showed bands at 2990 cm^{-1} (s, CH), 2240 cm^{-1} (w, CN), and 1740 cm^{-1} (s, CO). The coupled ^{13}C NMR spectrum ($CDCl_3$) showed a carbonyl singlet at δ 167.4, a vinyl triplet (J = 166.0 Hz) at δ 132.7, a vinyl singlet at δ 122.4, a nitrile singlet at δ 117.1, a quaternary carbon singlet at δ 84.5, a quaternary carbon singlet at δ 68.8, and a methyl quartet (J = 126.0 Hz) at δ 28.2.

β-Methylene-D,L-asparagine (I). A solution of 10.00 g (0.035 mol) of amino diester nitrile VI in 400 mL of 20% hydrochloric acid was heated at 40 °C for 12 h. The reaction mixture was concentrated under vacuum yielding a solid residue weighing 8.72 g. The solid was taken up in water, treated with 500 mg of charcoal, and filtered, yielding 7.48 g of yellow-white solid. This substance was then cooled to 0 °C and treated with small portions of cold (0 °C) 2 N sodium hydroxide until the solid dissolved and the pH of the solution became 5.5. At this point 2.8 g of a white solid precipitated from the solution. The mother liquor was concentrated, yielding an additional 1.49 g of tan solid. Recrystallization of the second crop from 8 mL of hot water yielded 938 mg of white crystalline product. The total combined weight was 3.738 g (72%). The NMR spectrum (D_2O/TSP reference) was taken of the hydrochloride and showed three singlets at δ 4.81, 6.12, and 6.39, corresponding to the methine and two vinyl protons. The proton-coupled carbon-13 NMR spectrum (D_2O, DCl, TSP reference) showed a methine doublet of quartets (^1J = 144.0, ^3J = 7.3 and 12.2 Hz) at δ 56.3, a vinyl methylene triplet of doublets (^1J = 161.1, ^3J = 4.9 Hz) at δ 131.2, a quaternary vinyl singlet (broadened and very slightly split) at δ 135.7, an amide carbonyl multiplet at δ 170 .7, and carboxyl doublet (^2J = 4.9 Hz) at δ 171.6.

The infrared spectrum (KBr) showed bands at 3450–3100 cm^{-1} (-OH, NH), 1600 cm^{-1} (C=O), 1495 cm^{-1}, and 1385 cm^{-1}. The negative LD mass spectrum showed m/z (relative intensity) 144 (100, M^-), 100 (33, $M^- - CO_2$), 82 (80, $C_4H_4ON^-$), 43 (44, $CHON^-$), 37, 35 (17, 85, Cl^-), and 28 (25, CN^-). The positive LD mass spectrum showed m/z (relative intensity) 190 (67, MNa_2^+), 81 (14, $C_4H_3ON^+$), and 22 (100, Na^+).

The amino acid I does not have a sharp melting point; it begins to decompose at 160 °C, becoming progressively darker as the temperature is raised above this point.

***N*-Acetyl-β-methylene-D,L-asparagine (VIII).** A suspension of 30 mg (0.16 mmol) of the amino acid I in 175 μL of H_2O was treated with 48 mg (0.47 mmol) of acetic anhydride. After stirring for 10 min, the reaction mixture became homogeneous and was allowed to stir an additional 20 min. The reaction mixture was then evacuated under high vacuum, yielding 34 mg (93%) of white foamy acetylated amino acid VII. The 60-MHz proton NMR spectrum (D_2O) showed a one-proton vinyl snglet at δ 5.96, a one-proton vinyl singlet at δ 5.76, a one-proton methine singlet at δ 5.20, and a three-proton acetate singlet at δ 1.96. The IR spectrum (KBr) showed bands at 3300 cm^{-1} (s, OH) and 1740 cm^{-1} (s, CO). The mass spectrum (15 eV) showed peaks at m/z (relative intensity) 170 (100, $C_7H_8O_3N_2^+$), 128 (50, $C_5H_6O_3N^+$), 127 (47, $C_5H_7O_2N_2^+$), and 43 (33, $CHNO^+$).

