

been examined in detail involves the binding of tris-(phenanthroline)ruthenium(II), Ru(phen)₃²⁺, to DNA.^{13,22,23} Each of the three propeller-like bidentate ligands of the molecule provides a planar aromatic surface for potential intercalation, and together they impart chirality to the structure. NMR²³ and photophysical²² experiments have established that two DNA-binding modes, intercalative and groove bound, are available to Ru(phen)₃²⁺. This case, therefore, allows us to ask whether, in the presence of alternative binding modes, intercalation can be firmly established.

In fulfilling the first criterion for intercalation, Ru(phen)₃²⁺ has been demonstrated to unwind helical DNA through two independent assays, one²² measuring altered electrophoretic mobility, another²⁵ using a topoisomerase assay. The second criterion, establishing an electronic interaction between the potential intercalator and the DNA bases, has been firmly established through observations of hypochromism and red shifts in the MLCT band of the complex upon binding and based upon increases in the MLCT excited state lifetime.^{13,22,26} A determination of rigid binding by Ru(phen)₃²⁺, the third experimental criterion, has been established through emission polarization measurements that indicate the retention of polarization in emitted light.^{13,22} In contrast, surface-bound molecules showed no retention of polarized emission.

The fourth criterion, a consideration of molecular shape and structure, is readily established through the comparison of Δ and Λ enantiomers with respect to each experimental determinant (structural changes, electronic interactions, and rigidity) for intercalative binding. In all of these experiments, the Δ enantiomer, at the same added concentration as the Λ isomer, shows an increased effect. This enantioselectivity is also supported by electric dichroism measurements.²⁷ The readily observed chiral discrimination provides perhaps the strongest evidence in support of intercalation based upon structural considerations and indicates that the symmetry of the metal com-

plex matches the symmetry for intercalation into a right-handed helix.¹

In contrast to these data, a recent publication²⁹ utilizing techniques (flow dichroism) that determine only the orientation of a bound species relative to the helix axis has described the construction of models for the interaction of Ru(phen)₃²⁺ with DNA, models in which intercalation was not predominant. The orientational data alone were clearly incapable of resolving the two binding modes for the complex as established by several different lines of evidence.^{22,23,26} Clearly, the above line of experimentation provides an example of how the application of any one of the four criteria alone may lead to ambiguities in characterizing the binding modes of a molecule.³⁰

In summary, to assess the binding interactions with DNA of "three-dimensional" DNA-interactive molecules in the absence of a well-resolved crystal structure, what is required is an evaluation that satisfies at least four criteria prior to establishing an intercalative interaction. Hopefully these criteria will set a standard by which other workers in the field may judge their data during the evaluation of binding mode and aid in the future rational design of DNA-interactive agents.

We are grateful to the National Institutes of Health for their support of our work. E.C.L. is a Fellow of the Jane Coffin Childs Memorial Fund for Medical Research.

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(30) It is noteworthy that none of the above experimental criteria speak to the question of the groove location (minor versus major) of a DNA-binding agent, and here as well experimental evidence is required.

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ARTICLES

Ketene Chemistry: The Second Golden Age

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A decade ago our group first began to examine the reaction mechanisms^{1a} and synthetic applications^{1b} of nucleophilic additions to ketenes. It appeared to us that this field had not received the attention warranted by the intrinsic interest and potential utility of these fascinating difunctional species. This area of study reached its first maturity very early, as it was the initial major research interest of Hermann Staudinger, who reported the first ketene in 1905. He summarized his work on the subject in a definitive monograph in 1912,²

which marked the culmination of the first golden age of ketene chemistry. Staudinger then went on to develop further interests, such as the creation of modern polymer chemistry.

The field did not languish thereafter, but received steady attention by some talented groups as summarized in several reviews,³ but only after Woodward and

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Born in 1939, Thomas Tidwell received his B.Sc. at Georgia Tech and his Ph.D. with Paul Bartlett at Harvard in 1964. He is presently Professor of Chemistry at the University of Toronto, where his main research interests lie in the areas of ketene and organofluorine chemistry.

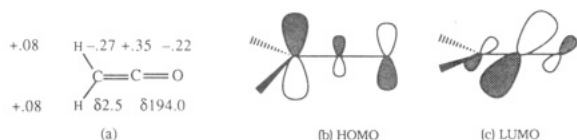


Figure 1. (a) Ketene charge densities and ¹³C NMR chemical shifts. (b) Ketene HOMO. (c) Ketene LUMO.

Hoffmann pointed out the unique ability of ketenes to undergo concerted [$\pi 2_s + \pi 2_s$] cycloaddition⁴ has it again become one of the "hot spots" of organic chemistry.⁵

Addition reactions of ketenes particularly attracted our attention, as we believed that the prevalent mechanistic rationales for these reactions were unsatisfactory and that their synthetic potential was neglected. Our work over the past decade has convinced us that our analysis was correct, and independently of our efforts there has been a worldwide blossoming of interest in ketene chemistry. It is our conviction that the current activity is only the beginning, and that ketene chemistry will continue to flourish.

