Reductively Triggered Internal Cyclisation Reactions

by

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To Peace and Harry.

Abstract

Reductively triggered internal cyclisation reactions have been investigated as a prodrug system for the hypoxia selective release of aromatic nitrogen mustards.

The observed pseudo-first-order rate coefficients of cyclisation of several model 2-aminoaryl-acetamides and propanamides have been measured. Cyclisation was observed to be strongly influenced by stereochemistry, whereas electron withdrawal from the amine-bearing ring resulted in a comparatively modest slowing of the rate of cyclisation. Protonation of the leaving group appeared to increase the rate of cyclisation, while changes in 4-substitution on the leaving amine had little effect on this rate. The cyclisation of 2-(2-aminophenyl) alkanamides was found to be subject to general catalysis by acidic buffer components, and rate determining formation of the tetrahedral intermediate has been proposed.

Ring closure reactions of several 2-hydroxylaminophenylalkanamides have been studied by γ-radiolysis. HPLC methods have been developed for the separation of reduction and cyclisation products. Reduction stoichiometry implicates the hydroxylamine as the predominant reduction product of radiolysis of the 2-nitrophenylalkanamide precursors, which varied in the nature of substitution of the nitrobenzyl ring, 4-substitution of the leaving aniline, and overall geometry. Cyclisation *via* the hydroxylamino was observed to be significantly faster than that of its amino counterparts, and was similarly influenced by

changes in geometry. The hydroxylamine undergoes a base catalysed, oxygen dependent reaction under aerobic conditions. This reaction did not appear to be influenced by the geometry of the compound. Substitution of the hydroxylamine-bearing ring with a carboxamide group (CONHR σ_p = 0.36) lowered the pH at which hydroxylamino-amide cyclisation was slowest, compared with its unsubstituted counterpart. The reaction was found to be aided by electron-withdrawal from the leaving amine. Rate determining breakdown of the tetrahedral intermediate has been proposed.

Preliminary investigations have been made on 2-nitrophenyl alkyl esters and a 2,6-dinitrophenylamide prodrug system. Rapid, reductively triggered release of coupled phenols and amines has been observed from the nitro-esters and -amides, respectively. In contrast to amino-amide and hydroxylamino-amide cyclisation, *gem*-dimethyl substitution did not facilitate reductive release from the nitro-ester. The inability to measure the rates of reductive release in radiolysis solutions suggests that these reactions occur significantly faster than hydroxylamino-amide ring closure.

Molecular mechanics calculations have been undertaken to investigate relationships between the geometry of 2-aminoarylalkanamides, and rates of cyclisation. The distance between, and angle of approach of the nucleophilic and electrophilic centres in the calculated minimum-energy conformer did not display a correlation with cyclisation rates.

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Abbreviations and Symbols

Å	angstrom
A_t	absorbance at time t
AA8	cell line
α	Brønsted reaction constant
^{60}Co	cobalt 60
d	dose rate
DNA	deoxyribose nucleic acid
E	reduction potential
E_a	activation energy
EDTA	ethylenediaminetetraaceticacid
ε	molar absorptivity
G	radiation chemical yield
γ	gamma radiation
HPLC	high performance liquid chromatography
HSC	hypoxia-selective cytotoxin
I	ionic strength
IC_{50}	the concentration of drug required to inhibit the growth of cell culture by 50%
K	equilibrium constant
k	rate coefficient
LET	linear energy transfer
LFER	linear free energy relationship
λ_{max}	wavelength of maximum absorbance
mu	mass unit
σ	Hammett substituent constant
psi	pounds per square inch
ρ	Hammett reaction constant
r	correlation coefficient
s.d.	standard deviation
SN1	unimolecular nucleophilic substitution
SN2	bimolecular nucleophilic substitution
T	temperature
$t_{1/2}$	half-life
υ	vibrational stretching frequency