

Rate and equilibrium constants for oxazolidine and thiazolidine ring-opening reactions

M. Canle, A. Lawley, E. C. McManus and R.A. More O'Ferrall

Department of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland

ABSTRACT

Rate and equilibrium constants have been measured for opening and closing 2-[(4 dimethylamino)phenyl]-1,3-oxazolidine and -thiazolidine rings to form iminium ions in aqueous solution at 25°. Comparing rates of closure of the oxazolidine ring with attack of external hydroxide ion on the iminium ion yields a ratio of rate constants of 25 for intra- and intermolecular attack of oxyanion nucleophiles in this *endo*-cyclic ring-closure reaction. This ratio is significantly less than the factor of 10^3 - 10^4 commonly observed for similar *exo*-cyclic ring closures and is consistent with the presence of ring strain in the *endo*-cyclic transition state as envisaged in Baldwin's rules. Changes in N-alkyl substituent (Me, Et, Bu, Pri, Bu^t and phenyl) lead to mild (and parallel) changes in reaction rates and equilibrium constants for oxazolidine ring closure. For the corresponding thiazolidine rings, comparison of the N-H thiazolidine derivative of benzaldehyde with N-butyl and N-phenyl derivatives of cinnamaldehyde shows a much larger variation in rate constants for ring closure with N-substituent (10^8 -fold), but still small changes in equilibrium constants and rate constants for attack of hydroxide ion upon the iminium ion (<100-fold). This surprising contrast in kinetic and equilibrium behaviour is discussed in terms of non-bonded interactions in the transition state for ring-closure reactions.

INTRODUCTION

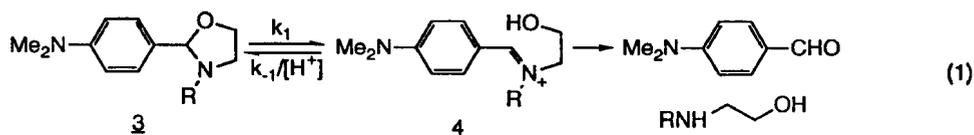
In a well known series of papers Baldwin (1) suggested that endocyclic opening or closing of small rings may be subject to a stereoelectronic constraint leading to ring-strain in the transition state not present in the reactants or products (2,3). In this paper we describe an attempt to quantify the magnitude of this strain for the oxazolidine ring by comparing measurements of rate and equilibrium constants with corresponding values for similar *exo*-cyclic ring closures and intermolecular reactions. As illustrated below the stereoelectronic effect is believed to arise from a less favourable trajectory of approach of the oxygen nucleophile to the iminium ion in *endo*- than *exo*-cyclic ring-closure.



In a related study we describe measurements of effects of N-alkyl and N-aryl substitution upon rates and equilibria for ring-closure. Kinetic and equilibrium substituent effects of substitution show a satisfactory correlation for oxazolidine rings but, surprisingly, not for similarly substituted thiazolidine rings.

OXAZOLIDINE RING-OPENING

The mechanisms of ring-opening of 2-aryl-N-alkyl-1,3-oxazolidines (e.g. **3**) have been thoroughly investigated by Fife and McClelland (4,5). When the 2-aryl substituent contains an electron donating group such as *p*-dimethylamino (**3**) the ring-opened iminium ion is sufficiently stable to be observed as a short-lived intermediate prior to its subsequent hydrolysis to *p*-dimethylamino benzaldehyde (equation 1).



The ring-opening and ring-closing reactions occur sufficiently rapidly for equilibrium constants to be measured spectrophotometrically as apparent pK_a values, ($K_a^{app} = [3][H^+]/[4]$), but slowly enough for rates of ring-opening and ring-closing to be measured using stopped-flow kinetics.