Ketene Structure. Molecular orbital calculated charge densities of ketene show positive charge on C_α and hydrogen and negative charge on oxygen and C_β, and these are paralleled by the ¹³C NMR chemical shifts^{6a} shown (Figure 1). Frontier molecular orbital calculations⁴ show the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) for ketene lie respectively perpendicular to and in the molecular plane, so that electrophilic attack is expected to occur at C_β from above while nucleophiles are expected to attack in the plane at C_α.

The molecular structure of ketene has now been refined^{6b} and is distinguished by the short CC and CO bond lengths of 1.3142 (5) and 1.1609 (4) Å, respectively, involving the sp-hybridized carbon. These are similar to distances recently found in crystalline ketenes by X-ray crystallography^{6c,d} and in dichloroketene by electron diffraction.^{6e}

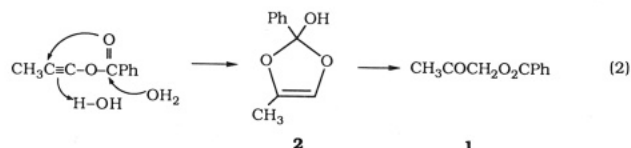
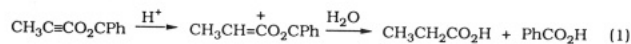
Current Ketene Studies. Some particularly active areas of ketene chemistry are conjugated ketenes,^{7a} including alkynylketenes,^{7b,c} the intramolecular 2 + 2 cyclization reactions of ketenes,^{7d} thioketenes,^{7e} and the interaction of ketenes with organometallic compounds.^{7f} Ketenes bearing electronegative heteroatom substituents are particularly reactive and useful in synthetic applications.^{3b,7g}

The 2 + 2 intermolecular cycloaddition reaction of ketenes with alkenes has now been reexamined by using

improved theoretical methods.^{8a-c} In one study this reaction is described as "quasi-pericyclic", with appreciable interaction of the central atom of the ketene with both termini of the alkene.^{8b} Asynchronous bond formation with generation of a short-lived biradical intermediate has also been proposed,^{8a} and all^{8a-c} of these studies emphasize that bond formation is much more advanced to one of the carbons of ethylene than the other. Theoretical studies of the reaction of the ketene radical cation with ethylene suggest that this reaction is best described as electrophilic attack of the terminal carbon of ketene radical cation to ethylene.^{8d} These fascinating stories^{7,8} will not be repeated here but are warmly recommended.

Ynol Esters. Laser photolysis of ketene in an argon matrix gives the tautomer ethynol (HC≡COH).^{9a} Ynols have also been generated in the gas phase,^{9b} in solution,^{9c} and in crystalline metal coordinated complexes.^{9d} Ynols are strongly acidic,^{9e} and ynolates (RC≡CO⁻), the conjugate bases of both ketenes and ynols, have become accessible synthetic intermediates.^{9f}

Ynol esters (RC≡COX; X = PhCO, PO₃Et₂, Ts) have also recently been prepared,^{9g} and the hydrolysis mechanisms of these ynol esters have been examined.^{9h} This is illustrated for the case of 1-propynyl benzoate, which reacts in acid by protonation on carbon to give a vinyl carbocation that leads to propanoic acid and benzoic acid as shown in eq 1.^{9h} In neutral solution the same acids are formed along with 1-(benzoxyloxy)-2-propanone (1, eq 2).^{9h} Compound 1 results from the cyclized dioxolene 2, as evidenced by ¹⁸O-labeling experiments and the isolation and purification of the methyl ether of 2 from the reaction of 1-propynyl benzoate in methanol.⁹ⁱ Precedent for this unusual cyclization exists for the corresponding thioalkynyl esters.^{9j}



Mechanistic Studies of Ketene Additions. The hydration reactivities of a representative group of ketenes in largely or totally aqueous solvents have now been measured, as summarized in Table I.^{10,11} There

