Nitrogen Kinetic Isotope Effects on the Acylation of Aniline

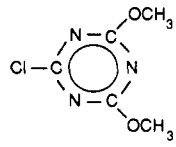
Z. J. Kamiński,*,† P. Paneth,†,‡ and M. H. O'Leary*,§

Institute of Organic Chemistry, Technical University of Łódź, Łódź, Poland, and Department of Biochemistry, University of Nebraska, Lincoln, Nebraska 68583-0718

Received February 14, 1991

Introduction

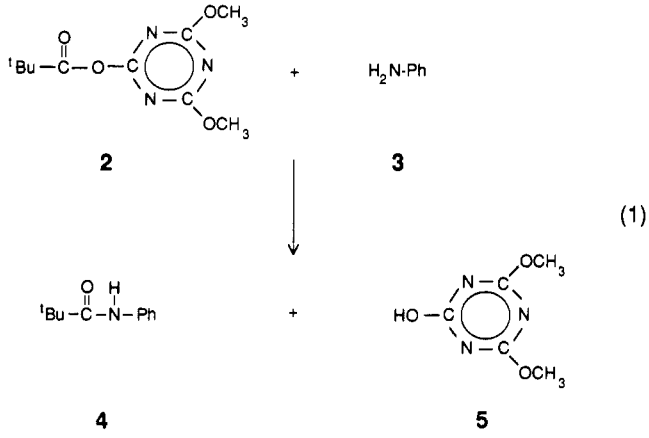
2-Chloro-4,6-dimethoxy-1,3,5-triazine (1) is a potent coupling reagent for synthesis of peptides.[1,2] Among its



1

advantages are high yields of products under mild conditions, easy removal of any excess reagent, and lack of racemization during the reaction. Upon reaction with carboxylic acids, it yields highly reactive esters that react further with alcohols, amines, and carboxylates to afford corresponding esters, amides, and anhydrides, respectively. These reactions are very important from the synthetic point of view because sterically hindered substrates can be used under mild conditions.[3,4]

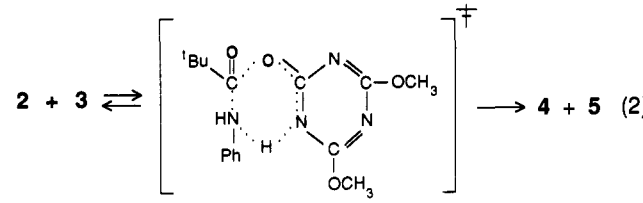
Kinetic measurements have been carried out[3] for the reaction (1) in order to learn the detailed mechanism.



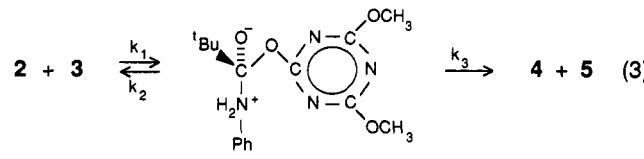
2 + 3 → 4 + 5 (1)

This reaction is second order (first with respect to each reactant) with rate constant $k = 1 \times 10^{-3}$ M^{-1} s^{-1}. No catalytic effects of acids and bases have been detected. The rate of acylation increases in the following series: piperidine ≫ aniline > *N*-methylaniline ≫ *p*-nitroaniline. The reaction proceeds even in nonpolar solvents (CH_2Cl_2), but increasing solvent polarity increases the reaction rate.

In view of these results, two alternative mechanisms are possible: a single-step reaction with a cyclic transition state or a stepwise reaction with formation of a tetrahedral intermediate:



2 + 3 → 4 + 5 (2)



2 + 3 → 4 + 5 (3)

6

These mechanistic alternatives can be distinguish on the basis of kinetic isotope effects.[5,6] Herein we report studies of kinetic isotope effects of nitrogen and deuterium that allow us to determine the actual reaction pathway.

Experimental Section

Materials. 2-(4,6-Dimethoxy-1,3,5-triazinyl) 2,2-dimethylpropanoate was synthesized from the chloride 1 and the corresponding acid, purified as described earlier,[1] and recrystallized twice from a benzene/light petroleum mixture immediately before use. Aniline (POCh, Poland) was dried with KOH, distilled with zinc dust, and then freshly redistilled before use. Aniline-d_2 was obtained[2] by isotopic exchange with D_2O (99.9%, Technabsexport, USSR) and purified in the same way as unlabeled aniline. Acetonitrile-d_3 (98.1%, Apolda, DDR) was distilled from P_2O_5 before use. Other reactants were analytical grade and were used without further purification.

