(η-C_5H_5)$_2Co_2SB_5H_7$.[12] Other isoelectronic clusters, such as *nido*-B_8H_{12},[13] *nido*-(η^6-$(CH_3)_6C_6$)$FeMe_4C_4B_3H_3$,[14] and *nido*-(η-C_5H_5)$CoPh_4C_4B_3H_3$,[15] have been shown to adopt structures based on a 10-vertex bicapped square antiprism missing two vertices, which is the same geometry expected for 8-vertex arachno clusters.[11] Thus, the question of which is the preferred geometry for 8-vertex nido cages has been a longstanding problem in cluster chemistry.[11e,f]

The NMR spectra obtained for 4,7-$C_2B_6H_{10}$ were originally interpreted as consistent with either static arachno or fluxional nido structures in solution. A recent ab initio/IGLO/NMR study[16] strongly favors the static structure for 4,7-$C_2B_6H_{10}$; however, its structure has not yet been crystallographically confirmed.

A single-crystal X-ray study of Bu_4N^+*nido*-4,5-$C_2B_6H_9^-$ confirmed the arachno-type structure shown in Figure 1,[17] and it is thus the first structural confirmation of this geometry for the parent carborane system. The carbon atoms occupy adjacent positions on the puckered six-membered open face with the single bridge hydrogen located at the B3-B6 edge, across from the carbons.

Ab initio[18]/IGLO[19]/NMR calculations[20] likewise favor an arachno-type geometry for *nido*-4,5-$C_2B_6H_{10}$, with the asymmetric placement of hydrogens in structure **1a** (C_1 symmetry) being favored over the symmetric arrangement in **1b** (C_s) (Figure 2). The 160.5-MHz ^{11}B NMR spectra[4,7] of K^+*nido*-4,5-$C_2B_6H_9^-$ and *nido*-4,5-$C_2B_6H_{10}$ both display a 2:1:2:1 ratio of resonances suggesting similar cage geometries, but also suggest a symmetric (**1b**) rather than asymmetric (**1a**) arrangement of bridging protons in the parent. However, the broad appearance of the B3,6 resonance in the spectrum of **1** suggests dynamic behavior. Indeed, rapid bridge-proton rearrangements across the B3-B8, B7-B8, and B6-B7 edges in **1** could account for both the apparent mirror symmetry present in the ^{11}B NMR spectrum and the broad nature of the B3-B6 resonance.

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Supplementary Material Available: Tables of positional parameters, anisotropic temperature factors, bond distances, and bond angles (12 pages); table of observed and calculated structure factors (10 pages). Ordering information is given on any current masthead page.

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(20) At the HF/3-21G level of ab initio theory, **1a** is ~22 kcal/mol more stable than **1b**. DZ//3-21G IGLO ^{11}B NMR chemical shifts for **1b** are δ 45.0 (B1), 29.2 (B7,8), -2.7 (B3,6), and -15.8 (B2), while those for **1a** are δ 38.9 (B8), 2.4 (B1), -12.7 (B3), -10.8 (B7), -16.4 (B6), and -20.7 (B2). Averaging the values of B3,B6 and B7,B8 for **1a** give the shifts for the proposed dynamic structure of **1** in solution of 14.1 (B7,8), 2.4 (B1), -14.5 (B3,6), and -20.7 (B2).

An ab Initio Study on the Mechanism of the Ketene-Imine Cycloaddition Reaction

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The ketene-imine cycloaddition reaction is one of the most widely used methods in the synthesis of the β-lactamic rings.[1,2]

In 1907, Staudinger[3] reported the first synthesis of a β-lactam by a [2 + 2] cycloaddition of diphenylketene with benzylideneaniline at 200 °C. The Staudinger reaction is now widely employed in the preparation of β-lactams, because it provides direct access to these compounds from simple precursors; in addition, there is increasing interest in the problem of control of the induction of asymmetry in the reaction.[4]

Nevertheless, despite the synthetic interest, the actual mechanism of the Staudinger reaction is still unclear.[1] The most widely accepted mechanism involves the participation of a ketene generated from an acid halide precursor under basic conditions;[5] the ketene generated in situ will cycloadd to the imine, leading to the β-lactam derivative (see Figure 1). According to the experimental results of Moore and co-workers,[6] the cycloaddition of the ketene to the imine is a two-step zwitterionic process rather than a concerted one (Figure 1). This mechanistic proposal is supported by the detection of the zwitterionic intermediate by infrared spectroscopy in thermal reactions of ketenes with imines[7a] and by a detailed kinetic analysis with low-temperature FT-IR spectroscopy.[7b]

The related reaction of ketene with alkenes has been studied theoretically by Burke,[8] by Bernardi and co-workers,[9] and by Wang and Houk.[10] The results of these calculations show that this reaction has a very asynchronic transition structure, with an appreciable charge separation, but no intermediates were located.