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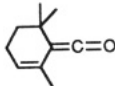
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Table I
Ketene Reactivities in H₂O and in H₂O/CH₃CN, 25 °C^{10,11}

ketene	solvent	k_{H^+} , M ⁻¹ s ⁻¹	k_{H_2O} , s ⁻¹	k_{OH^-} , M ⁻¹ s ⁻¹	k_{OH^-}/k_{H_2O}
CH ₂ =C=O	H ₂ O		44		
<i>n</i> -BuCH=C=O	H ₂ O	3.98 × 10 ³	99.4	3.29 × 10 ⁴	330
<i>t</i> -BuCH=C=O	H ₂ O		37.9 ^a		
Et ₂ C=C=O	H ₂ O		8.26 ^a		
<i>t</i> -Bu ₂ C=C=O	H ₂ O	434	1.57 × 10 ⁻⁴	—	—
PhCH=C=O	H ₂ O	—	4.77 × 10 ³	1.22 × 10 ⁶	260
Ph ₂ C=C=O	H ₂ O	—	275	6.11 × 10 ⁴	220
<i>i</i> -PrCPh=C=O	H ₂ O		1.23 ^b		
<i>t</i> -BuCPh=C=O	H ₂ O		0.370 ^a		
	H ₂ O	7.03	2.97 × 10 ⁻⁴	0.104	350
<i>t</i> -BuC(CO ₂ Et)=C=O ^d	H ₂ O		0.124	12.4	100
<i>t</i> -BuCH=C=O	20% CH ₃ CN	135	0.0780		
Et ₂ C=C=O	50% CH ₃ CN	13.0 ^c	0.10 ^c	79 ^c	790 ^c
<i>c</i> -Pr ₂ C=C=O ^d	50% CH ₃ CN		0.406		
<i>t</i> -PrCPh=C=O	50% CH ₃ CN	0.120	0.0424	58.4	1400
<i>t</i> -BuCPh=C=O	50% CH ₃ CN	0.488	0.00997	46.7	4700
<i>t</i> -Bu ₂ C=C=O	50% CH ₃ CN	3.6			

^a Extrapolated from values measured in H₂O/CH₃CN mixtures. ^b Average of values extrapolated from H₂O/CH₃CN and H₂O/dioxane mixtures. ^c Temperature 5.5 °C. ^d Reference 17c.

is a significant effect of structure on reactivity, as exemplified by the rate ratio for reaction in neutral H₂O $k(\text{PhCH}=\text{C}=\text{O})/k(\textit{t}\text{-Bu}_2\text{C}=\text{C}=\text{O}) = 3 \times 10^7$. This difference is readily understood in terms of the mechanism of eq 3, in which H₂O attack occurs at the LUMO on the less hindered side of C_α in the plane of the ketene. The crowded ketene *t*-Bu₂C=C=O is quite unreactive because of the bulky groups on each side of C_α. However, PhCH=C=O is very reactive because the phenyl group stabilizes the enolate-like transition state and one side of the ketene is unencumbered, presenting no steric barrier to nucleophilic attack.



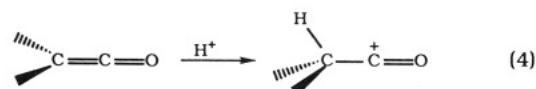
Further evidence for the importance of polar effects includes the Hammett correlation with $\rho = 1.9$ for the effect of aryl substituents in XC₆H₄CH=C=O.^{11b} The importance of steric effects in the ketene plane are illustrated by the similar H₂O reactivities of ketenes such as *n*-BuCH=C=O, *t*-BuCH=C=O, and CH₂=C=O. These have at least one side unencumbered, allowing the nucleophile to approach. Ketenes such as *i*-PrCPh=C=O and *t*-BuCPh=C=O with two sterically demanding substituents have low reactivity, consistent with this analysis.^{10c}

A calculated pathway for gas-phase hydration of ketene involves concerted addition of H₂O to the carbonyl group, giving an enediol.^{12b} Such enediols may well be transient intermediates in the solution-phase reactions, but the rate-limiting transition states have considerable polar character as shown in eq 3.

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The hydroxide-induced hydrolysis evidently resembles eq 3, with OH⁻ taking the role of the nucleophile. The rate ratios k_{OH^-}/k_{H_2O} are in the range 100–5000 for different ketenes, and the relative constancy of this ratio supports the similarity in the mechanism. However, the fact that the corresponding ratio for aldehyde and ketone hydration typically lies in the range 10⁵–10⁷ suggests a difference in these processes which is not understood.^{10a}

Acid-catalyzed hydrolysis shows different structure-reactivity patterns than the neutral and base reactions. Thus the rate ratio $k(\textit{n}\text{-BuCH}=\text{C}=\text{O})/k(\textit{t}\text{-Bu}_2\text{C}=\text{C}=\text{O})$ is 6.3 × 10⁵ for the neutral reaction, but only 9.1 in acid. The latter value shows that there are only modest structural barriers to protonation, which occurs in the plane perpendicular to that of the ketene and leads to an acylium ion (eq 4). The acylium ion is by far the most stable intermediate in ketene protonations by 6-31G*/3-21G calculations^{12a} and readily rationalizes the experimental results.

