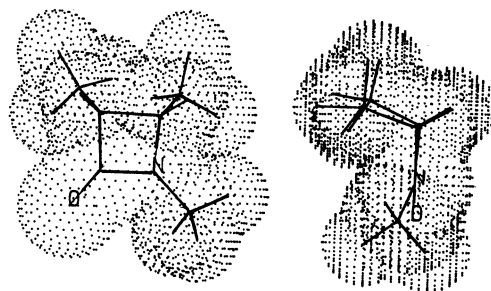
A relatively low energy transition intermediate (TI) structure was discovered. The energy of this zwitterion was about 22 kcal/mole above that of the reactants. (This energy from the MNDO heats of formation does not, of course, include solvation effects.) The remarkable feature of the TI was that the two ends of the molecule were nearly perpendicular to each other. The necessity for this conformational arrangement was readily appreciated by seeing the space-filling requirements of the substituents. The O-C-N-Me torsional angle was 98°. The bonding at both the α carbon of the ketene end and the nitrogen of the imine end of the TI was trigonal, so that each half of the TI was nearly planar (Scheme XXVII).

The equilibrium bond length of the central C-N bond was 1.70 Å. The other optimized bond lengths were 1.36 Å for the nominal C=C bond, 1.31 Å for the nominal C=N bond, and 1.22 Å for the nominal C=O bond. These lengths indicate that the double bond character in these bonds was only slightly diminished by formation of the central C-N bond.

Scheme XXVII



Scheme XXVIII



As is usual in electronic structure calculations, the electron density distributed itself widely throughout the molecule in order to reduce interelectron repulsions, but subject to the constraint of the electronegativity of the atoms. Thus, the electron density distribution does not always conform to the chemist's shorthand notation of formal charges. The MNDO net atomic charges were -0.38 on the oxygen and -0.23 on the nitrogen. The ketene half of the zwitterionic TI carried a net excess of 0.32 electrons, while the imine half was deficient by an equal amount.

The product from the model reaction was N-methyl-3,4-dimethyl-azetidin-2-one. Its energy was 26 kcal/mole below that of the starting molecules and 48 kcal/mole lower than that of the TI (Scheme XXVIII).

In addition to the structures depicted, other regions of the potential energy hypersurface have been investigated computationally, and this work is continuing. The barrier to rotation about the central C-N bond in the TI was about 8 kcal/mole. Rotation about either of the nominal double bonds in the TI was subject to barriers of about 12 kcal/mole. Other geometrical variables, such as the syn and anti imines, have also been investigated.

Thus from theoretical considerations, the zwitterionic intermediate was found to have a twisted geometry. The steric requirements of the substituents caused the ends of the molecule to be mutually perpendicular. Stereo control thus must begin when the two reactants first approach each other. In order to close the β -lactam, not only must the two nominal double bonds of the transition intermediate undergo conrotatory motion, but also the central C-N bond must rotate to its final eclipsed arrangement.

In conclusion, we now have a method for the chiral construction of β -lactams (and consequently other derivatives that use β -lactams as starting materials, e.g. amino sugars) in a versatile, high yielding, and predictable manner.

We have postulated a variation on the mechanism of the Staudinger reaction which explains the origins of the chiral induction in the reaction and using computational methods have been able to achieve a theoretical justification for our experimental observations.

Acknowledgements

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