The Decarboxylative Route to Azomethine Ylides. Mechanism of 1,3-Dipole Formation

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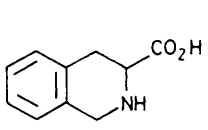
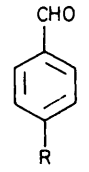
Evidence is presented that indicates that the decarboxylative route to azomethine ylides from both primary and secondary, cyclic and acyclic, α-amino acids involves an intermediate oxazolidin-5-one which loses carbon dioxide in a 1,3-dipolar cycloreversion reaction to generate an azomethine ylide stereospecifically.

Our stereochemical studies of the cycloadducts produced *via* the decarboxylative route to azomethine ylides[1,2] provided clear evidence of stereospecific formation of the *anti*-dipole in many instances and lack of stereospecificity in certain cases. Our previous extensive experience with maleimides as dipolarophiles[3] strongly suggested that the cycloadduct stereochemistry reported in the preceding paper[2] reflects the stereochemistry of the kinetically formed dipole(s), *i.e.* dipole stereomutation is not expected to occur with such a reactive dipolarophile.

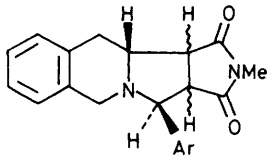
However, dipole stereochemistry is sensitive to both structural changes in the amino acid and aldehyde components, and temperature. Thus the tetrahydroisoquinoline 3-carboxylic acid (**1**) reacts [dimethylformamide (DMF),



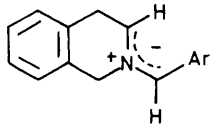
(**1**)



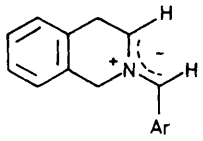
(**2**) a; R = NMe_2
b; R = NO_2



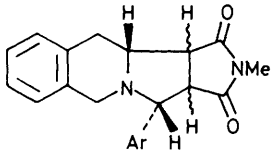
(**3**) a; Ar = p-$Me_2NC_6H_4$
b; Ar = p-$O_2NC_6H_4$



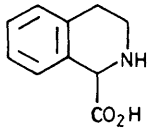
(**4**)



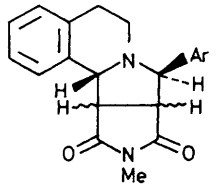
(**5**)



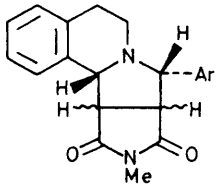
(**6**) Ar = p-$O_2NC_6H_4$



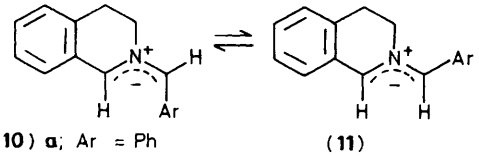
(**7**)



(**8**) a; Ar = Ph
b; Ar = 2-pyridyl

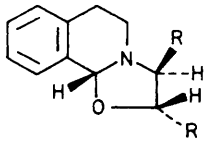


(**9**) a; Ar = Ph
b; Ar = 2-pyridyl

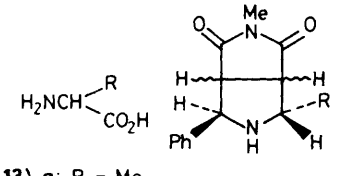


(**10**) a; Ar = Ph
b; Ar = 2-pyridyl

(**11**)

