graphs indicated triclinic Laue symmetry and yielded approximate cell dimensions. The crystal used for data collection was then transferred to our Enraf-Nonius CAD-4 diffractometer[51] and centered in the beam. Automatic peak search and indexing procedures yielded a triclinic reduced primitive cell. Inspection of the Niggli values[52] revealed no conventional cell of higher symmetry.

The 8563 unique raw intensity data were converted to structure factor amplitudes and their esd values by correction for scan speed, background, and Lorentz and polarization effects. Inspection of the intensity standards revealed a reduction of 5.5% of the original intensity. The data were corrected for this decay. Inspection of the azimuthal scan data showed a variation $I_{min}/I_{max} = 0.92$ for the average curve. An empirical correction based on the observed variation was applied to the data.

The structure was solved by Patterson methods and refined via standard least-squares and Fourier techniques. The benzene of solvation was discovered in a difference Fourier map after all of the expected atoms in the molecule were discovered. In a difference Fourier map calculated following the refinement of all non-hydrogen atoms with anisotropic thermal parameters, peaks were found corresponding to the positions of most of the hydrogen atoms. Hydrogen atoms were assigned idealized locations and values of B_{iso} approximately 1.3 times the B_{eqv} of the atoms to which they were attached. They were included in structure factor calculations but not refined. Hydrogen atoms for the benzene were not included. Details of the structure determination are given in Table II.[53]

The quantity minimized by the least-squares program was $\sum w(|F_o| - |F_c|)^2$, where w is the weight of a given observation. The p factor, used to reduce the weight of intense reflections, was set to 0.03 throughout the refinement. The analytical forms of the scattering factor tables for the neutral atoms were used and all scattering factors were corrected for both the real and imaginary components of anomalous dispersion.[54]

The structure consists of two independent molecules of the compound and a molecule of benzene packed in the unit cell. While the molecules are similar, they are not identical, having significant differences in the torsion angles, especially in the triphenylphosphine group. Selected bond distances and angles are given in Table III.

Acknowledgment. We are grateful for financial support of this work from the National Institutes of Health Grant No. GM 35669 We particularly wish to thank Dr. Mark Gallop for his assistance with the NOE experiments. We also thank Mr. Charles McElroy for experimental assistance.

(51) For a description of the X-ray diffraction and analysis protocols used, see: Hersh, W. H.; Hollander, F. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 5834-46.

(52) Roof, R. B., Jr. *A Theoretical Extension of the Reduced-Cell Concept in Crystallography*; Publication LA-4038, Los Alamos Scientific Laboratory: Los Alamos, NM, 1969.

(53) The atomic coordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW. Any request should be accompanied by the full literature citation for this paper.

(54) Cromer, D. T.; Waber, J. T. *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. IV, Table 2.2B.

A Structure–Reactivity Relationship for Base-Promoted Hydrolysis and Methanolysis of Monocyclic β-Lactams

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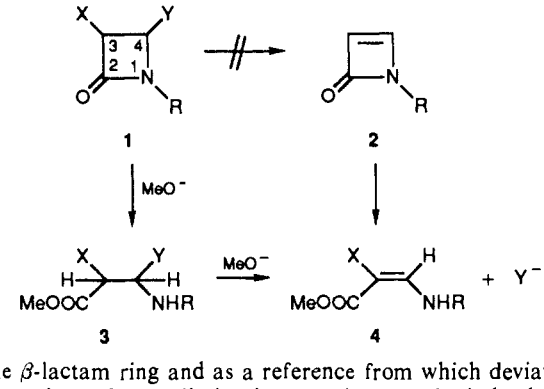
Received June 22, 1989

Abstract: A structure–reactivity relationship for base hydrolysis and methanolysis of nearly 50 azetidinones ranging in reactivity over nine powers of 10 is described. Substituents at 3- and 4-positions show similar effects upon reactivity and are correlated by a Taft relationship with $\rho_I = 5$, implying strong activation by electron withdrawal. Substituents at nitrogen show a linear dependence of log k upon the pK_a of the corresponding substituted dimethylamine with $\beta_{lg} = -0.35$. The effects are approximately additive and consistent with rate-determining attack of hydroxide or methoxide ions upon the carbonyl group of the ring. Large positive deviations occur for N–H β-lactams containing a good leaving group at the 4-position, which are subject to competing 1,4-elimination–addition, but there is no evidence of the corresponding 3,4-elimination or of a previously suggested change in the rate-determining step from nucleophilic attack upon the carbonyl group to ring-opening cleavage of the carbon–nitrogen bond. Steric effects lead to negative deviations and slower reactions of *trans*- than *cis*-azetidinones, but the effects are small (less than a factor of 10) unless the ring is heavily substituted, e.g., as in 1-phenyl-3,3-dimethyl-4-phenyl-4-(methylthio)azetidinone, which reacts 65 000 times more slowly than predicted. The accelerating effect of ring fusion on β-lactam reactivity is estimated to be 85-fold for the thiazolidine ring of penicillin and 16-fold for the dihydrothiazine ring of cephalosporins.

In methanolic sodium methoxide, 3-tosyloxy and 3-azido β-lactams bearing a chloro or methylthio leaving group at the 4-position (**1**, X = OTs, N_3; Y = SMe, Cl) have beeen shown to undergo ring opening followed by elimination of HCl or MeSH to form the enamine ester (**4**), as shown in the lower pathway of Scheme 1.[1] Similar behavior is observed for a wide range of β-lactam structures, and in the present paper we report a study of these reactions (a) to determine if alternative activating groups at the 3-position induce elimination within the β-lactam ring itself, as in the upper pathway of Scheme I, and (b) to establish a structure–reactivity relationship for the ring-opening reaction.

A structure–reactivity relationship for ring opening can be measured because ring opening (**1** → **3**) is rate determining in Scheme I and the enamine ester product provides a good chromophore for monitoring the reaction.[1] The relationship is of interest both for understanding factors influencing the reactivity

Scheme I



of the β-lactam ring and as a reference from which deviations representing a faster elimination reaction may be judged.

Previous studies of structure–reactivity relationships for β-lactam ring opening have been summarized by Page.[2,3] For

(1) Rao, S. N.; More O'Ferrall, R. A. *J. Org. Chem.* In press.

