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Received July 14, 1975

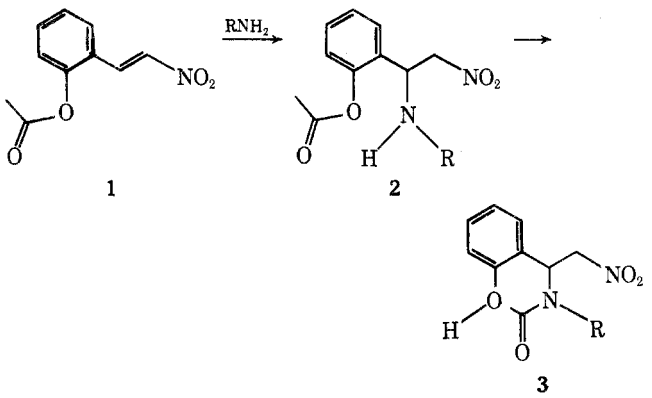
Anomalously Large Steric Inhibition of Intramolecular *O,N*-Acyl Transfer to Amino Acid Esters

Summary: Michael adducts of *o*-acetoxy-β-nitrostyrene and amino acid esters are found to undergo quantitative intramolecular, *O,N*-acyl transfer at anomalously slow rates; a model which rationalizes slow intramolecular acyl transfer to hindered amino acid derivatives is proposed.

Sir: Earlier,[1] we reported experiments demonstrating amide formation by intramolecular acyl transfer to an amine, trapped by a prior reaction with an electrophilic site. In the accompanying communication,[2] we apply this principle to peptide synthesis. Here we demonstrate and rationalize an unexpected, large steric inhibition of intramolecular *O,N*-acyl transfer which defines the scope of the principle.

In our earlier study, carbonyl functions were employed as amine trapping sites, and unwanted *O*-acyl transfer and dehydration were observed. To avoid these complications, we have investigated nitrostyrene derivatives. Reactions of **1** with primary amines yield Michael adducts in nearly quantitative yield;[3] rate constants fell in the range of 0.2 to 4 M^{-1} min^{-1}.[4]

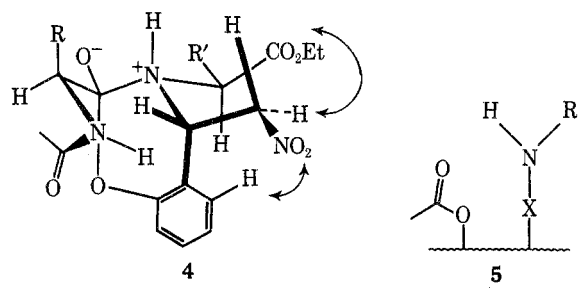
Most strikingly, the intramolecular *O,N*-acyl transfer, **2** → **3**, which can occur via an apparently favorable cyclic six-atom linkage, is slow and is subject to an exceedingly large steric effect. Thus, in acetonitrile a rate constant of 0.02 min^{-1} is observed at 25° for NH_2—R′=HGlyOEt, while for methyl esters of Ala, Phe, and Val, respective values of 2×10^{-4}, 7×10^{-5}, and 2×10^{-5} min^{-1} are observed. The rate ratios of 100 for Gly/Ala and 1000 for Gly/Val may be contrasted with the respective values of 4 and 10, observed for



the corresponding intermolecular aminolysis of *p*-nitrophenyl esters.[5]

Replacing acetoxy by carbobenzoxyglycyl resulted in no systematic change in acyl migration rate. More surprisingly, an attempt to buttress the acyloxy group by using 3,5-dibromo-2-acetoxynitrostyrene did not result in a significant change in acyl transfer rate or rate span. With alanine methyl ester **1** reacts to give two diastereomers, **2**, which rearrange to **3** at rates differing only by a factor of two.

A model which rationalizes the anomalous steric effect can be built from a successful model for steric effects on rates of aminolysis of peptide *p*-nitrophenyl esters.[5] Substitution of the additional linkages of **2** into the latter model yields **4** or a diastereomer as the structure of the



transition state for the conversion **2** → **3**. Steric interactions not shared with **2** or **3** arise in **4** between the nitromethylene group and the ester or alkyl substituent of the amine component. Stabilization of **4** through conformational changes is not possible, since the immediate environment of the carbon of the benzylamine moiety is bounded by the 3-H of the aromatic function, the alkyl substituent of the acyloxy function, and the nitromethylene group. The latter group encounters an interaction of the type found in a 1,3-diaxially substituted cyclohexane for any transition state **4** except that derived from glycine.

From this model, one predicts that anomalous steric sensitivity is expected for acyl transfer in all derivatives **5** except those in which the electrophilic site X is small and minimally substituted; e.g., for X equal to sulfur, methylene, or sp^2 carbon. In the accompanying communication we report normal transfer rates for a methylene system. [An attempt to prepare and study a sulfur case (derived from 1-acetoxy-2-chlorosulfenyl-4-chloronaphthalene) resulted in very slow transfer rates in an unhindered case (3×10^{-4} min^{-1} for HGlyOEt).]