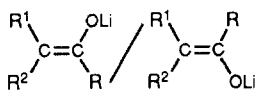


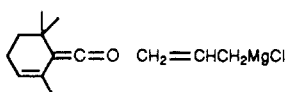
Aryl groups retard ketene protonation. Thus *t*-BuCH=C=O has k_{H^+} 277 times greater than for *t*-BuCPh=C=O,^{10c} and this closely resembles the average factor of 690 for protonation at the phenyl-substituted carbon of the *E* and *Z* isomers of PhCH=CHOCH₃.^{13a} The rate retardation is readily understood in terms of ground-state stabilization of the ketene and destabilization of the developing acylium ion *t*-BuCHPhC⁺=O by the phenyl. This substituent effect excludes a mechanism involving rate-limiting protonation on oxygen, which is not expected to be strongly affected by the groups at C_β.

The vinylketene 3 undergoes acid-catalyzed hydrolysis by protonation of the δ-carbon (eq 5).^{10c} This behavior is predicted by 6-31G*/3-21G calculations^{12a}

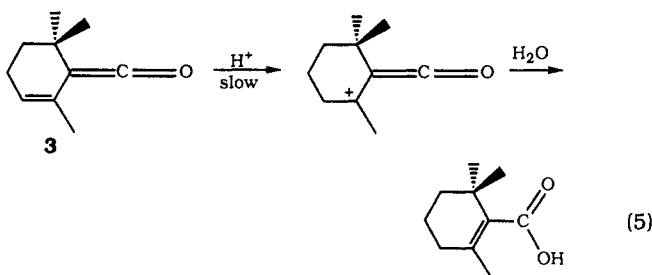
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Table II
Stereoselectivity in Ketene Additions According to Eq 7

R ¹	R ²	RLi		ref
<i>t</i> -Bu	H	<i>t</i> -BuLi	>95/5	15b
Et	Me	MeLi	1.7/1	16a
<i>i</i> -Pr	Me	MeLi	7.0/1	16a
<i>t</i> -Bu	Me	MeLi	>99/1	16a
<i>t</i> -Bu	<i>i</i> -Pr	<i>t</i> -BuLi	>95/5	17d
Ph	Me	<i>n</i> -BuLi	>95/5	15b
Ph	Et	<i>n</i> -BuLi	>95/5	15b
Ph	Et	Me ₃ SiLi	>95/5	17b
Ph	<i>i</i> -Pr	<i>t</i> -BuLi	1/4	17d
Ph	<i>t</i> -Bu	<i>t</i> -BuLi	<5/95	17d
Ph	<i>c</i> -Pr	<i>n</i> -BuLi	79/21	17c
Ph	<i>c</i> -Pr	<i>t</i> -BuLi	9/91	17c
Ph	<i>c</i> -C ₆ H ₉	<i>n</i> -BuLi	88/12	17d
Ph	<i>c</i> -C ₆ H ₁₁	<i>n</i> -BuLi	56/44	17d
			9/1	16b



and parallels the behavior of other 1,3-dienes, which also protonate on a terminal carbon.^{13b}



As noted above, hydration of ketenes may involve 1,1-enediols R₂C=C(OH)₂. These have been independently generated and observed spectroscopically when substituted with bulky aryl groups.¹⁴

Nucleophilic Additions. Synthetic Studies. Addition reactions to ketenes, including nucleophilic attack, were reviewed in 1986,^{15a} and the synthetic utility of the reaction of ketenes with organolithium reagents has continued to develop.¹⁵⁻¹⁷ Among the nucleophiles that have been examined are alkyl-, alkenyl-, alkynyl-, aryl-, and (trimethylsilyl)lithiums, and lithium and potassium enolates. The asymmetric synthesis of α -substituted alkanolic acids by the addition of chiral alcohols to ketenes has long been studied and has attracted further interest.^{18a}

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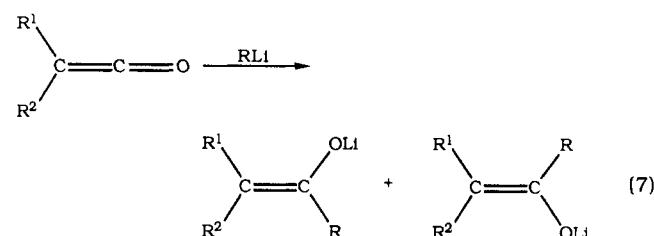
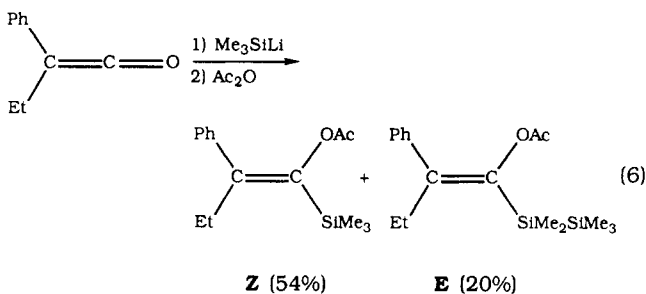
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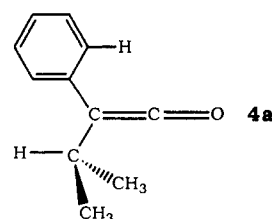
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Just as in hydration of ketenes (eq 3), addition of carbon nucleophiles to ketenes is expected to occur in the plane of the ketene. By trapping of the intermediate enolates by silylation or acetylation it has been demonstrated that approach occurs from the least hindered site as in the example of eq 6,^{17b} in which some Me₃SiMe₂SiLi was evidently generated during the preparation of Me₃SiLi. Many of the results obtained for eq 7 are compiled in Table II.