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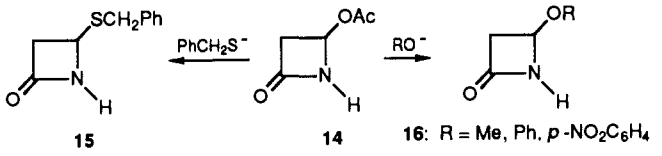
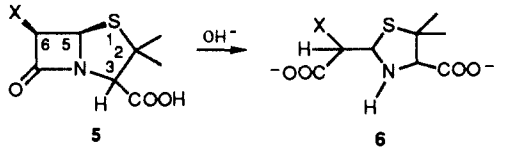
Scheme II



15 14 16: R = Me, Ph, *p*-$NO_2C_6H_4$

monocyclic β-lactams, substituents at the 3-position have been confined to methyl and phenyl groups,[4] but Page has shown that effects at the equivalent 6-position of penicillins are described by the Taft equation with $\rho_1 = 4.0$ (reaction **5** → **6**).[2] For the



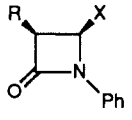
5 6

monocyclic rings, substituents at nitrogen correlate with the pK_as of the correspondingly substituted primary amines with $\beta_{lg} = -0.44$.[3,5] Both these parameters imply activation by electron-withdrawing substituents and are consistent with rate-determining attack of the hydroxide ion upon the carbonyl group of the ring.[2,3,5] By contrast, in the hydrolysis of simple amides, for which leaving group loss is believed to be rate-determining, β_{lg} has the lower value of −0.1.[2]

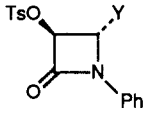
A feature of this last relationship, however, is that for very basic amines the dependence of log *k* upon pK_a appears to be weaker than for less basic amines and to approach that for amides ($\beta_{lg} = -0.1$). Page has suggested that this may indicate a change in rate-determining step from nucleophilic attack on the carbonyl group to breaking of the carbon–nitrogen bond in the β-lactam ring.[2,3] In this paper we show that by extending and modifying the correlation the evidence for a difference in slope is weakened and that probably a change in rate-determining step does not occur.

Results

Three groups of β-lactams with different substituents at nitrogen have been prepared. The first derives from *N*-phenyl-3-azido- and *N*-phenyl-3-(tosyloxy)-4-(methylthio)azetidinones prepared elsewhere.[1] The azido compound **7**[1,6,7] was converted via reduction of the azide group with H_2S to the amine **8** and thence to the benzyl amide **9**,[8] and by oxidation of the methylthio group with *m*-chloroperbenzoic acid to the methyl sulfoxides **10** and **11**;[9] the sulfoxide **10** was obtained as a mixture of isomers (presumably *R* and *S*), which were separated chromatographically, but the sulfoxide **11** was a single isomer. The trans (tosyloxy)azetidinone **12** was also converted to sulfoxide **13** and was obtained as a single isomer.



7: R = N_3, X = SMe
8: R = NH_2, X = SMe
9: R = $PhCH_2CONH$, X = SMe
10: R = N_3, X = SOMe
11: R = $PhCH_2CONH$, X = SOMe



12: Y = SMe
13: Y = SOMe

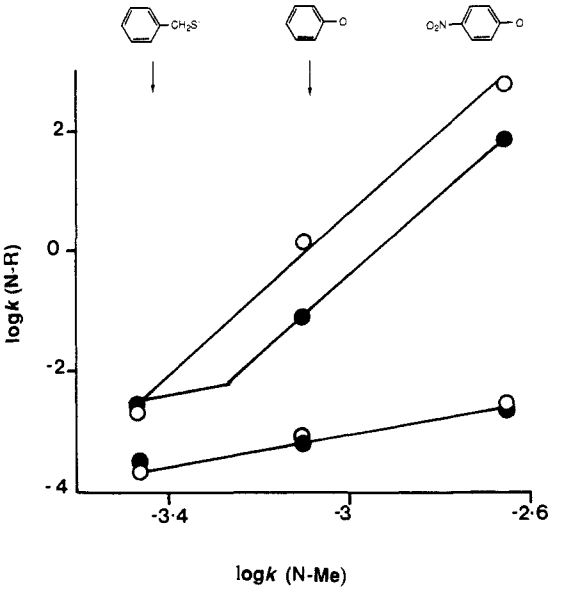
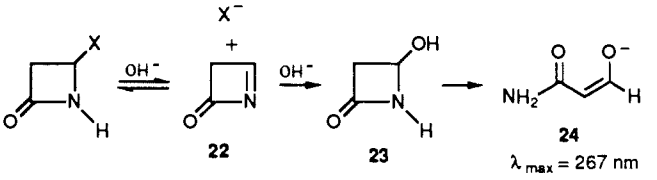
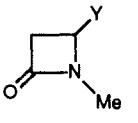


Figure 1. Upper lines are plots of log *k* for reaction of 4-substituted *N*-H β-lactams in aqueous NaOH (○) or methanolic NaOMe (●) against log *k* for similarly substituted *N*-methyl β-lactams in methanolic NaOMe (substituents indicated in plot). Lower lines are similar, but "identity" plots of *N*-methyl against *N*-methyl β-lactams.

Scheme III



The second group consists of β-lactams lacking substituents at either the nitrogen atom or the 3-position of the ring, and these were obtained as products of displacement reactions of 4-acetoxyazetidinone **14**, as in Scheme II;[8] a number of these compounds had been prepared previously and rates of reaction with sodium hydroxide measured by Fedor.[10] The third group was obtained from the benzylthio β-lactam **15** by methylation at nitrogen to form **17** followed by conversion to the corresponding *N*-methyl β-lactams with 4-substituents chloro (**18**), methylthio (**19**), phenoxy (**20**), and *p*-nitrophenoxy (**21**).[8]



17: Y = SCH_2Ph
18: Y = Cl
19: Y = SMe
20: Y = OPh
21: Y = *p*-nitrophenoxy

Rate constants for reaction of *N*-methyl and *N*-H β-lactams were measured in aqueous sodium hydroxide and methanolic sodium methoxide and are shown as a log–log plot of *N*-H versus *N*-methyl rate constants for corresponding 4-substituents ($PhCH_2S$, PhO, and *p*-nitrophenoxy) in Figure 1. The plot reveals that an *N*-H azetidinone with a good leaving group reacts much more rapidly than the *N*-methyl. This is because, as shown by Fedor,[10] the *N*-H azetidinones undergo a 1,4-elimination via a 1-azetinone intermediate (**22**, Scheme III) which is possible only if the β-lactam nitrogen bears a hydrogen atom. With sodium hydroxide the initial product is the hydroxyazetidinone **23** which fragments to the hydroxyacrylamide anion **24**, the characteristic chromophore of which ($\lambda_{max} = 267$) is used to monitor the reaction.[10] For aryloxy leaving groups the rates of appearance of

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(3) Page, M. I. *Adv. Phys. Org. Chem.* **1987**, *23*, 165–270.
(4) Washkun, R. J.; Robinson, J. R. *J. Pharm. Sci.* **1971**, *60*, 1168–1175.
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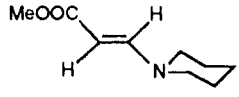
this chromophore and that of the aryl oxide anion are the same. For the corresponding reactions in methanolic sodium methoxide, however, the initial product is the nonchromophoric 4-methoxyazetidinone (**16**, R = Me), and the chromophore of the leaving group is used to monitor the reaction.