Plots of logs of rate constants against pH based on measurements for the *N*-butyl oxazolidine **3** ($R = \text{Bu}$) are shown in Fig 1. The upper line in this figure represents ring-opening and ring-closing and the lower line the hydrolysis reaction. The upward "break" in the upper line corresponds to an apparent pK_a for ring-closing, $pK_a^{\text{app}} = 9.28$. At pHs above this break the reaction observed is hydroxide-catalysed ring-closing of the iminium ion with rate-determining intramolecular attack of the oxyanion upon the carbon atom of the iminium ion as in **5**. At pHs below the break the reverse pH-independent unimolecular ring-opening to form the zwitterion intermediate **5** is the reaction observed. The downward "break" at pH 6.5 represents the pK_a for protonation of the oxazolidine ring.

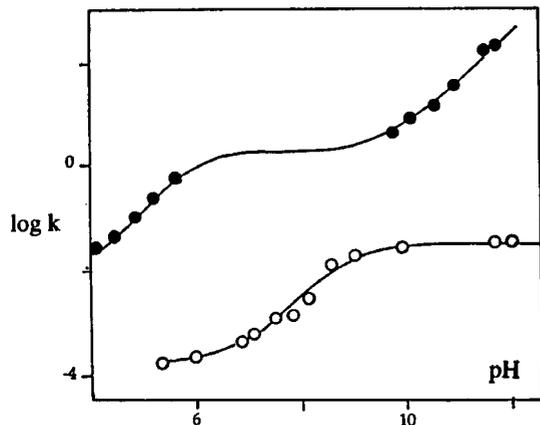
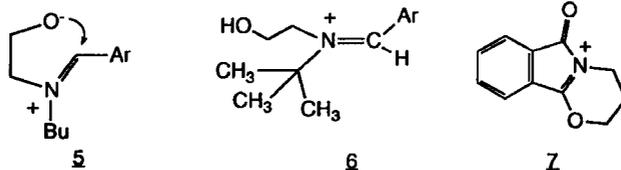


Fig. 1 pH Profiles for ring-opening and hydrolysis of 2-[(4-dimethylamino)phenyl]-*N*-butyl-1,3-oxazolidine.

For the hydrolysis reaction of **3** (lower curve in Fig. 1) the apparent pK_a for oxazolidine ring-opening appears as a downward break. The hydroxide-catalysed reaction at pHs below this pH represents hydroxide attack on the ring-opened iminium ion (**4**). The pH-independent reaction at lowest pHs presumably represents the reaction of water with this ion.



N-Alkyl Substituent Effects

Table 1 shows equilibrium constants and rate constants for ring-opening of 2-(4-dimethylamino)phenyl substituted oxazolidines (**3**) bearing *N*-alkyl substituents ranging in size from methyl to *t*-butyl, and also for *N*-phenyl. Unfortunately, no measurements could be made for the parent *N*-H oxazolidine for which the ring opened imine is stable at all pHs.

From Table 1 it can be seen that there is little difference between apparent equilibrium constants for ring-opening for the methyl, ethyl, butyl and isopropyl substituents ($pK_a^{\text{app}} = 9.1 - 9.3$) but that the pK_a^{app} for *t*-butyl (and also phenyl) is significantly smaller. The effect of *t*-butyl may be interpreted as a *cis*-steric interaction (**6**) which is relieved for other alkyl groups by replacement of one of the methyl groups by hydrogen. Probably the low pK_a^{app} for the phenyl group represents an unfavourable inductive effect from this substituent.

Inspection of ring-opening rate constants in Table 1 shows a parallel but less marked dependence on the *N*-substituent than do the equilibrium constants, as expected if the main influence on relative reactivities is the difference in thermodynamic stabilities of reactants and products. For both rates and equilibria therefore these reactions show normal behaviour, in contrast to the effects of *N*-substituents in the thiazolidine ring discussed below.

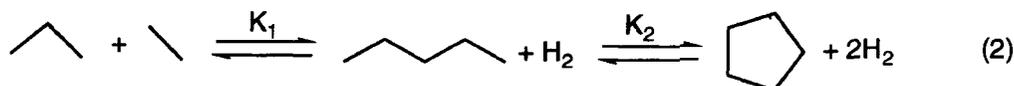
Ring-strain in the oxazolidine ring-closing transition state

In assessing the influence of ring-strain arising from stereoelectronic effects in the transition state for oxazolidine ring-closure it is useful to compare reaction rates and equilibria for *intra* and *intermolecular* reactions.