In this communication we report the first ab initio study on the mechanism of the Staudinger reaction.[11] Ketene plus form-

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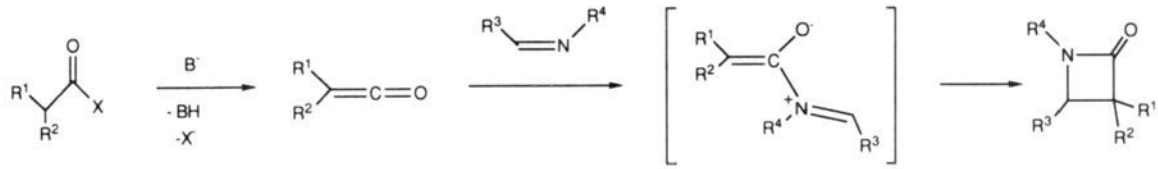

Figure 1. Proposed mechanism for the Staudinger reaction.

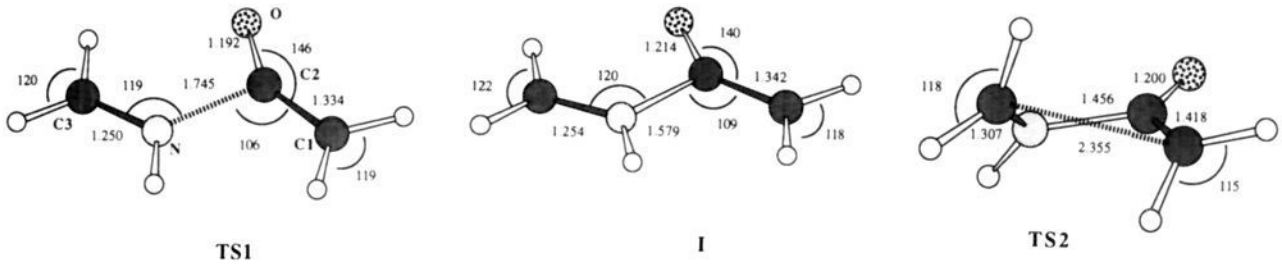

Figure 2. RHF/6-31G* optimized transition structures (TS1 and TS2) and intermediate (I) for the ketene–imine cycloaddition reaction. Lengths are in angstroms and bond angles in degrees.

aldimine has been chosen as a model system. Computations were performed by full optimization of the geometry. Stationary points have been characterized by calculation of the Hessian matrix. Examination of the transition structures shows that a conrotatory electrocyclic closure is the rate-determining step of a two-step mechanism.

In sharp contrast with the above mentioned reaction of ketene with alkenes, we have found in the study of the reaction of formaldimine with ketene a dramatic basis set dependence of the number and qualitative nature of the critical points. An extensive search at the RHF/3-21G level gave a concerted but very asynchronic mechanism in disagreement with experimental data.[6,7] The 3-21G transition structure is 33.9 kcal/mol above the reactants and shows C–N and C–C forming bond lengths of 1.478 and 2.359 Å.

Satisfactory agreement with experiment is obtained by using the 6-31G* basis set. Accordingly the Staudinger reaction was studied at RHF/6-31G* and RMP2/6-32G* theory levels. At both levels a nonconcerted mechanism was found. Our calculations predict the reaction to proceed through a first transition structure (TS1, Figure 2) leading to a zwitterionic intermediate (I, Figure 2) in agreement with the experiment,[7] which transforms into the product through a second transition structure (TS2, Figure 2). The energies of these systems are given in Table I. We present here the most interesting features of these stationary points at the RMP2/6-31G* level; for comparison the RHF/6-31G* values are given in parentheses.

The first transition structure, TS1 (see Figure 2), corresponds to the nucleophilic addition of the imine to the electrophilic ketene, to give a zwitterionic intermediate, I (see Figure 2). The length of the bond being formed (iminic N–central C of the ketene) in the first transition structure is 1.751 Å (1.745 Å), almost a fully formed single bond; also, the Mulliken population analysis shows a significant charge transfer, 0.216 electrons, from the imine to the ketene moiety in the transition structure TS1 (0.211 electrons). This first transition structure has an activation energy of 3.7 kcal/mol (12.5 kcal/mol) and leads to an intermediate, I, which is just 0.2 kcal/mol (0.4 kcal/mol) more stable than TS1.