By contrast the *N*-methyl azetidinones react initially via attack of base at the β-lactam carbonyl group with opening of the β-lactam ring. For poor leaving groups (SMe, SCH_2Ph, or OMe) the rate difference between *N*-H and *N*-methyl compounds (Figure 1) is much smaller than for good leaving groups, and presumably in these cases *N*-H and *N*-methyl azetidinones react in the same way. This is supported by the fact that the wavelength of the product (λ_{max}) shifts from 267 to 257 nm in H_2O and that in MeOH the same absorption is observed for *N*-H and *N*-methyl substrates (coincidentally also 267 nm), the latter presumably corresponding to the enamine **4** (Y = H, R = H or CH_3). This identification is based on analogy with the reactions of 3-tosyloxy and 3-azido substrates described elsewhere[1] and the fact that λ_{max} is close to the value of 270 nm for the similar trans cyclohexylamino ester **25**.[11]



25

For poor leaving groups the *N*-H azetidinones showed kinetic saturation consistent with ionization of the β-lactam hydrogen. Similar behavior was reported by Fedor,[10] and for the 4-(benzylthio)azetidinone **15** a rate constant for hydroxide attack on the unionized substrate was obtained by fitting measured rate constants to eq 1 with $pK_a = 13.1$. No significant saturation was observed in methanolic sodium methoxide [for **15** or 4-methoxyazetidinone (**16**, R = CH_3)].

$$k_{obs} = k_2[OH^-]/(1 + K_a/[H^+]) \quad (1)$$

By contrast, the combination of a good leaving group and basic nitrogen atom leads to solvolysis.[1] Thus 4-chloro-*N*-methylazetidinone **18** reacts rapidly in methanol in the absence of base to yield the 4-methoxy derivative. Ring opening competes with solvolysis only at high base concentration in a reaction too fast to measure.

Figure 1 reveals a difference in solvent effects upon β-lactam ring opening and 1,4-elimination. Of interest here is that the rate differences between water and methanol for the ring-opening reactions are small. This appears to be generally true and values of k_{HO}/k_{MeOH} for 15 out of 17 comparisons in this work and elsewhere fall in the range 0.5–2.0. Thus rate ratios for the following combinations of N-, 3-, and 4-substituents are as follows: H, H, $PhCH_2S$, 1.35; Me, H, H, 0.70; Me, H, Me, 1.30; Me, H, Ph, 1.46; Me, H, $PhCH_2S$, 0.78; Me, H, *p*-nitrophenoxy, 1.18; Me, H, phenoxy, 0.99; Me, H, MeS, 1.03; Ph, $PhCONH_2$, MeS (cis), 0.79; Ph, Br, MeS (cis), 0.47; Ph, N_3, MeS (cis), 0.59; Ph, $PhCH_2CONH$, MeS (cis), 0.79; Ph, Br, Cl (cis), 0.46; Ph, Br, MeS (trans), 2.2; H, H, $PhCH_2$, 0.93; $PhCH_2$, OTs, Cl (trans) 0.34; $PhCH_2$, N_3, Cl (trans), 0.90; Ph, Br, Cl (trans), 4.0.

This similarity of rate constants in water and methanol is convenient because measurements from the two solvents can be combined in a single free energy relationship. Thus, the earlier measurements by Washkun and Robinson,[4] Blackburn,[5] Butler et al.,[13] and Proctor, Gensmantel, and Page[2] used water as solvent whereas several of our substrates were too insoluble to be conveniently studied in water. In practice even the largest and smallest rate ratios between water and methanol, $k_{HO}/k_{MeOH} = 4.0$ and 0.34, respectively, represent small deviations in a correlation spanning eight powers of 10 in reactivity (see below). Sensibly, results in 85% ethanol–water mixtures obtained by Holley and Holley[14–16] may also be included in the correlation.

A number of kinetic measurements refer to 3,4-disubstituted azetidinones possessing cis or trans configurations. The stereochemistry of these was assigned on the basis of the coupling constants between 3- and 4-hydrogens,[1,6] and is consistent with expected stereochemical relationships between reactants and products of synthetic reactions. Also, as noted above, in the preparation of *cis*-azido-*N*-phenyl-4-methyl sulfoxide two products were obtained and presumed to correspond to *R* and *S* configurations of the methylsulfinyl group on the basis of their similar NMR spectra.

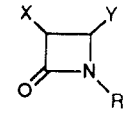
A solvent isotope effect $k_{MeOD}/k_{MeOH} = 2.2$, similar to that for related substrates, was measured for reaction of *cis*-1-phenyl-3-[(benzylcarbonyl)amino]-4-(methylsulfinyl)-2-azetidinone (**11**) with sodium methoxide.

Discussion

Structure–Reactivity Relationship for β-Lactam Ring Opening. Rate constants for base-promoted ring opening of 46 monocyclic β-lactams from the present measurements and from the literature are summarized in Table I. The table includes rate constants for water, methanol, and aqueous ethanol as solvents, and, as we have seen, differences between these media are usually small. For comparison, examples of penicillins and cephalosporins are also included.

The relationship between structure and reactivity in this large family of compounds is simplified by the finding that substituent effects at the 3- and 4-positions of the β-lactam ring are practically the same. This is apparent from plotting log *k* against the appropriate Taft substituent constants[18] with the substituents varied at one position only. It suggests that for multiple substitution, including both carbon atoms and the nitrogen atom, the relatively simple eq 2 containing a single Taft constant ρ_1 and a Brønsted leaving group coefficient β_{lg} should describe the observed behavior, provided that substituent changes are approximately additive.