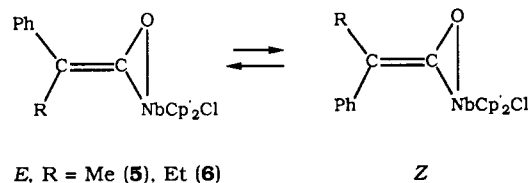


The steric situation in phenyl- α -alkylketenes such as phenylisopropylketene (4) is a dynamic one, in which the steric interaction of the incoming nucleophile with the syn substituent and the mutual interaction between the two ketene substituents are all involved. One extreme conformation (4a) has a planar phenyl group and maximum steric repulsion by the isopropyl methyls at C _{α} . Another extreme conformation has a perpendicular phenyl and minimal repulsion by the isopropyl methyls at C _{α} . In practice, attack from the phenyl side is favored in this case, and for phenyl-*tert*-butylketene this is the only mode of attack observed.^{17d} The *E/Z* product ratios also vary, depending upon the identity of the nucleophile,^{17c} as already observed for ketenes.^{17fg}



Bruno and co-workers have shown that the reaction of Cp'₂NbCl (Cp' = η^5 -C₅H₄SiMe₃) with PhCMe=C=O and PhC*t*Bu=C=O led to complexes 5 and 6, respectively. These exist as equilibrating mixtures of isomers, with *E/Z* ratios of 81/19 and 70/30 for 5 and 6, respectively.^{18b} The *E/Z* equilibration is slow, and an X-ray crystal structure of (*E*)-6 was obtained; the equilibration was shown to be intramolecular as exchange with added ketene did not occur during equilibration.

For reaction of LiOCR=CH₂ with ketenes, acylation of the enolate at either carbon or oxygen by the ketene may be envisaged. Interestingly, both of these processes are observed, with a strong preference for formation of the O-acylated lithium enolates 8 by relatively unhin-

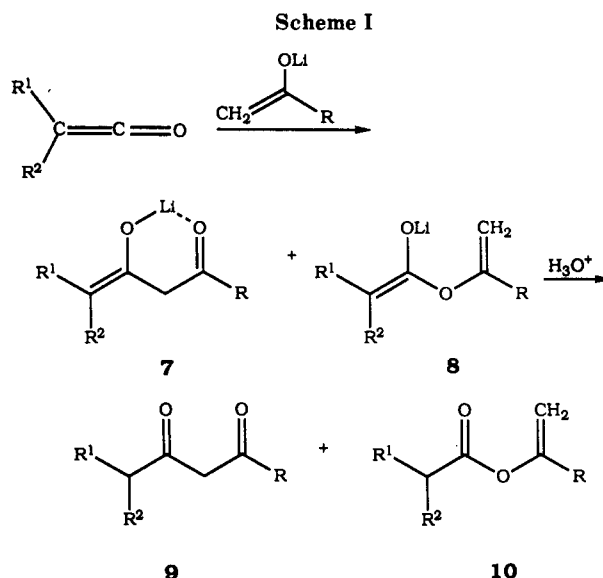


dered ketenes such as $\text{PhCMe}=\text{C}=\text{O}$ (Scheme I).^{17a,b} Even more surprisingly, the products isolated from potassium enolates and ketenes on long reaction times result from the exclusive C-acylation by ketenes to give 1,3-diketones 9. This result is directly opposite to the expectation that O-acylation is favored for potassium enolates and C-acylation for lithium enolates.