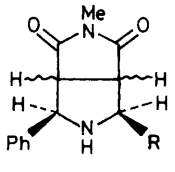


(**12**) R = 2-pyridyl



(**13**) a; R = Me
b; R = CH_2Ph
c; R = CH_2CH_2SMe

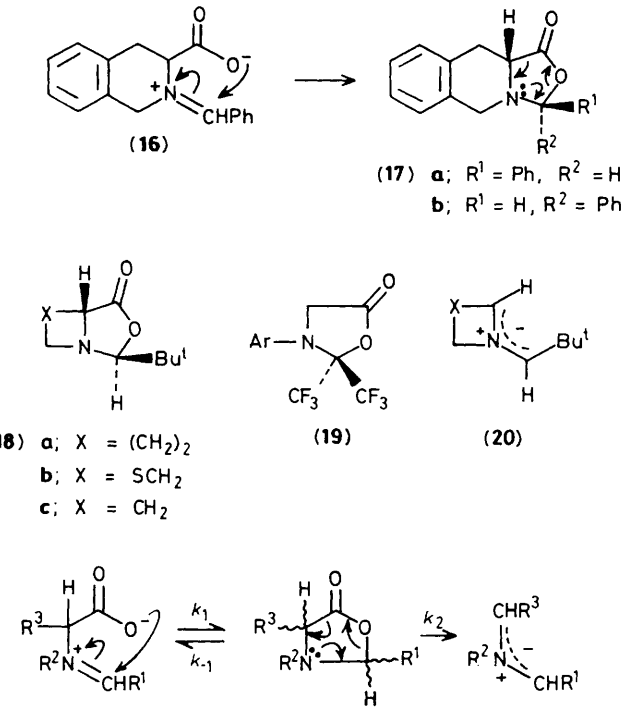
(**14**)



(**15**)

120 °C, 10 h] with (**2a**) and *N*-methylmaleimide to give (66%) a 1:1.2 mixture of *endo*- and *exo*-cycloadducts (**3a**) arising solely from the *anti*-dipole (**4**).† No products arising from the *syn*-dipole (**5**) could be detected. In contrast, (**1**) reacts (DMF, 120 °C, 0.5 h) with (**2b**) and *N*-methylmaleimide to give (98%) a 10:1 mixture of cycloadducts (**3b**, *endo*:*exo*, 1.6:1) and (**6**) arising from the *anti*- and *syn*-dipole respectively. At high temperature (DMF, 120 °C, 1 h), (**7**) reacts with benzaldehyde and *N*-methylmaleimide to give (83%) a 1:1 mixture of cycloadducts (**8a**) and (**9a**) (each comprising a mixture of *endo*- and *exo*-cycloadducts) arising from the *anti*- and *syn*-dipoles respectively. When the reaction is carried out at lower temperature (DMF, 21 °C, 120 h, incomplete reaction) the product consists of a 2.7:1 mixture of (**8a**) and (**9a**) (each comprising a mixture of *endo*- and *exo*-cycloadducts). It is tempting to conclude that this latter reflects the lower barrier to dipole stereomutation (**10a**) ⇌ (**11a**) compared with (**4**) ⇌ (**5**) owing to the greater charge delocalisation, and consequent reduction in bond order, afforded by the conjugation of two benzene rings to the dipole in the former case. Dipole stereomutation is unlikely with such a reactive dipolarophile but, if it occurred, might be expected to be facilitated by a polar solvent. However, the same mixture of (**8a**) and (**9a**) is obtained from reactions in DMF (120 °C) and toluene (110 °C). Nevertheless, it was felt that a definitive experiment was needed on the stereochemical integrity of the *anti*-dipole (**10**). This was provided by heating the oxazolidine (**12**)[4] (acetonitrile, 80 °C) in the presence of 1 mole of *N*-methylmaleimide. The product comprised a *ca.* 1:1 mixture of *endo*- and *exo*-cycloadducts (**8b**) derived solely from the *anti*-dipole (**10b**). In contrast, when the acid (**7**) was heated with 2-pyridaldehyde and *N*-methylmaleimide under the same conditions it gave a *ca.* 1:1 mixture of stereoisomers (**8b**) and (**9b**) (each a mixture of *endo*- and *exo*-cycloadducts) derived from both *anti*(**10b**)- and *syn*(**11b**)-dipoles. Thus 1,3-cycloreversion of (**12**) occurs stereospecifically to give (**10b**) and the stereochemical integrity of (**10b**) is retained in the subsequent cycloaddition with *N*-methylmaleimide. Similar trends are observed for the acyclic primary amino acids (**13a—c**) which give mixtures of (**14**) and (**15**) when reacted with benzaldehyde and *N*-methylmaleimide. Thus (**13c**) reacts (DMF, 153 °C) with benzaldehyde and *N*-methylmaleimide to give a 2.6:1 mixture of cycloadducts (**14c**) and (**15c**) (each comprising a mixture of *endo*- and *exo*-cycloadducts) arising from the *anti*- and *syn*-dipoles respectively. When this reaction is carried out at 100 °C and at 60 °C the ratio of (**14c**) to (**15c**) increases to 3.5:1 and 3.8:1 respectively. Analogous temperature dependent trends are observed in cycloadditions of (**13a**) and (**13b**).