In this equation the substituent constants σ_1^X and σ_1^Y refer to the 3- and 4-positions of the ring (cf. **26**) and the pK_a refers to



26

the dimethylamine ($RNMe_2$) of the group (R) bound to the nitrogen atom. The equation is an example of a dual-parameter relationship (parameters ρ_1 and β_{lg}) and as written is not easily displayed graphically. However, rearranging to eq 3 and assigning

$$\log k = \rho_1(\sigma_1^X + \sigma_1^Y) + \beta_{lg} \log K_a \quad (2)$$

$$\log k = \rho_1\{\sigma_1^X + \sigma_1^Y + (\beta_{lg}/\rho I)pK_a\} \quad (3)$$

$$\beta_{lg}/\rho_1 = -0.07$$

an optimum value of $\beta_{lg}/\rho_1 = -0.07$ allows the data to be plotted in the form log *k* versus $(\sigma_1^X + \sigma_1^Y - 0.07pK_a)$, and this plot is shown as the full line in Figure 2 with slope $\rho_1 = 5.0$ and intercept −1.70 (and by implication $\beta_{lg} = -0.35$).

It can be seen that much of the data from Table I fits this correlation. Significant deviations do occur, but for the most part they represent special features of the reaction. Thus the largest positive deviations (shown as open squares) are for *N*-H β-lactams containing a reactive leaving group at the 4-position. As noted above, these undergo a 1,4-elimination–addition reaction as in Scheme II.[10] In the absence of a leaving group, or for a poor

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Table I. Rate Constants[a] for Base-Catalyzed Ring Opening of 1,3,4-Substituted β-Lactams in NaOH–H_2O (or NaOMe–MeOH)[b] at 25 °C

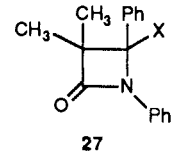
point[ref]	substituents: config	1-	3-	4-	10^2k	7 + log k	$\sum\sigma_1$	$\sum\sigma_1$ − 0.07 pK_a
(1)[14]		H	H	H	0.024[c]	3.38	0	−0.75
(2)		H	H	OMe	0.30[d]	4.48	0.29	−0.46
(3)		H	H	SCH_2Ph	0.27	4.43	0.27	−0.48
(4)		H	H	OPh	140.0	7.15	0.42	−0.33
(5)		H	H	Ar[e]	59000.0[f]	9.77	0.48	−0.27
(6)[4]		Me	H	H	0.0038	2.58	0	0.68
(7)[4]		Me	Me	H	0.0017	2.28	−0.04	−0.72
(8)[4]		Me	Ph	H	0.0045	2.66	0.12	−0.56
(9)		Me	H	SMe	0.030	3.48	0.25	−0.43
(10)		Me	H	SCH_2Ph	0.021[g]	3.32	0.27	−0.41
(11)		Me	H	OPh	0.069	3.84	0.42	−0.26
(12)		Me	H	OAr[e]	0.26	4.41	0.48	−0.20
(13)[4]		Et	H	H	0.0014	2.14	0	−0.70
(14)[4]		Et	Me	H	0.00062	1.79	−0.04	−0.74
(15)[4]		Et	Ph	H	0.00158	2.20	0.12	−0.58
(16)[27]		Pr	H	H[h]	0.0017	2.23	0	−0.68
(17)[5]		Ph	H	H[h]	0.127	4.10	0	−0.35
(18)[5]		Ar'[j]	H	H[h]	0.955	4.98	0	−0.18
(19)[5]		Ar[e]	H	H[h]	4.42	5.65	0	−0.0
(20)	cis	Ph	NH_2	SMe	7.1[d]	5.85	0.44	0.09
(21)	cis	Ph	RCONH[k]	SMe	7.3	5.86	0.52	0.17
(22)	cis	Ph	N_3	SMe	50.0	6.70	0.67	0.32
(23)	trans	Ph	OTs	SMe	36.0	6.48	0.84	0.49
(24)[16]		Ph	H	Ph	0.21	4.32	0.12	−0.23
(25)[16]	trans	Ph	NH_2	Ph	2.0	5.30	0.31	−0.04
(26)[16]	trans	Ph	R'CONH[l]	Ph	2.1	5.32	0.39	0.04
(27)	cis	Ph	N_3	SOMe	1400.0[d,m]	8.15	0.92	0.57
(28)	cis	Ph	N_3	SOMe	1050.0[d,m]	8.02	0.92	0.57
(29)	cis	Ph	RCONH[k]	SOMe	70.0[d]	6.85	0.77	0.42
(30)	trans	Ph	OTs	SOMe	182.0[d]	7.30	1.09	0.74
(31)	cis	Ph	N_3	Cl	1030.0[d]	8.01	0.89	0.54
(32)	trans	Ph	OTs	Cl	1350.0[d]	8.13	1.06	0.71
(33)	cis	Ph	OTs	Cl	1650.0[d]	8.22	1.06	0.71
(34)[15]		Ph	$(CH_3)_2$	Ph	0.00005[c]	0.70	0.04	−0.31
(35)[15]		Ph	$(CH_3)_2$	Ph, SMe	0.000015[c]	0.18	0.29	−0.06
(36)		$PhCH_2$	H	H	0.0053	2.73	0	−0.625
(37)[13]		$PhCH_2$	Me	H	0.00215	2.33	−0.04	−0.585
(38)		$PhCH_2$	Ph	H	0.0058	2.76	0.12	−0.505
(39)[13]		$PhCH_2$	H	Ph	0.0016	2.20	0.12	−0.505
(40)	trans	$PhCH_2$	N_3	SMe	4.5[d]	5.65	0.67	0.04
(41)	trans	$PhCH_2$	N_3	Cl	90.0	6.95	0.89	0.26
(42)	trans	$PhCH_2$	OTs	Cl	35.0	6.48	1.06	0.43
(43)	trans	$PhCH_2$	OTs	SMe	2.5[d]	5.40	0.84	0.21
(44)[13]		Ph_2CH	H	Ph	0.00041[c]	1.61	0.12	−0.39
(45)[1]		CH_2COO^-	RCONH[k]	H[n]	0.0060[k]	2.78	0.30	−0.39
(46)[1]		benzylpenicillin[n]			12.0	6.08	0.55	−0.14
(47)[1]		Δ-3-cephalosporin[n,p]			2.1	5.32	0.55	−0.14
(48)[1]		Δ-2-cephalosporin[n,p]			0.78	4.89	0.55	−0.14

[a] Values are expressed in units of 1 mol^{-1} s^{-1}; data from present work or references cited. Numbers refer to points in Figure 2; configuration (cis or trans) of 3,4-disubstituted azetidinones are indicated. [b] Rate constants in NaOMe–MeOH or other nonaqueous solvents indicated in footnotes. [c] Rate constant at 50 °C in 85% EtOH–H_2O extrapolated to 25 °C. [d] Rate constant in NaOMe–MeOH. [e] Ar = *p*-nitrophenyl. [f] 1,4-Elimination. [g] One measurement only. [h] M. I. Page, personal communication, extrapolated from 30 to 25 °C. [j] Ar' = *m*-nitrophenyl. [k] R = benzyl. [l] R' = phenyl. [m] Separate rate constants measured for R and S methylsulfoxides. [n] Rate constant extrapolated from 30 to 25 °C. [p] With 7-benzylamido and 3-methyl substituents.

leaving group, elimination fails to compete with hydrolysis, and the data are again correlated by a line with slope $\rho_1 = 5.0$, shown as the dashed line in the figure.

