Electronic Effects on the Stereochemical Outcome of the Photochemical Reaction of Chromium Carbene Complexes with Imines To Form β-Lactams†

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The results of calculations by Cossio and subsequently Sordo showing that stereoselectivity in the ketene–imine cycloaddition to form β-lactams could be determined by "torquoelectronic" effects similar to those used to rationalize cyclobutene ring opening reactions were used to rationalize the contrasteric outcome of over 40 chromium carbene complex-derived alkoxyketene–imine reactions. In addition, the high stereoselectivity observed in these reactions with optically active heterocyclic imines and the unusual instability of azapenams were rationalized using similar arguments.

Introduction

The development of the photochemical reaction of heteroatom-stabilized chromium carbene complexes with imines to produce β-lactams has engaged these laboratories for over 10 years. The process is efficient for the synthesis of a wide range of β-lactam types[1] and is thought to proceed through a photochemically generated chromium ketene complex.[2] Indeed, it shares many features of the classic Staudinger[3] ketene–imine cycloaddition process, including the unpredictability of the stereochemical outcome of any particular system. This unpredictability is due to the stepwise nature[4] of the cycloaddition with the resulting possibilities for isomerization of the initially formed intermediate prior to ring closure, a topic considered in detail in several recent publications.[3,5]

The stereoselectivity of a vast majority of ketene–imine cycloaddition reactions has been rationalized on the basis of steric effects alone, predicated on the reaction occurring by nucleophilic attack of the imine from the less hindered side of the ketene (over the small group) with the plane of the imine perpendicular to that of the ketene, followed by conrotatory ring closure. For acyclic *trans* imines which react without rearrangement of the zwitterionic intermediate, this results in the production of the more hindered (*cis*) β-lactam. For cyclic imines, which are necessarily *cis*, the endocyclic substituent and the small group end up *cis* (Figure 1). In the few cases for which this stereoselectivity is not observed, isomerization of the zwitterionic intermediate is invoked.

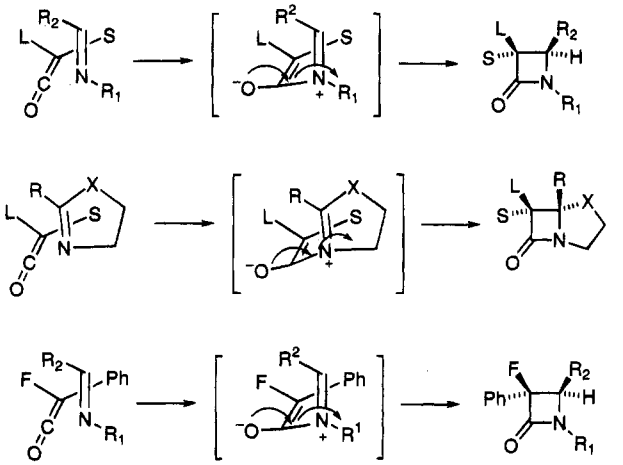

Figure 1.

A notable exception to this is the case of fluorinated ketenes,[6] on which, in β-lactam formation, attack must occur over the large substituent to rationalize the observed stereoselectivity (Figure 1). This was attributed to "simple dipolar effects or secondary orbital interactions".[6]

In a complex and detailed semiemperical theoretical treatment of the Staudinger reaction Cossio[7] related the formation of β-lactams to the conversion of cyclobutenes to butadienes and invoked Houk's[8] torquoelectronic effects to account for some aspects of stereoselectivity in the Staudinger reaction. Sordo[9] explicitly stated that the geometry of the transition structures for conrotatory ring closure of the zwitterionic intermediate in ketene–imine cycloadditions strongly resembled that for the electrocyclic ring opening of cyclobutenes (Figure 2) and that torquoselectivity arguments developed for that process should be applicable to the Staudinger reaction. This was used to rationalize the stereochemical outcome reported for fluoroketenes.[6] More recently torquoselectivity has been invoked to rationalize chiral control in the Staudinger reaction.[10]

† Dedicated to Professor Leon Ghosez for his 60th birthday.