TABLE 1. Rate and equilibrium constants for ring opening and closing of *N*-substituted 2-[(4-dimethylamino)phenyl]-1,3-oxazolidines (**3**).

<i>N</i> -sub	Me	Et	Bu	Pr ⁱ	Bu ^t	Ph
pK_a^{app}	9.3	9.1	9.3	9.1	8.4	6.9
k_1/s^{-1}	-	0.7	1.4	-	0.35	0.025

In the absence of direct measurements of equilibrium constants for intermolecular analogues of oxazolidine ring closing a ratio of equilibrium constants for intra- and inter-molecular reaction can be modelled by the ratio K_2/K_1 for the simple hydrocarbon reaction in equation 2. From measurements of free energies of formation of hydrocarbons in aqueous solution (6) $K_2/K_1 = 50$ may be calculated. As discussed by Mandolini, the advantage for the intramolecular cyclisation of pentane over bimolecular linking of ethane and propane reflects the entropic advantage of the former balanced by a small degree of strain ($\Delta H = 4.4$ kcal/mole) in the cyclopentane ring (3).



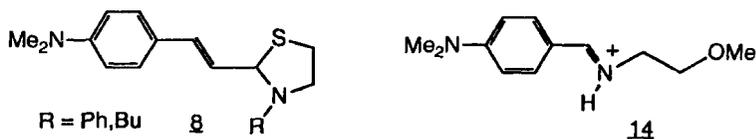
To assess the influence of ring-strain in the cyclisation transition state we may compare the ratio of $K_2/K_1 = 50$ with the ratio of rate constants for cyclisation of the zwitterion **5** and attack of an external alkoxide ion with the same $\text{p}K_a$ as the internal anion. One might suppose that the equilibrium value represents an upper limit for the kinetic difference if there is no greater strain in the transition state for cyclisation than in the cyclic product.

From Figure 1 we can obtain values of k_{OH} (a) for the hydroxide-catalysed ring closure of the ion **4** ($4 \times 10^4 \text{M}^{-1} \text{s}^{-1}$) and (b) for external attack of hydroxide ion on the carbon-nitrogen double bond ($1.3 \times 10^3 \text{M}^{-1} \text{s}^{-1}$). The first rate constant corresponds to k_{intra}/K_b where k_{intra} is the required cyclisation rate constant and K_b is the basic ionisation constant for the hydroxyl group of **4**. The value of K_b may be estimated as ~ 0.15 ($\text{p}K_a \sim 14.8$) by combining an estimated $\text{p}K_a = 9.7$ for the corresponding thiol iminium ion (**7**) with Taft plots for the ionisation of alcohols and thiols (8). The intermolecular rate constant k_{inter} for an alcohol of similar $\text{p}K_a$ may be derived from k_{OH} for hydroxide ion attack on the iminium ion and a ratio of 7.5 between rates of attack of hydroxide and an alkoxide ion of this $\text{p}K_a$, estimated from Jencks and measurements for attack of hydroxide and alkoxide ions on the iminium ion analogue **7**. We obtain the ratio of intra- and inter-molecular rate constants $k_{\text{intra}}/k_{\text{inter}} = 25$. This ratio differs little from the equilibrium value of 50 based on K_2/K_1 for the hydrocarbons reactions of equation 1. Therefore it would seem that there is no special strain in the transition state for cyclisation.

This conclusion would be premature, however, as general experience with exocyclic intramolecular nucleophilic attack, e.g. in ester hydrolysis, is that the intramolecular reaction is 10^3 - 10^5 times faster than the intermolecular reaction (9). For nucleophilic substitution, Mandolini has suggested that this may be because of lower non-bonding interactions in the transition state of a bimolecular reaction ($\text{S}_{\text{N}}2$) than of the corresponding intramolecular reaction (3). If this is true of nucleophilic attack at a π -bond then a small but significant strain for the endocyclic transition state (3-5 kcal/mole) may be implied.