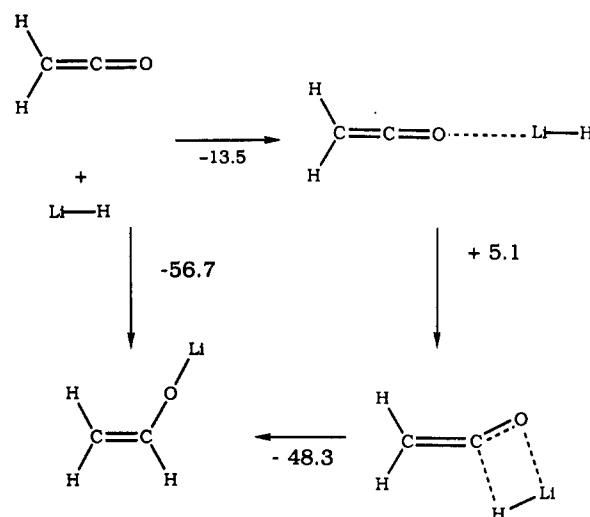
Experimental studies show that on prolonged reaction times the initial O-acylated lithium adducts 8 are converted to C-acylation products. The vinyl esters 10 resulting from O-acylation of potassium enolates may be isolated if the reactions are quenched after short reaction times at low temperatures.^{17b} These results indicate that O-acylation of both lithium and potassium enolates may be kinetically favored, but that the C-acylated products are thermodynamically more stable.

Nucleophilic Additions: Theoretical Studies. Important progress has been made recently in the theoretical understanding of the addition of LiH and organolithiums to carbonyl compounds including formaldehyde,^{19a-e} acetaldehyde,^{19a} carbon dioxide,^{19f} and acrolein.^{19g} We have now carried out 3-21G molecular orbital calculations of the interaction of ketenes with lithium reagents LiH, LiCH_3 , and $\text{LiOCH}=\text{CH}_2$. These reveal that all three of these reagents first form a complex involving O-Li interaction. The complex then proceeds to a transition state and product involving nucleophilic attack at C_α but maintaining the O-Li coordination.²⁰ This is illustrated in Scheme II for the reaction of ketene with LiH.^{20b}

These calculations do not consider solvation, but there is good reason to believe that solution-phase reactions do follow this same sequence. There is a strong resemblance between the calculated reaction pathway for ketenes with LiH, LiCH_3 , and $\text{LiOCH}=\text{CH}_2$ and for reaction of the same reagents with carbonyl compounds such as $\text{CH}_2=\text{O}$ and $\text{CH}_3\text{CH}=\text{O}$.^{19,20} The initially formed complexes with lithium coordinating to oxygen have been directly observed by both IR^{21a} and NMR^{21b} analyses for reactions of cyclohexanone with *n*-butyllithium. Solution NMR^{22a} and crystal structure analysis of solid enolates and aldol products^{22b,c} have shown the pervasive role of lithium coordination to oxygen atoms indicated by the calculations. The lithium reagents exist as aggregates, and the solvent interactions may not



Scheme II
Calculated Energy Changes (kcal/mol) for the Addition of
Lithium Hydride to Ketene (6-31G**/3-21G)



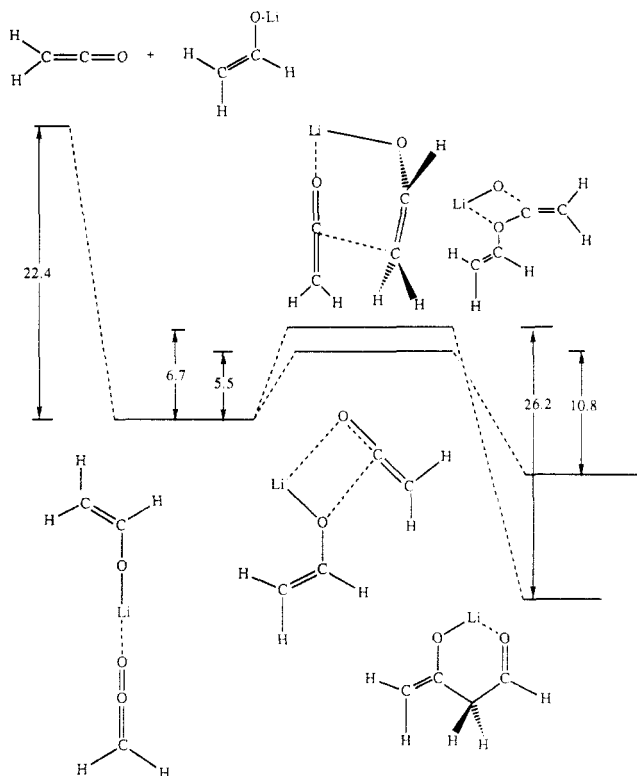
change greatly between reactants and products. There is also qualitative agreement between recent^{22a} thermochemical measurements of the heat of reaction for $t\text{-BuCH}=\text{O}$ and $t\text{-BuC(OLi)}=\text{CH}_2$ of -21.5 kcal/mol in hexane and the calculated gas-phase value of -40 kcal/mol for $\text{CH}_2=\text{O}$ and $\text{LiOCH}=\text{CH}_2$.^{20a} The less negative heat of reaction observed is expected for the former process because of the lower ground-state energy of $t\text{-BuCH}=\text{O}$.