Hydrolysis of I to β-Methylene-D,L-aspartic Acid. A solution of 500 mg (0.003 mol) of β-methylene-D,L-asparagine (I) in 20 mL of 20% hydrochloric acid was heated at 70 °C for 60 h. The reaction mixture was concentrated under vacuum, leaving a solid residue of off-white solid. The total recovered weight was 425 mg (82%). The NMR spectrum (D_2O/TSP reference) showed three singlets at δ 5.02, 6.37, and 6.73, identical with the spectrum of an authentic sample of β-methylene-D,L-aspartic acid.

Acknowledgment. We are grateful to Zbigniew A. Wilk for obtaining the LD mass spectrum of the final product amino acid (I).

Registry No. I, 94859-90-2; II, 94859-91-3; III, 94859-92-4; IV, 94859-93-5; V, 94859-94-6; VI, 94859-95-7; VII, 94859-96-8; VIII, 94859-97-9; β-methylene-DL-aspartic acid, 71195-09-0; 2-bromopropionitrile, 19481-82-4; 2-bromopropionamide, 5875-25-2; di-*tert*-butyl malonate, 541-16-2.

Notes

Leaving Group Ability and pK_a in Elimination Reactions

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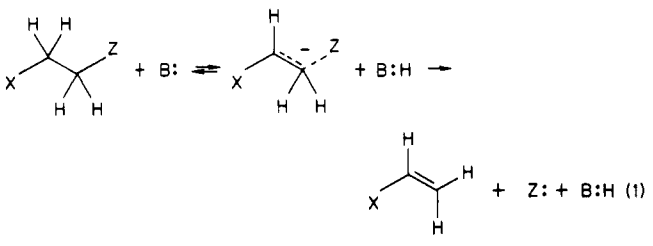
Alkene-forming elimination reactions are known to be sensitive to variations of the leaving group.[1] In the case of base-promoted, alkene-forming 1,2-eliminations, the rate of reaction depends primarily on the leaving group Z when the activating group X is constant. Rate data reported[2]



for a diverse set of Z groups when X = $PhSO_2$ span a range of at least 10^{16}. By comparing these rates to pK of the acid Z–H, C–Z bond strength, and the rate of reaction of the free leaving group with methyl iodide, Stirling et al. concluded that reactivity shows no correlation with these molecular properties for neutral leaving groups.[2] It has been emphasized repeatedly that there is no general correlation of the leaving group ability with pK_a of Z–H in water.[1-4] On the other hand, others have adopted the simple idea that the acidity of Z–H can parallel reactivity in mechanisms involving departure of a leaving group for a "related" series of structures.[5]

Recently, Stirling et al.[6] have pointed out that a corre-

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(5) See, e.g.: Gould, E. S. "Mechanism and Structure in Organic Chemistry"; Holt, Rinehart, and Winston: New York, 1959; pp 258–263. Hine, J. "Physical Organic Chemistry"; McGraw-Hill: New York, 1962; p 182. Vail, S. L.; Petersen, H. *Ind. Eng. Chem., Prod. Res. Dev.* **1975**, *14*, 50. Carey, F. A.; Sundberg, R. J. "Advanced Organic Chemistry. Part A. Structure and Mechanisms"; Plenum: New York, 1977; p 212. Maartmann-Moe, K.; Sanderud, K. A.; Songstad, J. *Acta Chem. Scand., Sect. B* **1982**, *36*, 211.

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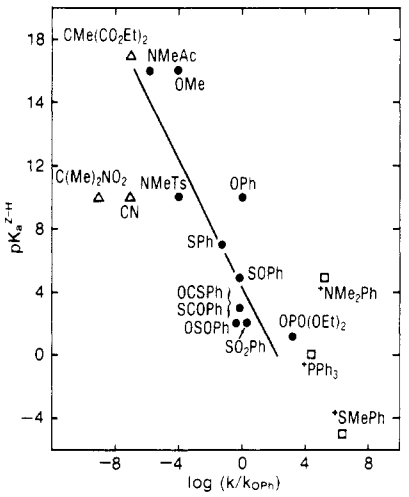
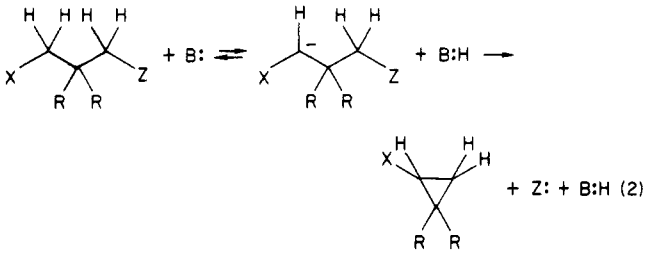