It can be seen that this dashed line lies parallel to but deviates positively from the main correlation. The residual deviation, and most of the negative deviations in the figure, are probably steric in origin. Thus all but one of the negative deviations are for substrates containing substituents at all three positions in the ring and all but one (see below) contain at least two phenyl rings. The positive deviations are for substrates having a hydrogen at nitrogen and hydrogens at one or both of the carbon atoms or for bicyclic β-lactams.

The influence of steric effects upon β-lactam reactivity has long been recognized,[3,19,20] but there has been little effort to separate quantitatively steric effects from electronic effects.[4] In this regard the first conclusion to be drawn from Figure 2 is that steric effects are usually quite small. Thus all but three of the negative deviations lie within a factor of 10 of a correlation spanning nine powers of 10 in reactivity. However, where there is an accumulation of bulky substituents, as in the heavily substituted 1,4-diphenyl-3,3-dimethyl β-lactam (**27**, X = H) and its 4-methylthio derivative (**27**, X = SMe), the effects become much



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larger, and these substrates react more slowly than predicted by factors of 1300 and 65000, respectively.

Steric effects have also been presumed to influence the stereochemistry of attack on the β-lactam ring.[3,19] In the penicillins,

(19) Indelicato, J. M.; Wilham, W. L. *J. Med. Chem.* **1974**, *17*, 528.
(20) Ballard, S. A.; Melstrom, D. S.; Smith, C. W. In *The Chemistry of Penicillin*; Clarke, T. H., Johnson, J. R., Robinson, R., Eds.; Princeton University: Princeton, NJ, 1949; pp 973–1003.

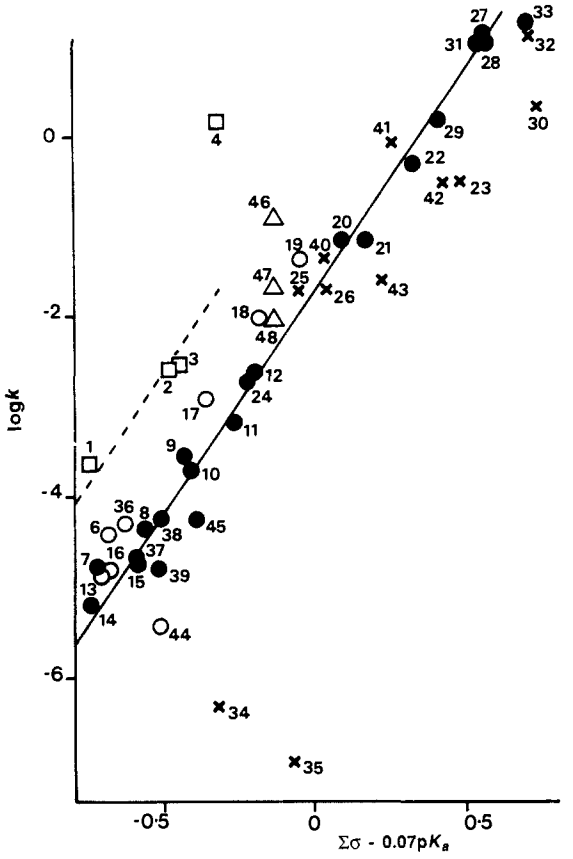
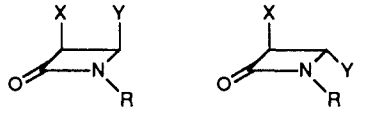


Figure 2. Taft-Brønsted plot for base-promoted hydrolysis or methanolysis of 1,3,4-substituted β-lactams at 25 °C: symbols denote 3,4-unsubstituted (○), mono- or cis-3,4-substituted (●), trans-3,4-substituted (×), and *N*-H β-lactams (□), or penicillins and cephalosporins (△). The full line refers to mono and cis-3,4-substituted β-lactams (except *N*-H). The dashed line refers to *N*-H β-lactams. Numbering of points refers to Table I.

attack is believed to occur more easily on the unsubstituted α-face of the ring than on the β-face bearing the 6-substituent and thiazolidine ring junctions (**5**). By extension a (smaller) preference can be expected for attack on cis-3,4-disubstituted monocyclic β-lactams, in which one face of the ring is free of substituents, compared with the corresponding trans isomer, in which both faces are substituted (**28**). In Figure 2 it can be seen that several of



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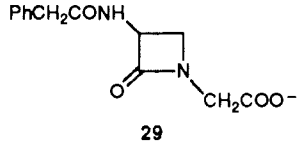
the negative deviations are for trans disubstituted β-lactams (shown as crosses), and strictly speaking the correlation should be considered as applying chiefly to mono- and cis-3,4-disubstituted substrates which are shown as closed circles.

This stereochemical dependence is not altogether straightforward, however. For *cis*- and *trans*-*N*-phenyl-3-tosyl-4-chloroazetidinones (**26**, X = OTs, Y = Cl, R = Ph) the cis–trans rate ratio in methanol solvent, k_{cis}/k_{trans} = 1.3, is surprisingly small, and a number of trans substrates with smaller 3-substituents (e.g., NH_2 and N_3, points 25, 40, and 41) fail to deviate from the correlation. The explanation of this is discussed more fully elsewhere,[12] but apparently electronic effects of substituents act more strongly from the trans configuration than cis so that the stereochemical dependence of steric and (–I) electronic effects are partly compensating, especially when the substituents are strongly electronegative.[12]

Because these effects are quite small, their significance need not be exaggerated. Nevertheless, negative deviations in Figure 2 tend to be largest for trans configurations of bulky, weakly electronegative groups where compensation between steric and electronegativity effects can be presumed to be poor. Thus *trans*-4-methylthio substrates deviate more strongly than 4-chloro, and *trans*-3-tosyloxy substrates more than 3-azido.

