The Influence of Remote Substituents on Amide Bond Formation. The Reaction of Oxazolinones with Benzylamine

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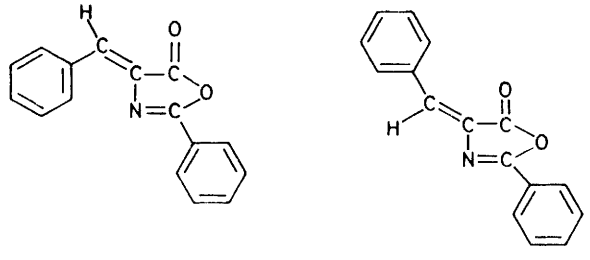
The second-order rate constants for the reaction of nine substituted (*Z*)-4-benzylidene-2-phenyloxazolin-5-ones with benzylamine in acetonitrile have been obtained. There is an electronic effect in the predicted direction for substitution in either ring. There is a difference in steric effects which appears to be ring specific. *ortho*-Substituents in the benzylidene ring lead to rate enhancement while *ortho*-substituents in the phenyl ring retard the rate. The reaction of the oxazolinones with α-methylbenzylamine indicates a large steric effect upon increasing steric demand in the nucleophile.

ALTHOUGH unsaturated oxazolinones have been known for nearly a century,[1] there have been very few reported studies on the quantitative aspects of their reactivity. The published work [2-5] involves the interests of enzyme mechanism and has utilized only (*E*)- and (*Z*)-4-benzylidene-2-phenyloxazolin-5-one. While there is no body of work on quantitative studies, oxazolinones have long been of interest for synthetic and mechanistic reasons. They are useful intermediates in the synthesis of amino-acids, peptides, and dehydropeptides,[6] they have been implicated in mechanisms of amino-acid racemization during peptide bond formation,[7,8] they have been postulated to be intermediates in protease-catalysed hydrolyses,[9-13] and they are useful spectroscopic probes.[14,15]

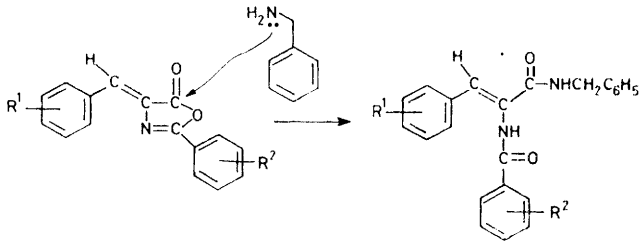
Considering the long history of oxazolinones, questions concerning their actual geometrical orientation have only recently been settled. The benzylidene moiety may have either an *E*- or *Z*-orientation about the exocyclic double bond. While earlier publications appear to have implied presence of the *E*-isomer,[2-4,16] it is now clear from absorption [5,14,15] resonance Raman,[14] n.m.r.,[17] and *X*-ray studies [18] that the 'stable' isomer formed from the Erlenmeyer azlactone synthesis [19] is the *Z*-isomer. The *Z*-isomer can be converted into the *E*-isomer by treatment with HBr.[20]



Z *E*

Geometric isomers of 4-benzylidene-2-phenyloxazolin-5-one

Because of continuing interest in the quantitative aspects of peptide bond formation,[8] spectroscopic studies,[14,15] and enzyme mechanisms,[11-13] it was considered that detailed study of oxazolinone reactions would be valuable as a model system as well as in its own right. Oxazolinones are activated internal esters of *N*-acylamino-acids and as such are susceptible to nucleophilic ring-opening reactions (Figure 2). These molecules lend themselves well to study by absorption spectroscopy because of their intense extinction coefficients in the visible region and because of the large difference in absorption maxima of the oxazolinones compared to the ring-opened products.



(1)

a; $R^1 = R^2 = H$
b; $R^1 = H$, $R^2 = p\text{-}CH_3$
c; $R^1 = H$, $R^2 = o\text{-}CH_3$
d; $R^1 = p\text{-}CH_3$, $R^2 = H$
e; $R^1 = o\text{-}CH_3$, $R^2 = H$
f; $R^1 = R^2 = p\text{-}CH_3$
g; $R^1 = R^2 = o\text{-}CH_3$
h; $R^1 = p\text{-}Cl$, $R^2 = H$
i; $R^1 = o\text{-}Cl$, $R^2 = H$

Reactions of benzylamine with oxazolines

In this paper we report, apparently for the first time, the second-order kinetics of the ring-opening reaction of oxazolinones with benzylamine. Compounds (1a—i) were chosen for two reasons. First, we were interested in the steric effect of remote substituents on peptide bond formation. We wished to determine what effect, if any, the *o*-methyl groups would exert at their relatively removed positions from the site of nucleophilic attack. Secondly, we wanted to determine if increasing steric demand in the nucleophile would increase any small *o*-methyl interactions. For this purpose α-methylbenzylamine was chosen as nucleophile.

EXPERIMENTAL

The synthesis of the alkylated oxazolinones has been reported.[21] The chlorinated oxazolinones were obtained by similar methods and had m.p.s in agreement with reported

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values.[22] The reactions were carried out at 25 °C in the jacketted cell compartment of a Cary 219 u.v.–visible spectrophotometer. The solvent was spectral grade acetonitrile (Eastman or Fisher) and was used without further purification. Benzylamine, (+)-α-methylbenzylamine, and (−)-α-methylbenzylamine were obtained from Aldrich Chemical Company and were used without further purification.