Although it is difficult to envisage a practical reversible trapping involving an sp^2 electrophile, it was of interest to study acyl transfer in such a system, and ethyl esters of *N*-(2-acetoxyphenyl)glycine, alanine, and valine were prepared and studied.[6] Most surprisingly, *O,N*-acyl transfer in the unhindered Gly case is exceedingly sluggish, showing rate constants of 5.5×10^{-4} ($CDCl_3$), 5.0×10^{-4} (PhH),

and 2.0×10^{-4} min^{-1} (CD_3CN). The Gly/Ala rate ratios are 2.8 ($CDCl_3$) and 3.3 (PhH), and the Gly/Val rate ratios are 8 (CD_3CN) and 22 ($CDCl_3$); they are thus comparable with the intermolecular cases.[7]

A successful intramolecular amide synthesis must exhibit (1) a rapid intramolecular *O,N*-acyl transfer in nonhindered cases and (2) a small sensitivity to steric effects. Our model has successfully rationalized and predicted steric sensitivity. We lack a satisfactory means of predicting nonhindered acyl transfer rates.[10] In this study, nearly a 10^6-fold range of rate constants have been observed for acyl transfer via cyclic five- or six-atom linkages, the noteworthy cases being the sluggish 5-ring acyl transfers observed for *o*-aminophenyl derivatives (low nucleophilicity of N and strain in the intermediate are important contributors)[11] and the very rapid 6- and 7-ring acyl transfers to carbinolamines.[1]

Although *O,O*-acyl transfers are well documented and almost invariably rapid,[10] the more interesting *O,N*-acyl shifts are rarer, and rapid cases are unusual. Despite the advanced state of knowledge concerning the principles of acyl transfer in biological systems, there remains a remarkable disparity between the facility of enzymatic acyl transfer and the ease with which it can be achieved in model systems.

Acknowledgment. Financial support from the National Institutes of Health (GM 13453) is gratefully acknowledged.

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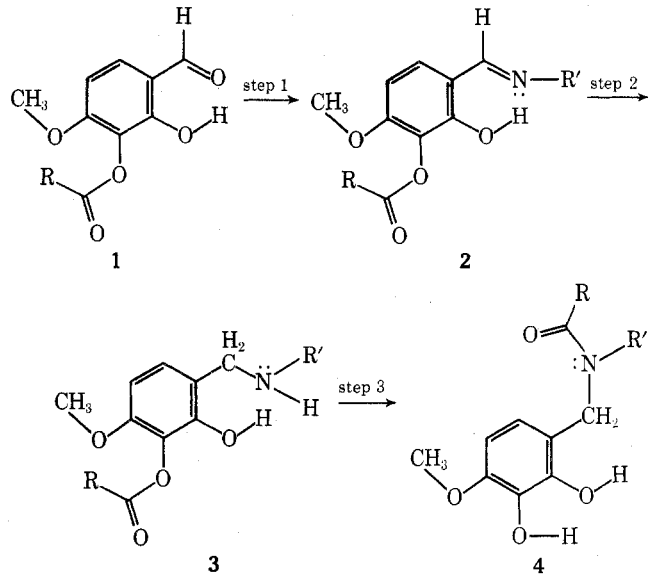
Received August 15, 1975

Peptide Bond Formation by the Prior Amine Capture Principle

Summary: Amino acid esters react with 4-methoxy-3-acyloxy-2-hydroxybenzaldehydes to form imines, which upon reduction undergo intramolecular acyl transfer to form *N*-4-methoxy-2,3-dihydroxybenzyl amides, useful in peptide synthesis.

Scheme I



Sir: As outlined in Scheme I, we wish to report the feasibility of peptide bond formation through a new principle of intramolecular acylation which is preceded by amine capture.[1]

Step 1—Amine Capture. Imine formation from salicylaldehydes occurs with unusually large rate and equilibrium constants.[2] Thus, **1**[3] (R = ZGly) reacts with methyl esters of Ala, Leu, or Phe (CH_3CN, 25°, 0.2–0.3 *M*) with half-times of 4–5 min. Only small rate changes result from variation of R ($t_{1/2}$ = 5–6 min for R = ZAla, R′ = HAlaOMe; R = HPhe, R′ = HValOMe). From two cases, rates appear to be ~10 times as fast as in DMSO.

Step 2—Reduction. As a reducing agent for **2**, pyridine borane in acetic acid[4] is mild, rapid, and quantitative. With a 1:1 molar stoichiometry, reaction is complete in <3 min; somewhat slower, complete reaction is also observed with 0.5 equiv of borane. In practice, solvent is removed from **2**, which is dissolved without purification in acetic acid, followed by pyridine borane. Disappearance of the yellow color of **2** indicates complete reaction, whereupon solvent is removed, and **3** is isolated by partitioning between an organic solvent and aqueous bicarbonate.

Step 3—Acyl Transfer. Although the unimolecular[5] isomerization, **3** → **4**, is somewhat retarded by polar solvents (slow in DMSO),[6] it occurs with half-times in the range of 0.2–4 hr in other media, including neat **3**. Thus for **3** (R = ZGly) transfer to captured Ala, Leu, and Phe occurs with half-times of 15, 40, and 70 min, respectively ($CDCl_3$, 25°). For **1** (R = ZPhe or ZAla) transfer to Ala gives $t_{1/2}$ values of 120 and 70 min. Steric effects at the amine substitution site are normal[7] (the Val/Gly rate ratio appears to be ~10). Preparatively, reaction times of 12 hr were convenient.

The yield for the conversion of **1** (R = ZGly) and 1 equiv of DL-HPheOEt to **4** was 85%.[8] Reaction of **1** (R = ZGly) with HLeuGlyOH tetramethylguanidine salt (DMSO, 25°, 5 min), followed by precipitation with ether, reduction, and isomerization, resulted in an isolated yield of 92% **4**.

Step 4—Cleavage. Cleavage of this **4** with HBr/HOAc yielded 84% HGly-L-LeuGlyOH, after neutralization. With trifluoroacetic acid in the presence of the trapping agent resorcinol, the 4-methoxy-2,3-dihydroxybenzyl moiety (DHMB) could be selectively cleaved.[9] Treatment of PhthGly(N-DHMB)PheOEt with Tfa (1 hr, 25°, 5 equiv of resorcinol) generated 100% PhthGlyPheOEt. A similar