Steric effects are not confined to trans-3,4-disubstituted substrates. Negative deviations for the 4-phenyl-*N*-benzyl (point 39) and *N*-benzhydryl (point 44) azetidinones presumably are also steric in origin. On the other hand, the similar deviation for the β-lactam bearing a CH_2COO^- substituent at nitrogen (**29**, point 46) is probably again the result of an electronic effect. The



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behavior recalls the rather large difference in reactivity toward hydroxide ion of penicillins (**5**) containing carboxylate anion and ester groups respectively at the 3-position of the thiazolidine ring.[2] It probably represents the known failure of linear free energy relationships to adequately accommodate substituent effects of monopoles.[21]

Mono- and Bicyclic β-Lactams. A striking feature of Figure 2 is the wide variations in reactivity of differently substituted β-lactams. This is of interest in relation to the relative reactivities of mono- and bicyclic structures. It now seems clear that earlier work led to a somewhat exaggerated impression of the reactivity of penicillin because rate comparisons were made with monocyclic β-lactams lacking activating amide or sulfur side chains and containing bulky phenyl and methyl substituents, which place them in the small group of β-lactams (of which there are two in Figure 2) subject to strong steric hindrance.[14-16,20] Page has pointed out that although fusion to the thiazolidine ring to form penicillin increases the reactivity of the β-lactam significantly the factor cannot much exceed 100.[2,3] In fact, comparison of the reactivity of penicillin and the monocyclic β-lactam **29** corrected for the absence of a 4-alkylthio substituent on the basis of Figure 2 ($10^{5.0}\sigma_1$MeS) shows that the ring fusion increases the rate by 85-fold. A similar comparison for 7-[(benzylcarbonyl)amino] cephalosporins shows that a 3-methyldihydrothiazine ring increases the rate by 16-fold for a Δ^3 double bond and 6-fold for Δ^2. Rate constants for penicillin G and the cephalosporins are included in Figure 2 (points 46–48, triangles) based on σ_1 values for MeS and PhCONH and a pK_a for *N*,*N*-dimethylglycine.

Mechanism of Reaction. Figure 2 also offers a number of mechanistic insights. As we have seen, the presence of 1,4-elimination[10] is revealed by strong positive deviations from the correlation by *N*-H β-lactams with good leaving groups at the 4-position. By the same token the absence of such deviations for *N*-alkyl or *N*-aryl substrates, even with a leaving group as reactive as chloride, implies that there is no incursion of 3,4-elimination prior to opening the β-lactam ring (Scheme I). This is discussed in more detail elsewhere[1] but is perhaps the clearest evidence that reaction via the upperpathway of Scheme I does not occur. In this connection, it may be noted that the correlation includes substrates with 4-substituents, such as hydrogen and phenyl, which are incapable of undergoing elimination.

The lack of strong negative deviations in Figure 2 (other than accountable for by steric effects) also confirms[1] that in the lower pathway of Scheme I reaction of the β-lactam is rate determining, rather than elimination of the initially formed ring-opened product **3** to yield the enamine **4**. This behavior contrasts with that of bicyclic β-lactams, notably penicillins **5**, for which the elimination (opening the thiazolidine ring) is the slower process and the β-lactam ring-opened species builds up in an initial rapid reaction.[22]

(21) Hoefnagel, A. J.; Hoefnagel, M. A.; Wepster, B. M. *J. Org. Chem.* **1978**, *43*, 4720–4745.

(22) Davis, A. J.; Page, M. I. *J. Chem. Soc., Chem. Commun.* **1985**, 1702–1704. Pratt, R. F.; Cahn, D. J. *J. Am. Chem. Soc.* **1988**, *110*, 5096–5104. Golden, P.; More O'Ferrall, R. A.; Rao, S. N. Unpublished results.

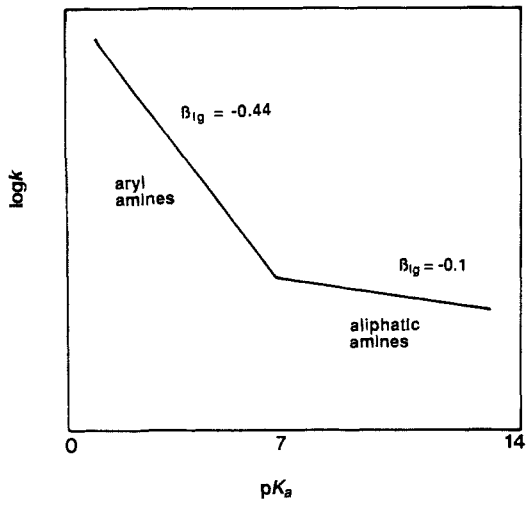
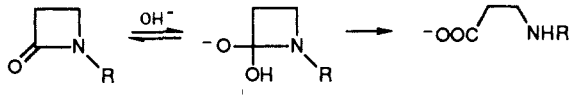


Figure 3. Schematic plot of log k for hydrolysis of N-substituted β-lactams against the pK_a of one of the correspondingly substituted primary amines.

Scheme IV



With respect to β-lactam ring opening, Figure 2 greatly extends the range of structures for which rate measurements are available. Previous correlations have focused on substituents at nitrogen and log k was plotted against the pK_a of the correspondingly substituted primary amine. A feature of these correlations shown schematically in Figure 3 is that a change in slope (β_{lg}) was observed between β-lactams of more and less basic amines.[2,3] For N-aryl β-lactams, derived from substituted anilines (pK_a < 5), β_{lg} was found to be −0.44 whereas for N-alkyl β-lactams, from aliphatic amines (pK_a < 9), β_{lg} was −0.1.[2] As noted by Page the latter slope matches β_{lg} for acyclic amides, for which expulsion of the amine rather than attack by hydroxide is believed to be rate determining.[2] It thus suggested a change to a similar rate-determining step for the β-lactams (Scheme III).

However, as Page has pointed out, a change in slope of a free energy relationship signaling a change in rate-determining step should lead to a decrease in reactivity and a downward or concave "break" in the correlation. On the contrary, what was found was an *increase* in reactivity and an upward or convex break in the relationship. This is not consistent with a change in the rate-determining step.[23]

Interestingly, when the data are replotted as in Figure 2 the "break" disappears and measurements for both strongly and weakly basic amines lacking substituents at the 3- and 4-positions (open circles), which were used in Page's correlation, follow a single line with slope close to β_{lg} = −0.35. The main factor responsible for this difference is that in Page's correlation log k was plotted against the pK_a of the appropriate primary amine whereas in Figure 2 pK_as of tertiary (dimethyl) amines are used. The tertiary amines have somewhat smaller pK_as than primary amines in the aliphatic series and also give a shallower slope for the N-aryl β-lactams:[24] both factors diminish the difference between these groups of compounds, a difference which in Figure 2 is also masked by the greater number and dispersion of points. Strictly speaking pK_as of primary amines should be used in a β_{lg} plot but, arguably, for nucleophilic attack upon N-substituted β-lactams (which do not have a hydrogen attached to the nitrogen atom) tertiary amines are more appropriate. Certainly a mechanistic distinction should not hinge on the difference.