The intermediate I has a planar geometry, with a bond length between the nitrogen and the central carbon of the ketene of 1.587 Å (1.579 Å). The zwitterionic character of I is shown in its important charge separation: the Mulliken charges on C1, C3, O, and N (see Figure 2 for numbering scheme) are −0.291, 0.505, −0.724, and −0.215 electrons, respectively (−0.304, 0.495, −0.712, and −0.205); in the separated reactants, the charges on the same atoms are −0.110, 0.225, −0.470, and −0.225 electrons, respectively (−0.134, 0.225, −0.438, and −0.225). This strong charge separation is consistent with the experimental observations in the reaction of ketenes with imidazole.[6,7] This planar conjugated π-system is more stable than the proposed intermediate for the ketene–ethylene reaction, where the cationic and anionic centers are in different planes and separated by a CH_2 group.[8]

The next step in the reaction path is the closure of the intermediate I, to give the 2-azetidinone. A saddle point connecting the two structures (TS2, Figure 2), corresponding to an electrocyclic conrotatory closure, was located. This transition structure has an activation energy of 21.3 kcal/mol (39.6 kcal/mol), making it the transition structure of the rate-determining step of the ketene–imine cycloaddition reaction. The forming bond length in this transition structure between C1 and C3 is 2.465 Å (2.355 Å), with the hydrogens attached to these terminal carbons rotated out of plane, and the four atoms, C1, N, C2, and C3 twisted with a dihedral angle of 39.2° (36.2°).

It is interesting to note the close similarity between TS2, corresponding to the electrocyclic conrotatory closure of the intermediate I, and the transition structures of the electrocyclic ring opening of cyclobutenes located by Houk and co-workers.[13] Accordingly, it will be interesting to ascertain if torquoelectronic effects[13e,f] are involved in the control of the stereochemistry of

Table I. Relative Energies (kcal/mol) of the Intermediate and Transition Structures for the Ketene–Imine Cycloaddition Reaction, Compared to the Reactants[a]

species	RHF/6-31G*	RMP2/6-31G*
TS1	12.5	3.7
I	12.1	3.5
TS2	39.6	21.3

[a] The total energies (au) of the reactants are as follows: ketene −150.876 53 (RHF/3-21G), −151.724 67 (RHF/6-31G*), −152.160 08 (RMP2/6-31G*); imine −93.494 78 (RHF/3-21G), −94.028 46 (RHF/6-31G*), −94.323 08 (RMP2/6-31G*). The total energies of the transition structures are the following: TS1 −245.733 15 (RHF/6-31G*), −246.477 21 (MP2/6-31G*); 3-21G transition structure −244.317 28; TS2 −245.690 03 (RHF/6-31G*), −246,449 20 (RMP2/6-31G*). The total energies of the intermediate and the product are as follows: I −245.733 87 (RHF/6-31G*), −246.477 61 (RMP2/6-31G*); 2-azetidinone −244.432 94 (RHF/3-21G*), −245.810 43 (RHF/6-31G*), −246.5488 (RMP2/6-31G*).

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ketene–imine cycloaddition reactions in the substituted systems.

The structure of the 2-azetidinone was optimized at the RHF/3-21G, RHF/6-31G*, and RMP2/6-31G* levels; the heat of reaction is calculated to be -38.7, -35.9, and -41.2 kcal/mol, respectively.

In summary, the problem of the mechanism of the ketene–imine cycloaddition reaction has been addressed by ab initio calculations. A very strong dependence of the predicted mechanism on the basis set has been found. At the RHF/3-21G theory level the reaction is a concerted but very asynchronic process, while at RHF/6-31G* and MP2/6-31G* theory levels the reaction is not a concerted cycloaddition, but a two-step process with a zwitterionic intermediate, in agreement with all experimental findings. The electrocyclic conrotatory closure of this intermediate leading to transition structure TS2 is predicted to be the rate-determining step of the process. Further work to study the effect of substituents in the energetic and stereochemistry of the process is in progress.

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Registry No. I, 930-21-2; ketene, 463-51-4; formaldimine, 2053-29-4.

Structure-Induced Carbon-13 Chemical Shifts: A Sensitive Measure of Transient Localized Secondary Structure in Peptides

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NMR methods based on nuclear Overhauser effects (NOEs) have become routine tools for determining the secondary and tertiary structure of proteins and peptides in solution.[1] One drawback to these methods, however, is that NOEs require tens to hundreds of milliseconds to manifest themselves, and therefore the existence of multiple conformations in rapid exchange complicates quantitative interpretation of the data. Because of its much faster time scale, circular dichroism (CD) is often more useful in assessing secondary structure[2] in systems such as flexible peptides. It is not possible, however, to distinguish between conformational flexibility and local differences in structure on the basis of CD spectra alone. Recently, Spera and Bax[3] demonstrated that strong correlations exist between the Cα and Cβ chemical shifts and backbone conformation in proteins of well-defined structure. The effect of secondary structure on CαH and NH proton chemical shifts has been reported,[4] but a strict interpretation of these shifts is complicated because, unlike ^{13}C chemical shifts, they are affected by other anisotropic factors such as ring current effects and hydrogen bonding. In this report we demonstrate that the Cα chemical shifts are a sensitive means of identifying domains of polypeptides that have a propensity toward α-helix formation.