Calculations at the 3-21G level for the reaction of LiH and LiCH_3 with $\text{CH}_3\text{CH}=\text{C}=\text{O}$ indicate no preference for the stereochemistry of addition of the former reagent, but indicate a 4 kcal/mol kinetic preference in the latter case for formation of the product with an anti disposition of methyl groups,^{20b} in conformity with the experimental trends shown in Table II. Experimental results have not been obtained with LiH, but the bulkier LiAlH_4 gives a 9/1 preference for attack anti to the phenyl in $\text{PhCR}=\text{C}=\text{O}$ ($\text{R} = \text{Me}, \text{Et}$).^{17e}

The 3-21G level calculations for the reaction of $\text{CH}_2=\text{CHOLi}$ with $\text{CH}_2=\text{C}=\text{O}$ (Scheme III) are also in accord with the experimental results. Thus the calculated barrier for O-acylation is 1.2 kcal/mol lower than for C-acylation, whereas the product of the latter

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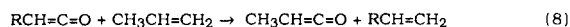
Scheme III
Calculated Relative Energies (kcal/mol) for O-Acylation
and C-Acylation of $\text{CH}_2=\text{CHOLi}$ by $\text{CH}_2=\text{C}=\text{O}$
(3-21G//3-21G)



process is 14.2 kcal/mol more stable.^{20a} Thus this level of theory does surprisingly well at predicting the experimental results in solution, even though the latter involves lithium aggregates and solvent. Evidently the changes in the interaction of the different species with the hexane solvent are not large enough to alter the qualitative agreement, and there is no large differential behavior induced by the state of aggregation.

Scheme III shows the overall mechanism for reaction of ketenes with enolates that agrees with both the experimental and theoretical results. There is initial formation of an O-lithiated complex, which undergoes preferential but reversible formation of the O-acylated adduct, but this can revert back to the complex and eventually to the much more stable C-acylated product. The greater stability of the O-acylated relative to the C-acylated transition structure evidently arises from more favorable lithium coordination in the former and steric repulsions in the latter.

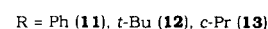
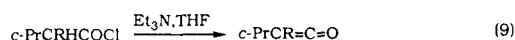
Conjugated Ketenes. A variety of substituted ketenes have been prepared and studied, but there has not been a systematic effort to understand the way in which the substituents influence the stability and reactivity of the ketenes. As an approach to this problem, we have now carried out *ab initio* molecular orbital calculations at the 3-21G//3-21G level for the isodesmic reaction of eq 8^{17c} and find ΔE (kcal/mol) for this process for selected conjugating substituents to be -1.9 (c-Pr), -0.1 ($\text{HC}\equiv\text{C}$), -0.2 ($\text{CH}_2=\text{CH}$), and 3.3 ($\text{O}=\text{CH}$).



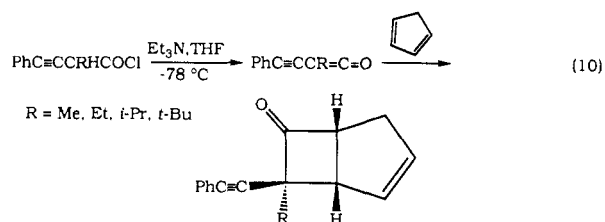
These results suggest that relative to methyl the cyclopropyl group is relatively more stabilizing as a substituent on ethylene compared to ketene, whereas the

reverse is true for formyl. There is a negligible preference for the vinyl and ethynyl groups compared to methyl. These ground-state energies do not give a direct measure of the reactivity of these ketenes, which will also be strongly influenced by the effect of the substituents on the transition states for reaction, but the calculations do suggest that experimental approaches to these ketenes are warranted.

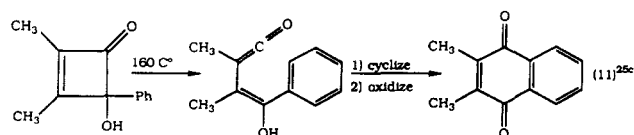
Cyclopropylketenes have been generated before²³ but only as reactive intermediates that were characterized by their IR spectra and reaction products. We find that the cyclopropylketenes 11-13 are readily prepared by the dehydrochlorination of the corresponding acid chlorides (eq 9) and are sufficiently long-lived for purification and full spectral characterization at room temperature.^{17c} Their reactivity toward hydration (Table I) and with alkyl lithium reagents (Table II) has also been examined.