For these reasons and because there is no evidence in Figure 2 of a break in the correlation of log k with σ_1, it seems reasonable to conclude that, after all, there is no dependence of the rate-determining step for basic hydrolysis of the β-lactam ring upon the basicity of the amino group.

Experimental Section

Instrumentation and chromatographic methods have been described elsewhere.[1] A number of the β-lactams studied had been prepared previously by Clauss et al.;[8] these included *cis*-3-azido-4-(methylthio)-1-phenyl-2-azetidinone (**7**) 4-acetoxy-2-azetidinone (**14**), 4-(benzylthio)-2-azetidinone (**15**), the 4-(aryloxy)-2-azetidinones (**16**), 4-(benzylthio)-1-methyl-2-azetidinone (**17**), 4-chloro-1-methyl-2-azetidinone (**18**), 4-(methylthio)-1-methyl-2-azetidinone (**19**), and the 4-(aryloxy)-1-methylazetidinones (**20** and **21**). The same preparations were used here and melting points and NMR data were in satisfactory agreement with those reported previously.[8,10] The 4-chloro-1-methyl-2-azetidinone (**18**) solvolyzed rapidly in methanol to the corresponding methyl ether (with OMe replacing Cl) and kinetic measurements for this substrate refer to the ether prepared in situ in this way. The corresponding N-H methyl ether was prepared in the manner described by Fedor.[10]

The following compounds were prepared for the first time. Their IR spectra are reported for the neat liquid or KBr disk, and assignment of the configuration of 3- and 4-substituents as cis or trans is based on the coupling constant between 3- and 4-hydrogens in the NMR.[1,6]

***cis*-1-Phenyl-3-amino-4-(methylthio)-2-azetidinone (8).** To an ice-cold solution of *cis*-1-phenyl-3-azido-4-(methylthio)-2-azetidinone (**7**, 0.59 g, 2.13 × 10^{-3} mmol) in 20 mL of methylene chloride was added 0.45 g (2 equiv) of triethylamine. Hydrogen sulfide gas was bubbled through the mixture for 5 min at ice temperature and for 30 min at room temperature. The reaction mixture was washed with water and dried. Removal of the solvent under vacuum gave the product as a fairly pure solid which was used for further reactions and kinetics without additional purification: IR 1775 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.95 (br s, NH_2, disappears with D_2O), 2.1 (s, CH_3), 4.6 (d, J = 4.5 Hz, 3-H), 5.2 (d, J = 4.5 Hz, 4-H), 7.1–7.6 (m, aryl).

***cis*-1-Phenyl-3-[(benzylcarbonyl)amino]-4-(methylthio)-2-azetidinone (9).** To a solution of the amine **8** (0.4 g) in chloroform (5 mL) and pyridine (0.3 g) cooled to −5 °C in an ice–salt bath was added dropwise phenylacetyl chloride (0.35 g) in 5 mL of chloroform over a period of 30 min. The reaction mixture was stirred at −5 °C for a further 1 h, diluted with 50 mL of water, and extracted with chloroform (3 × 20 mL). The combined organic phase was washed with 5% HCl and water and dried. Removal of the solvent under vacuum afforded a solid: mp 134–136 °C; IR 1775 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.9 (s, CH_3), 3.7 (s, CH_2Ph), 5.15 (d, J = 4.5 Hz, 4-H), 5.6 (dd, J = 4.5 and 9.0 Hz, 3-H), 6.8 (d, 9.0 Hz, N-H), 7.1–7.7 (m, aryl). Anal. Calcd for $C_{18}H_{18}N_2O_2S$: C, 66.26; H, 5.52; N, 8.59; S, 9.83. Found: C, 65.94; H, 5.55; N, 8.47; S, 9.93.

***cis*-1-Phenyl-3-[(benzylcarbonyl)amino]-4-(methylsulfinyl)-2-azetidinone (11).** To a solution of benzyl amide **9** (0.2 g, 0.61 mmol) in 10 mL of dry chloroform at room temperature was added 0.124 g of *m*-chloroperbenzoic acid in 10 mL of chloroform over a period of 2 h. The chloroform layer was washed with 10% sodium bicarbonate followed by water and dried. Removal of the solvent under vacuum gave 0.18 g of a solid: mp 160 °C dec; IR 1775 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.8 (s, CH_3), 3.7 (s, CH_2), 5.5 (d, J = 5.0 Hz, 4-H), 6.2 (dd, J = 5.0 Hz, 9.0 Hz, 3-H), 7.1–7.8 (m, 10 H, aromatic H), 8.8 (d, J = 9 Hz, NH).

***cis*-1-Phenyl-3-azido-4-(methylsulfinyl)-2-azetidinone (10, *R* and *S*).** To a solution of *cis*-1-phenyl-3-azido-4-(methylthio)-2-azetidinone (**7**, 0.4 g, 1.7 mmol) in 20 mL dry chloroform at room temperature was added 0.294 g of *m*-chloroperbenzoic acid in 20 mL chloroform over a period of 2 h. The chloroform layer was washed with 10% sodium bicarbonate solution, followed by water, and dried. Removal of the solvent under vacuum afforded 0.34 g of a solid which was separated on a silica column (eluting with hexane–ethyl acetate, 70:30) into two fractions A and B. Fraction A, a solid: mp 110–115 °C; IR 2120 cm^{-1} (azide) 1775 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.7 (s, CH_3), 5.3 (s, 3-H and 4-H), 7.1–7.8 (m, aryl). Fraction B, an oil: ^1H NMR ($CDCl_3$) δ 2.8 (s, CH_3), 5.15 (s, 3-H and 4-H), 7.1–7.8 (m, aryl). Anal. Calcd for $C_{10}H_{10}N_4O_2S$: C, 48.00; H, 3.99; N, 22.40; S, 12.81. Found: C, 48.15; H, 4.22; N, 20.77; S, 12.85.