Figure 1. pK_a of the conjugate acid of the leaving group and relative reaction rates for 1,2-elimination. The regression line is fit to the data for eleven Z groups (solid circles). Two of these points coincide. The rates for the three Z groups linked through carbon (open triangles) were only determined to be *less* than the value plotted. The three onium Z groups are denoted by open squares.

lation between leaving-group ability and pK_a does exist for 1,3-eliminations (2) and that even in 1,2-eliminations good



correlations exist if the variation in the leaving group is small. In the present study, regression analysis is used to show that for a broad range of leaving groups in reaction 1 a relationship between acidity and reaction rate can exist.

Let us reexamine the data of Stirling et al., for the case of 1,2-elimination (1), which was the basis of their original conclusion.[2] Reaction rates relative to that for Z = OPh were reported for 19 Z groups. The data were incomplete or not exactly quantitative for five of the Z groups. Data were reported for only three onium groups (Z^+), which is too few to conclude anything statistically. For the remaining eleven Z groups, regression analysis can be done to find the following correlation with pK_a^{Z-H}. The sta-

$$\log (k/k_{OPh}) = -1.96pK_a^{Z-H} + 4.84 \qquad (3)$$

$$n = 11 \quad r = -0.85 \quad r^2 = 0.72 \quad s = 3.0$$
$$p = 0.0009$$

tistics clearly reflect the scatter of the data points as seen in Figure 1. The standard error of estimate of 3.0 is large. However, the variation in pK_a^{Z-H} is, nevertheless, able to explain 72% of the variance in the relative reaction rate, and the correlation is statistically significant with greater than 99% probability of not being fortuitous. Note that the regression includes a diverse set of Z groups linked through C–N, C–O, and C–S bonds. Qualitatively similar results are obtained by plotting nucleofugality ranks[3,6] against pK_a^{Z-H}.

Whereas Figure 1 shows that relative leaving-group ability (or nucleofugality[3,6]) does not vary monotonically with acidity of Z:H, the trend is apparent and in the direction expected. Even though not all data points shown in Figure 1 could be included in the regression, it is noteworthy that the excluded points roughly follow the trend. Of course, it is always possible to select a few isolated points from a figure like Figure 1 to claim there is no simple correlation.

Acids Z:H that dissociate more easily can, in some instances, correspond to leaving groups that promote the elimination reaction. It is true, based on the published data,[2] that the nucleophilicity of Z: is not related to rate of elimination. The important property of the leaving group is being able to stabilize the electron density transferred to it in the course of the reaction.[7-9] The leaving group must be able to act as an electron sink in the transition state for elimination. Thus, properties like inductive effect, electron affinity, and polarizability of Z can be expected to be related to leaving-group ability.

Acknowledgment. W. H. W. Lunn and C. J. M. Stirling provided helpful comments on the manuscript.

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Elucidating the Leaving Group Effect in the β-Lactam Ring Opening Mechanism of Cephalosporins

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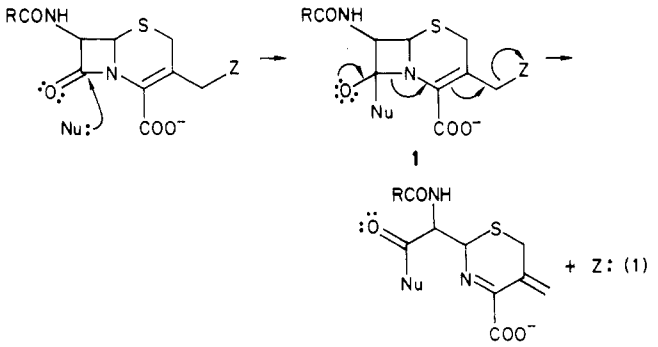
Antibacterial activity of cephalosporins against sensitive Gram-negative pathogens is observed to be better when there is a potential leaving group at the 3′ position.[1-4] One possible explanation of this fact is that when the serine hydroxyl group in the active site of the target enzymes is acylated by the β-lactam ring, acylation proceeds at a rate influenced by both the inductive effect and leaving group ability of Z. The neighboring-group participation of Z can be denoted summarily by 1. However, as has been care-



fully pointed out before,[1,2,4] mechanism 1 can take place

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