A kinetic preference for the *anti*-dipole is thus confirmed and sensitivity to temperature and structural features clearly demonstrated in certain cases. However, the mechanistic basis for the observed initial kinetic preference for the *anti*-dipole in both cyclic secondary amino acids and acyclic primary amino acids remained to be defined and numerous possibilities were considered.‡ MNDO calculations on the *anti*- and *syn*-dipoles (**4**, Ar = Ph) and (**5**, Ar = Ph) showed the *syn*-dipole (**5**) was 1.8 kcal mol^{-1} (1 kcal = 4.184 kJ) more stable than the *anti*-dipole (**4**). Further MNDO calculations of the reaction path for the decarboxylation of the *anti*- and *syn*-zwitterion (**16**) to give the corresponding dipoles (**4**) and (**5**) revealed



Scheme 1

how favourable the cyclisation (**16**) → (**17**) was even though it is a 5-*endo*-trig process. The cyclisation (**16**) → (**17**), if stereospecific, would provide the necessary mechanistic control over dipole stereochemistry since (**17**) could undergo a retro-1,3-dipolar cycloaddition (**17**, arrows) generating the azomethine ylide.

Retro-1,3-dipolar cycloadditions occur stereospecifically[5] and (**17a**) would be expected to furnish the *anti*-dipole (**4**), whilst (**17b**) should give rise to the *syn*-dipole (**5**). MNDO calculations on (**17a**) and (**17b**) show that (**17a**) is more stable by 2.8 kcal mol^{-1}. Strong support for the involvement of oxazolidin-5-ones such as (**17**) in the decarboxylative route to azomethine ylides is provided by the observation that proline, thiazolidine-4-carboxylic acid, and azetidine-2-carboxylic acid react stereospecifically with pivalaldehyde to give a single oxazolidin-5-one (**18a—c**, respectively).[6] Moreover, (**18a**) is reported to undergo cycloaddition (toluene, 105 °C, 16 h) to tetramethyl ethylene-1,1,2,2-tetracarboxylate with loss of carbon dioxide.[7] The oxazolidin-5-ones (**19**) also generate azomethine ylides on heating.[8] However, neither of these reports addresses the question of dipole stereochemistry. Nevertheless, loss of carbon dioxide from (**18a—c**) in a 1,3-dipolar cycloreversion is expected to generate the *anti*-dipole (**20**).§ Huisgen's extensive work on cycloadditions of mesoionic oxazolones (munchnones)[9] provides further numerous examples where transient bicyclic oxazolidin-5-ones give rise to azomethine ylides by loss of carbon dioxide. These intermediates can be isolated in certain bridged ring systems where decarboxylation is sterically disfavoured[10] or where the cycloreversion involves loss of carbonyl sulphide.[11] Nitrile ylides can be generated by thermolysis of oxazolin-5-

† All new compounds gave satisfactory microanalytical and spectral data. Stereochemical assignments are made on the basis of nuclear Overhauser effect (n.O.e.) difference spectroscopy.

‡ These will be discussed in the full paper on this work.

§ Note that stereospecific formation of (**20**) need not necessarily occur if oxazolidin-5-one equilibration is faster than cycloreversion.

ones,[12] and 1,3-oxathiolan-5-ones decarboxylate to give thiiranes, presumably *via* a 1,3-dipole, at high temperatures.[13]

The results reported herein and in the preceeding communication[2] support the suggestion that the decarboxylative route to azomethine ylides from both primary and secondary, cyclic and acyclic, α-amino acids involves an intermediate oxazolidin-5-one which loses carbon dioxide in a 1,3-dipolar cycloreversion generating an azomethine ylide (Scheme 1). The stereochemistry of the oxazolidin-5-one is thus dependent on the steric and electronic effects of R^1, R^2, and R^3 (Scheme 1), and their influence on the rate constants k_1, k_{-1}, and k_2 determines whether oxazolidinone formation is kinetically or thermodynamically controlled. The stereochemistry of the oxazolidin-5-one(s) determines the stereochemistry of the kinetically formed azomethine ylide(s) but this azomethine ylide(s) may then undergo stereomutation if both (i) dipolarophiles less active than maleimides are used as trapping agents and (ii) sufficient conjugating substituents are present on the azomethine ylide to lower the bond order in the central C–N–C moiety.

Added in proof. Compound (**18a**) reacts slowly with *N*-phenylmaleimide in boiling benzene (44 h, incomplete reaction) to give (>90% at 65% conversion) a 2.3 : 1 mixture of *endo*- and *exo*-cycloadducts derived solely from the *anti*-dipole (**20**, X = $[CH_2]_2$).

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