THIAZOLIDINE RING-OPENING

For thiazolidine ring-opening it is more difficult to compare intra- and inter-molecular reactions because measurements are only now beginning to be made on the intermolecular attack of thiolate ions upon iminium ions (10). However, it is possible to examine the effect of N-alkyl and N-aryl substituents upon rates and equilibria for ring-opening and ring-closing. These reactions are closely analogous to those of the corresponding oxazolidine rings save that the ring-closed thiazolidine is more strongly favoured relative to ring-opened thiol imine or iminium ion by about five orders of magnitude. Therefore the unsubstituted (N-H) 1,3 thiazolidine derivative of *p*-dimethylamino benzaldehyde may be prepared and rates and equilibria for ring-opening compared with previously measured values for N-butyl and N-phenyl thiazolidine derivatives of *p*-dimethylamino cinnamaldehyde (**8**) studied by Fife and coworkers (11).



Studies of 2-[(4-dimethylamino)phenyl]-1,3 thiazolidine (**9**) show that as the pH decreases from 7 to 5 a strong absorption appears at 400nm. As the pH decreases further, from 4 to 2, this absorption disappears again. The overall dependence of the absorption upon pH is shown in Fig 2.

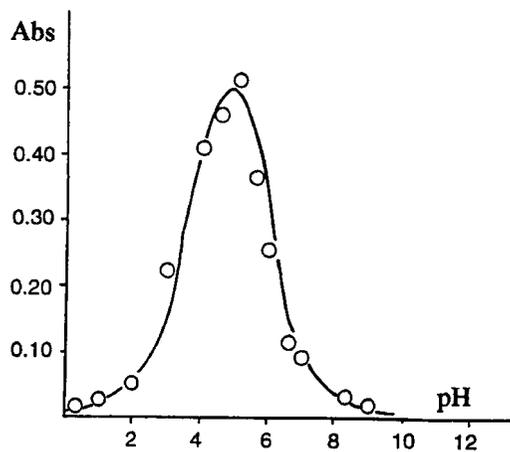


Fig. 2 Absorbance of solutions of 2-[(4-dimethylamino)phenyl]-1,3-thiazolidine ($2.0 \times 10^{-4} \text{M}$) at 400nm as a function of pH.

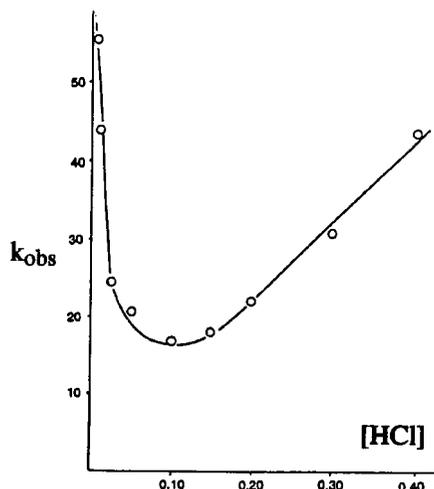
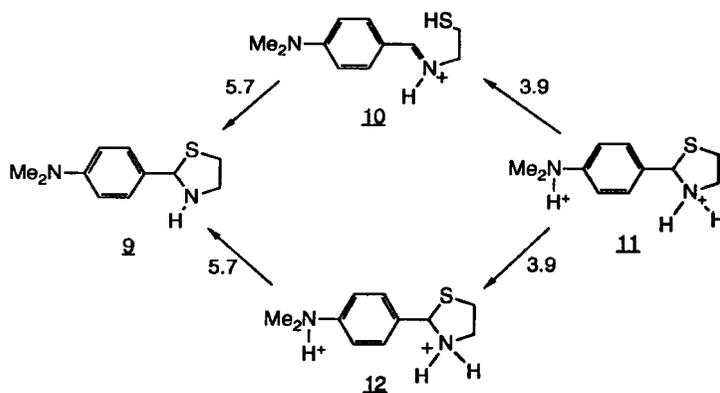


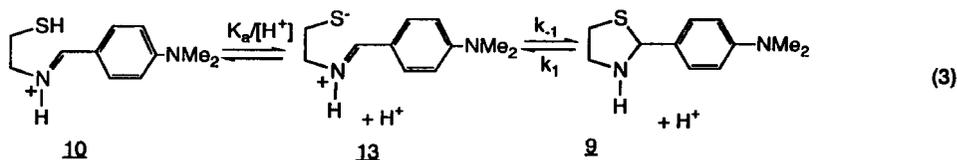
Fig. 3 Plot of first order rate constants for ring closing of the thiol iminium ion **10** against acid concentration.