Alkynylketenes with cyano and (trimethylsilyloxy) substituents have recently been obtained as reactive intermediates from thermolysis reactions.^{7a-c} We find that alkynylketenes with simple hydrocarbon substituents can be generated by dehydrochlorination of the acid chlorides and trapped with cyclopentadiene as single stereoisomeric adducts (eq 10).^{17c} The stereochemistry of the products follows the previously mentioned trend for ketenes to give the adducts expected from $[\pi_2\text{s} + \pi_2\text{s}]$ cycloaddition^{4,8} where the largest ketene substituent, even *tert*-butyl, occupies the hindered endo position in the product.²⁴



Some reactivity studies of the persistent vinylketene 3 are noted above (eq 5).^{10c} Vinylketene intermediates are also formed from thermal ring opening of cyclobutenones and cyclize to six-membered rings. This process is being actively studied by three different groups²⁵ and is illustrated in eq 11. Vinylketenes also give intermolecular cycloadditions to useful adducts.^{24c}



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The acylketene $t\text{-BuC}(\text{CO}_2\text{Et})=\text{C}=\text{O}$ is also persistent^{26a} and is found to be considerably more reactive than **3** in hydration, but less reactive than $n\text{-BuCH}=\text{C}=\text{O}$ (Table I).^{17c} Other studies of acylketenes have recently appeared.^{26b,c}

The second golden age of ketene chemistry is just beginning. New syntheses of ketenes are being developed,²⁷ new classes and reactions of ketenes are being

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found, and there is a better understanding of ketene structure and reactivity. But many potentially useful ketenes have not yet been made, and many attractive reactions have not been explored, so the thrill of discovery still awaits the investigator of these fascinating compounds.

Our work would not have been possible without the contributions of a group of co-workers of rare charm and talent, who are cited in the references. Financial support by the National Sciences and Engineering Research Council of Canada and the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged. Thanks are due to Professors Houk and Bernardi for preprints of ref 8a and 8b, respectively.

Gas-Phase Ion/Molecule Reactions as Studied by Fourier Transform Ion Cyclotron Resonance

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Introduction

Studies of reactions between ions and molecules in the gas phase have received considerable interest over many years. This derives mainly from the fact that such studies in principle can provide a detailed and often quantitative insight into the intrinsic reactivity and properties of the ions and molecules involved based upon their interactions in the absence of solvent molecules or counterions. This insight in turn may lead to a better understanding of the role of solvent molecules or counterions in reactions that take place in the condensed phase and is very relevant to theoretical considerations and calculations.

Equally important to note is that the research interest in gas-phase ion/molecule reactions has grown because of the development of instrumental methods such as chemical-ionization mass spectrometry,¹ flowing afterglow,² and Fourier transform ion cyclotron resonance (FT-ICR).³ The last method, first introduced by Comisarow and Marshall in 1974,⁴ has blossomed since 1980.

This paper will give an account of a variety of results of research carried out in my group⁵ concerning gas-phase organic ion/molecule reactions as studied by the FT-ICR method. The principles of this method have been described in other recent reviews.^{3,6-8}

Nico M. M. Nibbering was born in Zaandam, The Netherlands, in 1938. He studied physical organic chemistry at the University of Amsterdam, where he received his Ph.D. degree in 1968 under the direction of Thymen J. de Boer. Since 1966 he has been a faculty member in the Department of Chemistry at the University of Amsterdam, where he became associate professor in 1975 and full professor of organic mass spectrometry in 1980. He is director of the Institute of Mass Spectrometry, founded in 1988 by the Department of Chemistry at the University of Amsterdam. In 1989 he became a member of the Royal Netherlands Academy of Arts and Sciences. His current research interests include unimolecular gas-phase ion chemistry as studied by time-resolved mass spectrometry via the method of field-ionization kinetics and bimolecular gas-phase ion chemistry as studied by chemical-ionization and Fourier transform ion cyclotron resonance mass spectrometry.

Experimental Method

The heart of an FT-ICR spectrometer is the so-called trapped-ion cell, which may have different geometries, one of them being cubic (usually 2.54 cm long) (Figure 1). Ions in this cell, which is located in a high-vacuum chamber ($\leq 10^{-5}$ Pa) between the poles of an electromagnet or a superconducting magnet, are generated from gas-phase sample molecules by an electron beam pulse or from solid samples by, for example, a laser pulse. The ions move in circular orbits perpendicular to the direction of the magnetic field, B , and are trapped in the cell by a potential of about -1 V, in the case of anions, on the trapping plates. The angular or cyclotron frequency ω_c of the ions, which have nearly thermal translational energies and random phases in their cyclotron motion, is given to a first approximation by eq 1, where q is the charge, v the velocity, m the mass of the ion, and r the radius of its circular orbit.

$$\omega_c = v/r = qB/m \quad (1)$$

One of the methods used to detect the ions after a certain trapping time (1-100 ms), i.e., the time between ion formation and ion detection (Figure 2), is to apply a fast-swept radio-frequency field of 1-2 MHz/ms to one of the pair of plates of the cell parallel to the magnetic field lines (transmitter plates). This excites the ions translationally and brings them into a large

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