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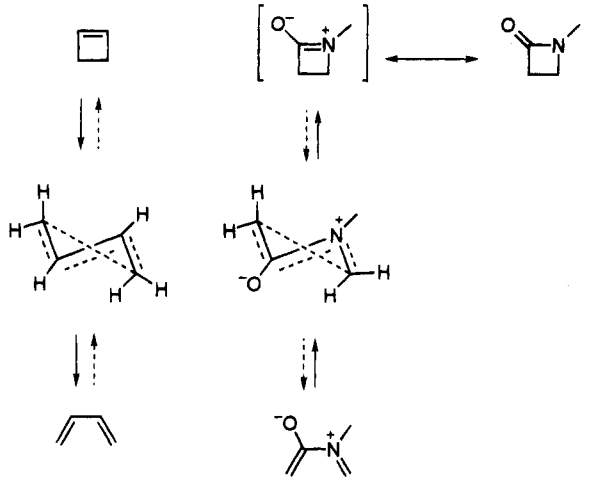
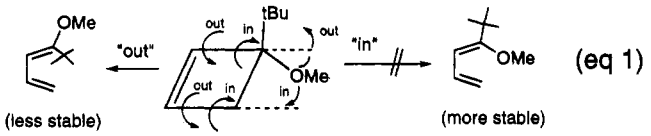


Figure 2.

Torquoselectivity is a concept developed by Houk[8] to rationalize a number of contrasteric (and counterintuitive) thermal cyclobutene ring opening reactions. A striking example is seen in eq 1,[11] wherein the cyclobutene opened exclusively in the conrotatory MeO group "out" mode, even though the resulting diene is considerably less stable than that which would result from the MeO group "in" mode, because of the *Z* disposition of the large *tert*-butyl group and the vinyl group. *Ab initio* molecular orbital calculations showed a very strong electronic bias for electron-donating groups to rotate "out", regardless of the steric consequences.



(eq 1)

To view the β-lactam cycloaddition reaction in this context, it is necessary to consider the process in the reverse sense and the "in-out" designations for cyclobutene ring opening become confusing. In the ketene–imine cycloaddition reaction, the *ab initio* calculations[9] show a 10–12 kcal/mol preference for the hydroxy group of a hydroxy ketene toward "outward" rotation, which translates to attack of the ketene from the side opposite the donor group, regardless of the size of the other substituent (eq 2). To put it another way, the zwitterionic intermediate resulting from attack opposite (*anti*) the electron-donating group has a barrier to conrotatory closure to the β-lactam 10–12 kcal/mol lower than that arising from attack *syn* to the donating group. Thus, in many cases, the stereochemically more favored direction of initial attack may well generate the electronically less favored intermediate for closure, resulting in stereoselectivity opposite that expected from steric arguments alone. This concept permits the rationalization of a substantial amount of seemingly anomalous data acquired over the last 10 years in the study of the reactions of imines with alkoxyketenes generated by the photolysis of chromium alkoxycarbene complexes. This accumulated data and its rationalization in the context of torquoselectivity is presented below.

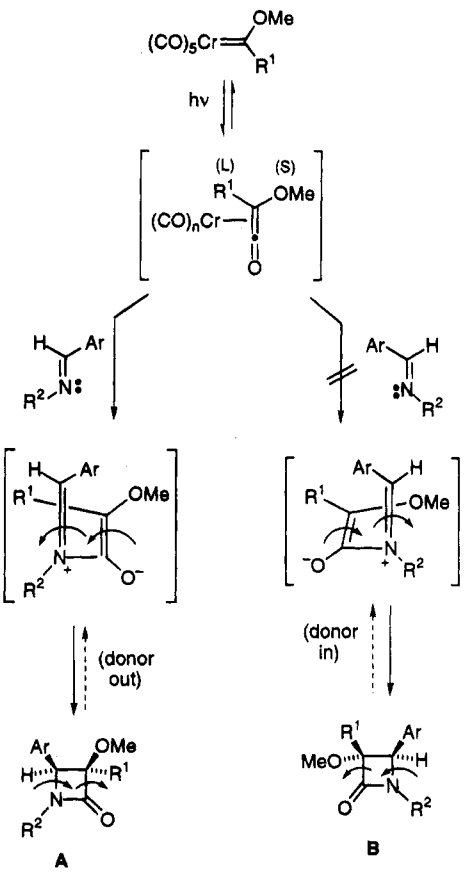
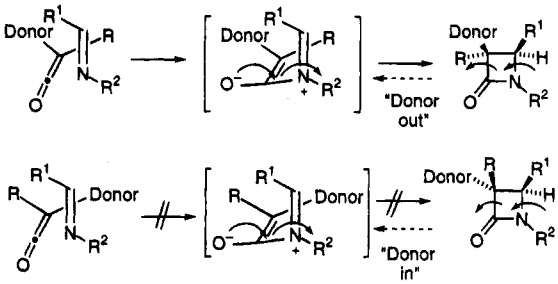


Figure 3.