***trans*-1-Phenyl-3-(tosyloxy)-4-(methylsulfinyl)-2-azetidinone (13).** To a solution of *trans*-1-phenyl-3-(*p*-tosyloxy)-4-(methylthio)-2-azetidinone (**12**, 0.4 g in 20 mL of chloroform was added *m*-chloroperbenzoic acid (0.35 g in 20 mL of chloroform) over a period of 30 min. The solution was stirred for a further 1 h, washed with 10% sodium bicarbonate solution, followed by water, and dried. Removal of the solvent under vacuum afforded 0.36 g of a mixture of compounds from which the methyl sulfoxide was recrystallized (MeOH): mp 155–156 °C; IR 1780 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.4 (s, tolyl CH_3), 2.8 (s, $SOCH_3$),

(23) Jencks, W. P. In *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969.

(24) Because pK_a measurements appear to have been reported for only a few *N,N*-dimethylanilines in aqueous solution,[25] Figure 2 includes a smaller number of points for N-aryl β-lactams than Page's correlation.[2]

5.3–5.4 (s, 3-H and 4-H), 7.2–8.0 (m, aryl). Anal. Calcd for $C_{17}H_{17}O_5NS_2$: C, 53.80, H, 4.52; N, 3.69; S, 16.89. Found: C, 53.95; H, 4.57; N, 3.61; S, 16.44.

Reaction Products. The products of the reactions of the β-lactam substrates with methanolic sodium methoxide were presumed to be the enamine esters **4** derived from β-lactam ring opening followed by elimination of a leaving group at the 4-position as in Scheme I. As noted above, this conclusion is based on analogy with the products isolated from the related *N*-phenyl and *N*-benzyl-3-tosyloxy and 3-azidoazetidinones with chloro and methylthio leaving groups at the 4-position[1] and the similarity of their UV spectra to those of the products obtained here. The UV spectra of the products depend on the substituents at the nitrogen atom and the 3-carbon atom in the reactant. For *N*-phenyl β-lactams values of λ_{max} (nm) for different 3-substituents were as follows: NH_2, 330; N_3, 327; T_sO, 317; and $PhCH_2CONH$, 315; for *N*-H and *N*-methyl substrates lacking a 3-subsitutent, λ_{max} was 267 nm.

Products from reactions with aqueous sodium hydroxide generally showed λ_{max} values at slightly shorter wavelengths than in methanol, e.g., 306 rather than 315 nm for the *N*-phenyl-3-benzylamido products and 257 instead of 267 nm for the 3-unsubstituted *N*-H and *N*-methyl substrates. The values presumably correspond to formation of amino acrylate anions (rather than the esters **4**). Although we found no report of these in the literature, the corresponding 3-trialkylammonium acrylate betaines have been prepared.[26]

Details of Kinetic Measurements and Taft Correlation. Kinetic measurements were made with aqueous sodium hydroxide and methanolic sodium methoxide following the procedures described earlier.[1] Values of rate constants at 25 °C are collected in Table I together with measurements from the literature and are analyzed in terms of a combined Taft–Brønsted free energy relationship in Figure 2.

Of the data taken from the literature, Holley and Holley's measurements in 85% ethanol–water[14-16] had to be extrapolated from 50 to 25 °C. Where the temperature dependence had been measured, the extrapolation was based on the appropriate Arrhenius equation, but where a measurement at only one temperature was available, a value of ln *A* was interpolated from measurements of values for other β-lactams[16] based on the observation that ln *A* tended to increase with decreasing reactivity.

In the case of 1-methyl- and 1-benzylazetidinones the extrapolated rate constants at 25 °C (0.0024 and 0.0029, respectively) could be compared with direct measurements in aqueous solution (0.0038 and 0.0053, respectively).[4] Again the approximate nature of the extrapolation is justified by the wide range of magnitudes of rate constants in Table I and Figure 2. Other values from the literature were extrapolated from 30 to 25 °C. These include the measurement for *N*-propylazetidinone made by Page[27] and the values quoted by him for penicillin G, the 7-[(benzylcarbonyl)amine]-3-methyl-ceph-3-em, and -ceph-2-em cephalosporins and **29**.[1]

The rate constants of Table I are plotted as a Taft–Brønsted relationship in Figure 2 against values of σ_I for the 3- and 4-substituents and the pK_a of the dimethylamine ($RNMe_2$) of the nitrogen substituent (R). Values of σ_I were taken from the compilation by Exner[18] except for the *p*-nitrophenoxy value which was based on the ionization constant of *p*-nitrophenoxy acetic acid.[28] The relevant values are as follows: Me, −0.04; Ph, 0.12; NH_2, 0.19; MeS, 0.25; $PhCH_2S$, 0.27; $PhCH_2CONH$, 0.27; $PhCH_2S$, 0.27; MeO, 0.29; PhCONH, 0.30; N_3, 0.42; Br, 0.46; Cl, 0.47; OTs, 0.59; *p*-nitrophenoxy, 0.48. The dimethylamine pK_as were taken from the compilation by Jencks in the *Handbook of Biochemistry*[25] and may be compared with pK_as of the corresponding primary amines used in previous correlations [R in $RNMe_2$, pK_a, (pK_a of RNH_2)]: H, 10.64 (10.62); Me, 9.76 (10.62); Et, 9.99 (10.63); Pr, 9.99 (10.53); Ph, 5.06 (4.62); *m*-nitrophenyl 2.63 (2.45); *p*-nitrophenyl, 0.61 (0.98); $PhCH_2$, 8.93 (9.34); Ph_2CH, 7.3 (estimated); CH_2COO^-, 9.8. Few pK_as in water are available for substituted *N*,*N*-dimethylanilines,[25] and only three of the nine rate constants reported by Blackburn and Plackett for hydrolysis of *N*-aryl β-lactams were used in the correlation.

The stereochemistry (cis or trans) of 3,4-disubstituted substrates prepared for this study or reported elsewhere[1] were assigned from the coupling constants of their 3- and 4-hydrogens as noted above. Most of the data from the literature refer to compounds with a single substituent and no stereochemistry. Butler[13] has reported rate constants for 1,4-diphenyl-3-amino and 3-benzamido azetidinones without indicating stereochemistries, but from the method of preparation (via the corresponding 3-phthalimidoazetidinone) these could be inferred to be trans.[29]

For *cis*-3-azido-4-(methylsulfinyl)azetidinones two isomers whose NMRs were indistinguishable except for the chemical shifts of their CH_3SO- peaks were isolated and presumed to have *R* and *S* configurations of the methylsulfinyl group.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research. We thank Frances Martin for experimental assistance.

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