Bombesin is a well-characterized 14 amino acid peptide known to exist as a random coil in H_2O solution and to adopt a helix between Asn-6 and Met-14 at high concentrations of 2,2,2-trifluoroethanol (TFE)[5] and in phospholipid bilayers.[6] The effect of up to 70% (by volume) of TFE on the CD spectrum of bombesin in aqueous solution is shown in Figure 1. The increase in negative ellipticity, Θ, at 220 nm as a function of TFE concentration is indicative of increasing helical content. These results, however,

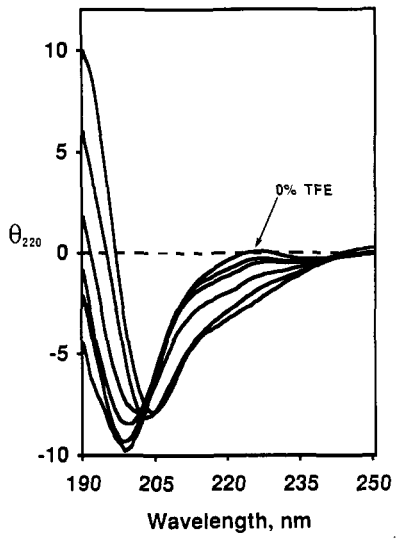

Figure 1. CD spectra of bombesin as a function of TFE concentration. The spectrum of bombesin in H_2O (0% TFE) is indicated. Successive traces (decreasing θ_{220}) are 10%, 15%, 20%, 30%, and 70% TFE (v/v). The averaged spectra (three independent acquisitions) were recorded on a 0.6 mg/mL sample in a 0.1-cm cell. The results were subtracted from the spectrum of a solvent blank and smoothed with a third-order polynomial.

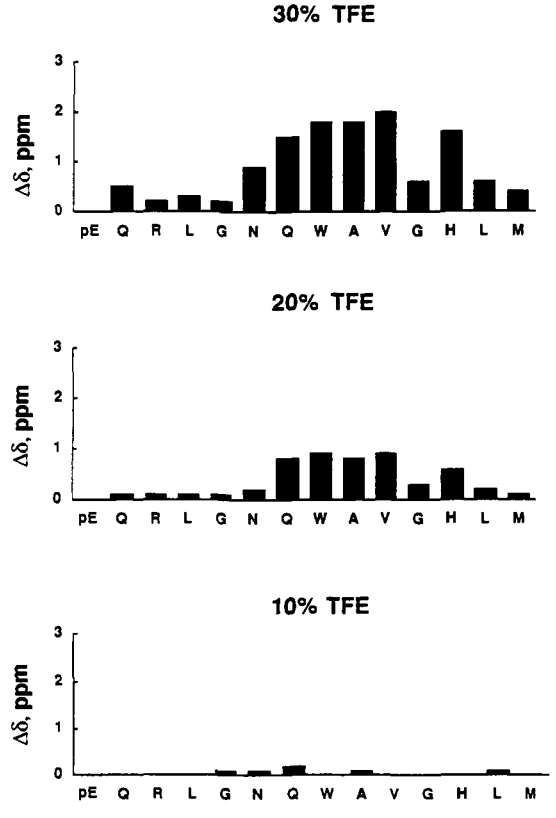

Figure 2. Secondary chemical shifts, Δδ (ppm), of the Cα carbons in bombesin as a function of added TFE. The heights of the bars indicate the change in chemical shift ($\Delta\delta = \delta_{obsd} - \delta_{^2H_2O}$) for each of the Cα carbons relative to the chemical shift measured in 100% ^2H_2O solution, where bombesin is known to exist as a random coil (see text). The NMR measurements were made on 5 mg of bombesin dissolved in H_2O or ^2H_2O mixed with varying amounts of TFE (ca. 0.5 mL total volume) at pH ~3.1, 298 K. Proton assignments were made on the basis of sequentially related NOEs, and heteronuclear multiple quantum coherence (HMQC) spectroscopy was then used to correlate carbon resonances to the assigned protons. HMQC experiments were recorded at natural abundance of ^{13}C in ^2H_2O and increasing amounts of TFE in ^2H_2O.

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