(eq 2)

Results and Discussion

Photolysis of chromium carbene complexes (visible light) is thought to generate species with ketene–like reactivity.[2] Early studies from these laboratories focussed on the photochemical reaction of (methoxy)(alkyl)-carbene complexes with simple imines to produce β-lactams having an alkyl group and a methoxy group at the α-position. From the outset, the stereochemical outcome of these reactions was exactly opposite that predicted by the conventional view involving attack over the small (in this case the methoxy) group of the ketene, followed by conrotatory ring closure (Figure 3, Table 1). These results are only consistent with electronic control ("donor out") not steric control and provide the first *broad* demonstration of the role of "torquoelectronic" effects in ketene–imine reactions.

More compelling still are the results obtained with cyclic imines, which cannot isomerize at the zwitterionic intermediate stage (eq 3, Table 2). Again, in all cases, the stereochemistry observed is that due to electronic

(10) Cossio, F. P.; Arrieta, A.; Lecea, B.; Ugalde, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 2085. This paper appeared after the submission of this manuscript. No examples of disubstituted ketenes were treated, nor were any of the results contained in this manuscript.

(11) Houk, K. N.; Spellmeyer, D. C.; Jefford, C. W.; Rimbault, C. G.; Wang, Y.; Miller, R. D. *J. Org. Chem.* **1988**, *53*, 2125.

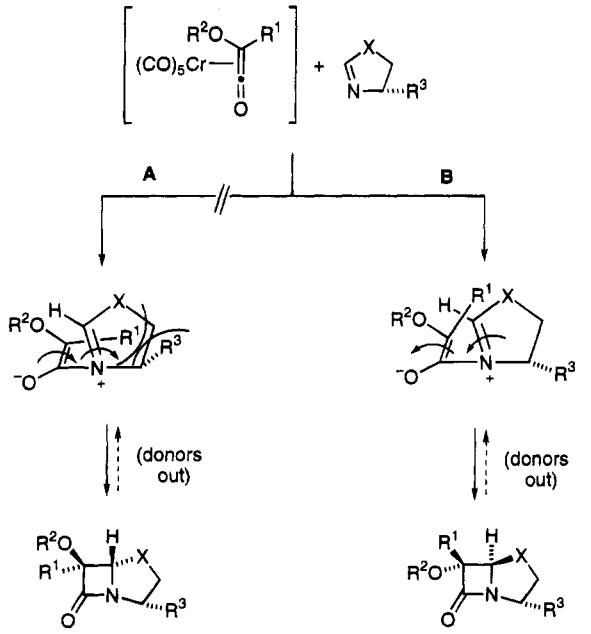
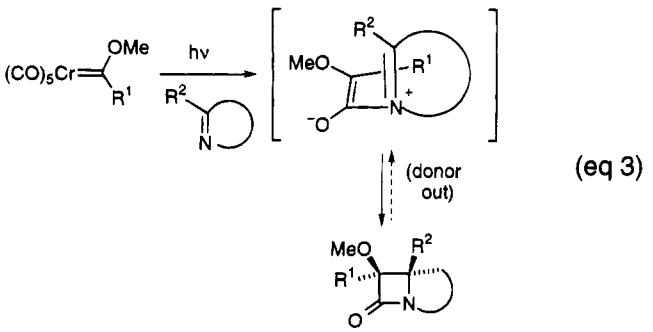


Figure 4.

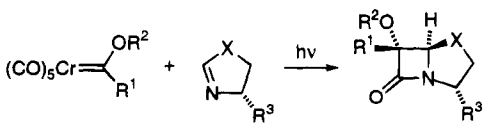


(eq 3)

control (torquoselectivity) not steric control (attack over the small group), and only a single diastereoisomer is produced. As the steric hindrance increases the yield of β-lactam decreases, but none of the sterically favored but electronically disfavored isomer is seen.

Of the 27 compounds in Tables 1 and 2, stereochemistry could be unequivocally assigned from ^{1}H NMR chemical shift data for 20 of them and was confirmed by X-ray crystallography for two of them. The remaining seven were assigned by analogy, with some degree of confidence, based upon this and the data in Table 3 (see below).