This behaviour may be interpreted in terms of Scheme 1. The observed absorbance is attributed to the iminium ion **10** formed by opening of the thiazolidine ring **9** at moderate pH. At low pH the ring closes again to form the diprotonated thiazolidine **11**. Comparison of the apparent extinction coefficient of the iminium ion at maximum ring-opening with the measured extinction coefficient of the methoxyethyliminium ion **14**, a model for the fully-formed iminium ion, indicates that the greatest degree of ring-opening is about 50%. Combining this measurement with the pH-dependence of the absorbance in Figure 2 allows the pK_a s and apparent pK_a s (ionisation plus ring-opening) shown in Scheme 1 to be derived, the arrows indicate directions of ionisation.

Scheme 1



The rate of ring-opening is too rapid for kinetic measurements, but quenching the ring-opened ion at pH 5-7 into strong acid between pH 0 - 2 allows the rate of the ring-closing reaction to be measured. As shown in Fig. 3, this displays two reactions showing a normal and an inverse dependence upon hydrogen ion concentration. We interpret the inverse dependence as reflecting pre-equilibrium ionisation of the thiol group of the iminium ion (**10** \rightarrow **13**) followed by rate-determining ring-closure of the zwitterion (**13** \rightarrow **9**) as shown in equation (3).



The measured rate constant for ring-closure $k_{-1}K_a = 0.5 \text{ s}^{-1}$ may be combined with the apparent equilibrium constant for ring-closing ($pK_a^{\text{app}} = 5.7$) to obtain a rate constant k_1 in the ring-opening direction. Unfortunately, no measurements for N-alkyl substituted thiazolidines derived from dimethylamino benzaldehyde could be made because ring-opening occurred to too small an extent to be easily measurable. Nevertheless the rate and equilibrium constants for ring-opening of the N-H compound may be compared with values for N-butyl and N-phenyl thiazolidine derivatives of *p*-dimethylaminocinnamaldehyde measured by Fife (**8**, R = Bu, Ph).

These rate and equilibrium constants are listed in Table 2. The rate constants (k_1) refer to ring-opening and the equilibrium constants (pK_a^{app}) to the apparent ionisation constants for ring-closing, e.g. $pK_a^{app} = 6.2$ for ring-opening of the N-H thiazolidine derivative of *p*-dimethylaminocinnamaldehyde (**8**, R = H) which was measured (without making kinetic measurements) by Fife and coworkers (11). This has practically the same value as for the corresponding *p*-dimethylamino benzaldehyde thiazolidine (5.7), but measurements for oxazolidines show that the cinnamaldehyde ionisation may be more favourable, by as much as two orders of magnitude, when the nitrogen bears an alkyl group, presumably because of greater steric interactions from *cis*-substituents in the benzaldehyde iminium ion than its cinnamaldehyde counterpart.

N-alkyl substituent effects

What is surprising about the results in Table 2 is that the rate constants for opening the thiazolidine ring (k_1 of equation 3) show a very marked dependence upon N-substituent (H, Bu, Ph), with the largest value ($2.5 \times 10^5 \text{ s}^{-1}$ for H) nearly 10^8 times greater than the smallest ($5.7 \times 10^{-3} \text{ s}^{-1}$ for phenyl), whereas the corresponding variation in equilibrium constants is less than 30-fold ($pK_a^{app} = 5.7 - 7.1$). Strictly speaking the equilibrium constant does not refer to the same process as the reaction rate, namely ring-opening to the zwitterion (**9** \rightarrow **13** in equation 3), but to this reaction plus the subsequent protonation equilibrium yielding the iminium ion (**9** \rightarrow **10**). However, the protonation equilibrium should depend only weakly on N-substituent so there should be little difference in the substituent dependence of the two equilibrium constants.

