

Δ^3 - Δ^2 ISOMERISATIONS IN CEPHEMS AND THEIR 1-OXA CONGENERS[†]

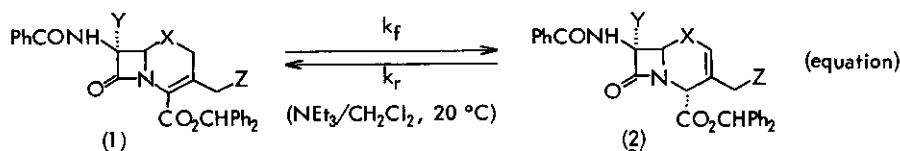
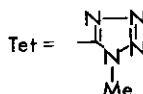
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Abstract — Base-catalysed isomerisation of the 3-cephems (1a)-(1d) to their Δ^2 -isomers (2a)-(2d) was compared with that in the 1-oxa congeners [(1e)-(1h) $\rightleftharpoons$ (2e)-(2h)]. Effects of the 1-hetero atom and the 7- and 3'-substituents on the rates and the equilibrium constants in these isomerisations are discussed.

INTRODUCTION

IN contrast to the well-studied isomerisation of 3-cephems to their Δ^2 -isomers,¹ only partial results² are available on the double-bond isomerisation of 1-oxa-cephems. We have measured the apparent rate constants of forward and reverse reactions, k_f and k_r , and the equilibrium constants K (k_f/k_r) in triethylamine-catalysed isomerisations of the cepheems (1a)-(1d) and their 1-oxa congeners (1e)-(1h) (equation). Effects of the 1-hetero atom, X, and of the substituents

a X = S, Y = H, Z = Hb X = S, Y = OMe, Z = Hc X = S, Y = H, Z = S-Tetd X = S, Y = OMe, Z = S-Tete X = O, Y = H, Z = Hf X = O, Y = OMe, Z = Hg X = O, Y = H, Z = S-Teth X = O, Y = OMe, Z = S-Tet

[†] This paper is dedicated to Dr. Kyosuke Tsuda, Emeritus Professor of Tokyo University, on the occasion of his 75th birthday.

at C-7 and C-3', Y and Z, on these kinetic parameters are discussed.

The Δ^3 -derivatives (1a)-(1h) used as the substrates were prepared by known methods,³ and the Δ^2 -isomers (2a)-(2h) by base treatment of (1) (i-Pr₂NLi, THF, -70 °C or NEt₃, CH₂Cl₂, room temperature; acid work-up; purification by re-crystallisation or column chromatography on silica gel). The isomerisations were carried out at 20 ± 0.2 °C in dichloromethane under argon at an initial substrate concentration of 0.05 M and a triethylamine concentration of 0.15 M. Aliquots withdrawn at appropriate intervals were quenched with a cold, diluted hydrochloric acid and the amounts of the Δ^3 - and Δ^2 -compounds in the dichloromethane extracts were determined by HPLC [Waters Associates, μ -Porasil, n-hexane-CHCl₃ (1:1) or (1:2)]. Table shows the kinetic data calculated from the conventional equations for the first-order reversible reactions.⁴

Table. Apparent rate constants, k_f and k_r , and equilibrium constants K

[[1]_{initial} = 0.05 M, [NEt₃] = 0.15 M, CH₂Cl₂, 20 ± 0.2 °C]

Entry	Reaction	K	$k_f \times 10^4 \text{ (sec}^{-1}\text{)}$	$k_r \times 10^4 \text{ (sec}^{-1}\text{)}$
a	(1a) $\rightleftharpoons$ (2a)	0.653	3.88	5.95
b	(1b) $\rightleftharpoons$ (2b)	1.02	11.8	11.6
c	(1c) $\rightleftharpoons$ (2c)	2.27	85.4	37.6
d	(1d) $\rightleftharpoons$ (2d)	10.2	>395	>38.8
e	(1e) $\rightleftharpoons$ (2e)	0.563	0.0127	0.0226
f	(1f) $\rightleftharpoons$ (2f)	2.13	0.0764	0.0359
g	(1g) $\rightleftharpoons$ (2g)	9.00	0.245	0.0272
h	(1h) $\rightleftharpoons$ (2h)	28.4	3.59	0.126

Comparison of the data in entries a-d with those in entries e-h indicates that both forward and reverse reactions of the cepheids are more than 100 times faster than the reactions of the corresponding 1-oxa compounds and that the equilibrium concentrations of the Δ^2 -isomers are 2-4 times higher for 1-oxa-cepheids, except for the 7 α -unsubstituted 3-methyl compounds (entry a vs. e). The faster isomerisation of the cepheids can be attributed to a larger stabilisation of the intermediary carbanion with sulphur than with oxygen,⁵ and a higher stability of the 1-oxa-2-cepheids to a higher resonance effect in the vinyl ether system than in the corresponding thia system.⁵

Comparison of the data in adjacent entries (a vs. b, c vs. d and so on) demonstrates enhanced effects of the 7 α -methoxy substitution on the forward and reverse reactions as well as on the Δ^2 equilibrium concentrations, irrespective of the cepheids and the 1-oxa counterparts. The enhancement can be explained from release of the steric repulsions of the methoxy group in the more flexible Δ^2 -isomer to lower the potential energies of the Δ^2 -isomer as well as the transition state to greater extents in 7 α -methoxy compounds than in 7 α -unsubstituted ones.

The effects of the 3'-(1-methyl-1H-tetrazol-5-yl)thio (S-Tet) substituent are significant, irrespective of the 1-hetero atom (compare the data in entry a vs. c, b vs. d, e vs. g, and f vs. h). Thus, the substitution increases the forward rate, the reverse rate, and the Δ^2 equilibrium concentration more than 20-, several-, and 3 to 16-fold, respectively. These increases are attributable to a great decrease in the steric hindrance⁶ between the 3'-substituent and the diphenylmethyl ester grouping for the flexible Δ^2 -isomer, lowering the potential energies of the Δ^2 -isomer and the transition state.

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