Photolysis of chromium alkoxycarbene complexes in the presence of optically active thiazolines or imidazolines produces β-lactams with a very high degree of stereocontrol, again with relative stereochemistry opposite that expected from steric control (eq 4). Electronic control in



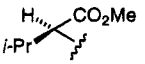
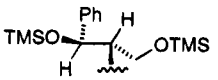
(eq 4)

X = S, NCBz R^3 = *i*-Pr

the ring closure step based on the torquoselective "donor out" paradigm can account for both the relative and absolute stereochemical outcome of this process. These results are summarized in Table 3.

Again, electronic control dictates ring closure only from the zwitterionic intermediate resulting from attack over

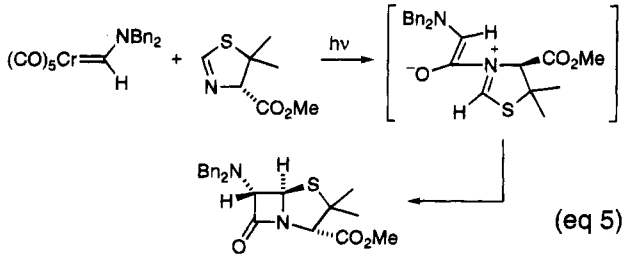
Table 1 (see Figure 3)

R^1	R^2	Ar	Yield, %	A/B (δ OMe)[a]	Ref.
Me	Me	Ph	76	**A** (3.00)	12
Me	Ph	Ph	52	**A** (3.10)	12
Ph	Me	Ph	72	**A** (3.18)	12
Ph	Ph	Ph	20	**A** (3.26)	12
Me	pMeOPh	Ph	60	**A** (3.10)	12
Me	Bn	PhCHCH	45	**A** (3.45)[b]	12
Me	$CH_2PO(OEt)_2$	Ph	90	**A** (3.06)	13
Me	$CHCO_2Me$ | $PO(OEt)_2$	Ph	80	**A** (3.10, 3.14)[c]	13
Me	$CH{=}CH_2$	Ph	41	**A** (3.06)	13
Me	Bn	Ph	53	**A** (3.15)	13
Me		Ph	74	**A** (2.95, 2.97)[c]	12
Me		Ph	65	**A** (3.04, 3.05)[c]	12
Me		Ph	91	**A** (3.01, 3.09)[c]	12

[a] Structure assigned on the basis of δ OMe, which is ≈3.6 if *anti* to Ar, ≈3.0 if *syn*. [b] Methoxy group is less shielded by a PhCHCH group than by an Ar group. [c] Mixture of *syn* (**A**) diastereoisomers because of additional chiral center.

the large (R) group, but with optically active imines, two different diastereoisomeric modes of attack are available (paths A and B, Figure 4) and conrotatory closure from each of these will produce diastereoisomeric β-lactams having the same relative configuration at the two new stereogenic centers, but different absolute configuration. Only the diastereoisomer produced by path B is observed, perhaps because path A results in steric interference of the R^1 group on the ketene with that (R^3) on the heterocyclic imine. The high stereoselectivity must, in part, be due to the rigidity of the heterocyclic imine which prevents the R^3 group from rotating away from this situation.

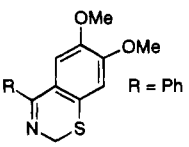
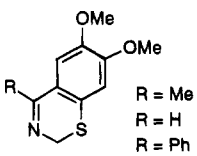
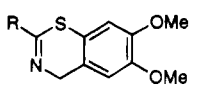
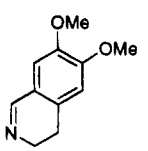
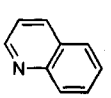
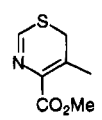
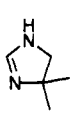
When chromium aminomethylene complexes are used in place of alkoxycarbene complexes, both the steric and electronic biases are complementary since in this case the donor group is the large group, and attack opposite it is sterically favored and closure of the resulting zwitterionic intermediate is electronically favored. However the arguments in Figure 4 similarly rationalize the stereochemical outcome when optically active thiazolines are used as substrates (eq 5).[12]



(eq 5)

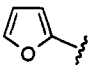
Finally, torquoelectronic effects may rationalize the unusual instability of amino azapenams recently reported from these laboratories.[16] Although the synthesis of the

Table 2 (see eq 3)

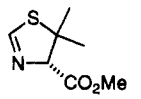
R^1	Imine	Yield, %	δ OMe	Ref.
Me		70	3.01	14
Me		63	2.95	14
Me		52	3.00 (X-ray)	12
Me		81	3.48[a]	12
Me	 R = Ph	51	3.07	12
Me	 R = Me	38	3.59[a]	12
Me	R = H	37	3.57[a]	12
Ph	R = Ph	27	3.35	12
Me	 R = Ph	61	2.92	12
Ph	R = Ph	25	3.21	12
Me		43	3.6[a]	12
Me		38	3.56[a]	12
Me		52	3.50[a]	13
Me		69[b]	3.46 (X-ray)	1c