TABLE 2. Rate and equilibrium constants for opening of N-substituted thiazolidine rings (**8** and **9**).

N-sub	Aldehyde ^a	pK_a^{app}	k_1/s^{-1}	$k_{OH}^b/M^{-1}\text{s}^{-1}$
H	B	5.7	2.5×10^5	5.5×10^3
H	C	6.2	-	1.3×10^4
Bu	C	6.3	1.4	9.1×10^3
Ph	C	7.1	5.7×10^{-3}	1.7×10^2

^aThiazolidine derived from *p*-dimethylaminobenzaldehyde (B), *p*-dimethylaminocinnamaldehyde (C).

^bRate constant for hydroxide attack on ring-opened iminium ion.

It thus appears that opening of the thiazolidine ring displays a large mismatch between effects of changing the substituent on nitrogen upon reaction rates and upon equilibrium constants, with the former very sensitively affected by the substituent and the latter affected very little. In seeking an explanation of this behaviour we note again that the N-H substituent refers to a benzaldehyde thiazolidine and iminium ion, while the N-butyl and N-phenyl substituents refer to the corresponding cinnamaldehyde derivatives. However, equilibrium constants for the *p*-dimethylamino benzaldehyde and cinnamaldehydes are nearly identical and there seems no reason to doubt that their rates would also be similar.

Also included in Table 2 are rate constants (k_{OH}) for attack of hydroxide ion upon the iminium ion. These were measured from the rates of hydrolysis of the iminium ion to *p*-dimethylaminobenzaldehyde and cinnamaldehyde following thiazolidine ring-opening. It can be seen that, again in contrast to the intramolecular reaction, the variation in rate constant for hydroxide attack is quite small (90-fold compared with 10^8 -fold). Strictly speaking, hydroxide attack might be better compared with intramolecular attack of the thiolate ion upon the iminium ion. However, the mild variation in equilibrium constants for this reaction with N-substituent implies that the same substituent sensitivity applies to the ring-closing reaction as to the reverse process of ring-opening.

Unfortunately, a detailed comparison of oxazolidine and thiazolidine ring-opening is not possible because only two N-substituents are unchanged between Tables 1 and 2 and, in particular, no N-H substituent has been studied for the oxazolidine rings. However, for the alkyl and aryl N-substituents of Table 1 there is no suggestion of a breakdown of the interdependence of rate and equilibrium constants that would offer a hint of the behaviour observed in Table 2.

It seems unlikely that a stereoelectronic constraint of the kind suggested by Baldwin, specifically affecting the transition state, could explain the observed behaviour because all the reactions correspond to *5-endo-trig* ring-opening and closure of the thiazolidine ring. In this respect there is no differentiation between them.

More likely as an explanation would seem to be that in the transition state for ring-opening, non-bonded interactions between a bulky N-substituent and the dimethyl aminophenyl or styryl groups are greater than in the ring-opened iminium ion. Such non-bonded interactions presumably arise principally as a result of a stereoelectronic preference for *anti*-periplanar orientation of the carbon-sulphur bond subject to cleavage and the lone pair of electrons on the nitrogen atom. However an additional constraint may be imposed because relief of non-bonded interactions incurs additional strain of the type envisaged by Baldwin. It is also possible that the behaviour partly reflects an intrinsic difference in reactivity between N-H, N-methyl and N-aryl nitrogen lone pairs, but if so, it is hard to see why this would not appear in the intermolecular reactions with hydroxide ion. Moreover, the explanation offered needs to be consistent with the apparent difference in behaviour of oxazolidine and thiazolidine rings. A difference in stereoelectronic requirements of oxygen and sulphur, for example as expressed in the relative ease of cyclisations to different ring sizes, is well known (12). However, further studies, e.g. of N-H and N-alkyl substituted *p*-dimethylamino cinnamaldehyde thiazolidines, may be required before a firm conclusion can be drawn.

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