The rate constants were calculated by least-squares analysis of a plot of $(a - b)^{-1} \ln[b(a - x)/a(b - x)]$ *versus* time, where a = initial concentration of oxazolinone, b = initial concentration of amine, and x = product at time t. The rate constants are the average of 3—7 determinations. Extinction coefficients were obtained from Beer's law plots. Correlation coefficients of the lines obtained in all cases were at least 0.99. Intercepts were zero within experimental error. Reactions were followed to at least 50% completion. No deviation of kinetic data was noted up to 90% completion. Concentration of amines ranged from 2.84×10^{-2} to 4.80×10^{-2}M. Concentrations of oxazolinones ranged from 0.78×10^{-3} to 3.69×10^{-3}M. Because of the intense extinction coefficient at the absorption maximum and to avoid any absorption tail of the product, reactions were followed at 400—415 nm (see Table).

Data for the reaction of oxazolinones with amines in acetonitrile at 25 °C

Compound	λ/nm	ε	Benzylamine 10^2k_2/l mol^{-1} s^{-1}	(+)-α-Methylbenzylamine 10^2k_2/l mol^{-1} s^{-1}	(−)-α-Methylbenzylamine 10^2k_2/l mol^{-1} s^{-1}
(1a)	400	390 ± 15	4.80 ± 0.12	0.37 ± 0.01	0.39 ± 0.01
(1b)	400	1 089 ± 74	2.54 ± 0.13		
(1c)	400	613 ± 37	1.25 ± 0.02	0.076 ± 0.002	
(1d)	410	746 ± 29	2.26 ± 0.06		
(1e)	410	504 ± 17	4.16 ± 0.17	0.31 ± 0.01	
(1f)	412	760 ± 7	1.17 ± 0.07		
(1g)	410	636 ± 5	1.10 ± 0.07		
(1h)	405	531 ± 17	10.04 ± 0.04		
(1i)	403	708 ± 20	30.50 ± 0.60		

RESULTS AND DISCUSSION

In this study we were primarily interested in the steric effects of *o*-methyl groups on nucleophilic attack on oxazolinones. Because the methyl and chloro-substituents introduce electronic effects into the reaction, both *ortho*- and *para*-substitution were studied in order to assess their effects. It is obvious from the data in the Table that this reaction is influenced by electronic effects. This was expected because of the observation that the absorption spectra of oxazolinones are dramatically altered depending on substituents.[15] In the case of methyl and chloro-groups, the *o*-substituent parameters (σ_o) are not very different from the *p*-substituent parameters (σ_p) [23] so to a good approximation electronic effects for (1b—e) are the same; (1f—g) are the same; and (1h and i) are the same. Thus any significant reactivity differences can be attributed to steric effects.

There is a significant rate difference between the *para*- and *ortho*-pairs (1b and c), (1d and e), and (1h and i). This is approximately a factor of two in the case of the methyl substituents and a factor of three in the case of the chloro-substituents. While the effects of the electron-donating *p*-methyl group are nearly the same regardless of which phenyl ring is substituted ($k_{(1b)} \simeq k_{(1d)}$), the effects of *ortho*-substitution differ dramatically. In addition, these effects are ' ring-selective '. Generalizing on the relatively small sample, *ortho*-substitution in the 2-phenyl ring slows down the rate of nucleophilic attack while *ortho*-substitution in the 4-benzylidene ring speeds up the rate of nucleophilic attack. Presumably, the planar oxazolinone exhibits hindrance between the 4-benzylidene *o*-substituent and the ethylenic hydrogen. When the molecule is ring opened, this strain is relieved. This steric acceleration is noted for an electron-attracting substituent as well as an electron-releasing group and is thus due to size effects rather than electronic effects. Steric acceleration of a similar type has recently been noted in the hydrolysis of substituted furyl- and thienylacryloylimidazoles.[24]

Fortuitously, the steric acceleration by *o*-substitution in the 4-benzylidene ring is almost exactly counterbalanced by steric inhibition of *o*-substitution in the 2-phenyl ring. Within experimental error, the reactions of (1f and g) with benzylamine are identical. The effects of the two *p*-methyl groups (1f) are simply additive ($k_{(1b)}/k_{(1a)} \simeq k_{(1d)}/k_{(1a)} \simeq k_{(1f)}/k_{(1b)} \simeq k_{(1f)}/k_{(1d)}$).

While effects of substituents in the oxazolinone are relatively small, there is a much larger effect on increasing steric demand in the nucleophile. The reaction of (+)- or (−)-α-methylbenzylamine with (1a) is slower by a factor of 13 than reaction of (1a) with benzylamine. Not surprisingly, there is no difference in the rate of the reaction dependent upon which optical isomer is employed. Relatively, there is little change when comparing $k_{(1e)}/k_{(1c)}$ for benzylamine (3.32) *versus* α-methylbenzylamine (4.08) attack.

While there is no information concerning the position of the transition state or tetrahedral intermediate along the reaction co-ordinate for this reaction, it is clear from the good kinetic data that the rate-determining step involves attack of one molecule of benzylamine on one molecule of oxazolinone. It is also clear that electronic effects exert a strong influence on kinetic parameters and thus charge separation is important in the transition state. We are currently carrying out studies to determine in more detail the nature of the transition state in this reaction and to determine other effects on amide bond formation.

In conclusion, it has been demonstrated that oxazolinone ring-opening reactions can be studied readily by second-order kinetics and that electronic effects of groups in either ring are important. Further, there is a small steric effect of *ortho*-substituents in the two rings, but this

effect is in opposite directions and does not depend on the electronic nature of the substituent.

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