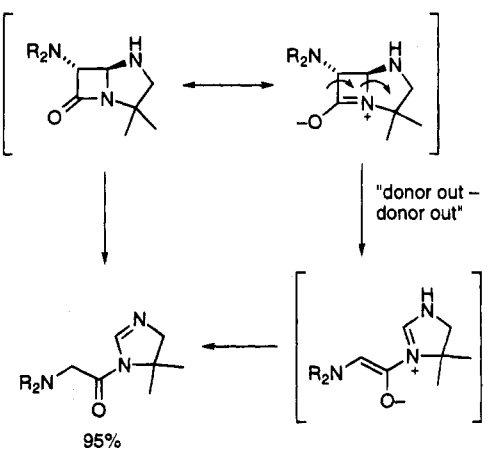
[a] Assigned by analogy to cases containing phenyl groups. [b] Reaction carried out on CBz protected imidazoline.

Table 3 (see eq 4)

R^1	R^2	R^3	X	Yield, %	ee[a]	Ref.
Me	Bn	*i*-Pr	S	76	>97%	15
n-Bu	Bn	*i*-Pr	S	78	>97%	15
	Bn	*i*-Pr	S	39	>97%	15
Ph	Bn	*i*-Pr	S	42	>97%	15
p-MeOPh	Bn	*i*-Pr	S	42	>97%	15
	Bn	*i*-Pr	S	29	>97%	15
Me	Me	[b]		42	>97% (X-ray)	12
Me	Me	*i*-Pr	NCbz	41	>97% (X-ray)	1c
Me	Bn	*i*-Pr	NCbz	54	>97%	1c
—$(CH_2)_3$—		*i*-Pr	NCbz	69	>97%	1c

[a] Absolute configuration determined by conversions to compounds of known absolute configuration, and by correlation to closely related compounds for which X-ray structures are available.

[b] The substrate was 



(eq 6)

protected amino azapenam proceeded without incident, giving the expected *trans* β-lactam, all attempts to generate the free azapenam resulted in an unexpected cleavage to produce an *N*-acylimidazoline (eq 6). However, when the deprotected azapenam is viewed as the imidate tautomer it corresponds to a cyclobutene with two strong donor groups *trans*, having the required disposition for a conrotatory ring opening in which both donors can rotate out, a highly favored process. For *trans*-3,4-dihydroxycyclobutene, calculations show an activation barrier for ring opening in the out-out sense 18 kcal/mol lower than that for cyclobutene itself.[8a] Since amino groups are better donors than hydroxy groups,[8a] the azapenam ring opening should be even more favored, a feature which may account for the general instability of azapenam systems.

Azapenams having an alkoxy substituent *trans* to the ring nitrogen have been isolated and are sufficiently stable to be purified, characterized, and utilized as reagents for other transformations.[1c] However upon gentle heating (75 °C) these, too, underwent ring opening to form an *N*-acylimidazoline (eq 7). Again, the two donor substituents can undergo an "out-out" rotation which is electronically favored. The alkoxyazapenams are slightly more stable than the aminoazapenams because an alkoxy group is a weaker donor than an amino group.

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(13) Hegedus, L. S.; Schultze, L. M.; Toro, J.; Chen, Y. *Tetrahedron* **1985**, *41*, 5833.
(14) Borel, C.; Hegedus, L. S.; Krebs, J.; Satoh, Y. *J. Am. Chem. Soc.* **1987**, *109*, 1101.
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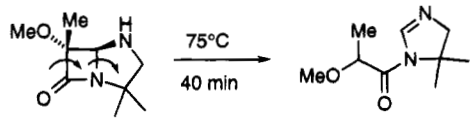
(16) Ronan, B.; Hegedus, L. S. *Tetrahedron* **1993**, *49*, 5549.



(eq 7)

Summary

Torquoelectronic effects nicely account for over 40 cases of contrasteric formation of alkoxy β-lactams and for the unusual instability of aminoazapenams. The concept may be broadly useful for both the rationalization and prediction of the stereochemical outcome of ketene–imine reactions.

Acknowledgment. Support for this research under Grant No. GM26178 from the National Institutes of General Medical Sciences (Public Health Service) is gratefully acknowledged.