Isotope Effects. Experiments were carried out at 30 °C and concentrations of reactant 0.2 M in CD_3CN. The reaction progress was monitored by observing the ^1H NMR (80 MHz Tesla 487 BS) signals of product (singlet at 1.25 ppm) and reactant (singlet at 1.15 ppm) in small aliquots. The product **5** precipitated quantitatively and was isolated by filtration, washed with cold CH_2Cl_2, and dried. The combined filtrates were diluted with cold CH_2Cl_2 (4 volumes), extracted with 1 M sulfuric acid, and washed with water. The organic phase was dried with anhydrous magnesium sulfate. The combined acidic aqueous extracts were washed with CH_2Cl_2, and traces of organic solvent were removed by evaporation. The residue was treated with KOH pellets, and aniline **3** was removed by steam distillation and extracted with ether. These ether extracts of aniline were then dried with KOH and the solvent removed at room temperature.

The CH_2Cl_2 extract after drying over $MgSO_4$ was treated with equimolar *N,N*-dimethylethylenediamine for 1 h at room temperature. The clear solution was then washed with sulfuric acid to remove any basic contaminants, washed with water, and dried with $MgSO_4$. After filtration and evaporation to dryness the product **4** was obtained.

Compounds obtained in the above way were combusted with a Heraeus elemental analyzer, and the isotopic composition of nitrogen was measured using a Finnigan Delta S isotope-ratio mass spectrometer. About 10 mg of sample was required per measurement. The natural isotopic composition of nitrogen was used. The aniline nitrogen kinetic isotope effect for the reaction (1) was calculated from the equations

† Technical University of Łódź.

‡ On leave from Institute of Applied Radiation Chemistry, Technical University of Łódź, Poland.

§ University of Nebraska.

(1) Kamiński, Z. T. *Tetrahedron Lett.* **1985**, *26*, 2901. Kamiński, Z. J. *Synthesis* **1987**, *10*, 917.

(2) Harada, M.; Titani, T. *Bull. Chem. Soc. Jpn.* **1936**, *11*, 465.

(3) Kamiński, Z. J. Submitted for publication.

(4) Kamiński, Z. J. *J. Prakt. Chem.* **1990**, *332*, 579.

(5) Melander, L. *Isotope Effects on Reaction Rates*; Ronald Press: New York, 1960. Melander, L.; Saunders, W. H., Jr. *Reaction Rates of Isotopic Molecules*; Wiley: New York, 1980.

(6) Paneth, P.; O'Leary, M. H. *J. Am. Chem. Soc.* **1991**, *113*, 1691.

0022-3263/91/1956-5716$02.50/0

$$^{15}k = \frac{\ln (1 - f)}{\ln [1 - f(1000 + \delta_{4f})/(1000 + \delta_{30})]} \quad (4)$$

$$^{15}k = \frac{\ln (1 - f)}{\ln [(1 - f)(1000 + \delta_{3f})/(1000 + \delta_{30})]} \quad (5)$$

where δ_{3f} and δ_{30} are relative isotopic compositions of the reactant 3 at fraction of reaction f and at the beginning of the reaction ($f = 0$), respectively. δ_{4f} is the relative isotopic composition of the product 4. The δ value is related to the isotopic ratio as $\delta_i = (R_i/R_{st} - 1)1000$ and depends on the isotopic composition of the standard used in the mass spectrometric measurements. R's are isotopic ratios ($^{14}N^{15}N/^{14}N_2$).

The deuterium kinetic isotope effect was obtained from comparison of separate rates measured using ^1H NMR (80 MHz, Tesla 487 BS) for deuterated aniline and aniline with natural isotopic composition at 30 °C (reaction in CD_3CN). The deuterated compound consisted of three isotopomers $NH_2Ph/NHDPh/ND_2Ph$ (7:37:56 mol) as determined by mass spectrometry (isotope ratio mass spectrometer MI 1201 E).

Results

Isotope effects on the reaction between 2-(4,6-dimethoxy-1,3,5-triazinyl) 2,2-dimethylpropanoate and aniline were studied at $t = 30$ °C and $c_0 = 0.2$ M where the reaction exhibits second-order kinetics, first with respect to each reactant. The deuterium kinetic isotope effect for aniline-d_2 is equal to 1.29 ± 0.04. This isotope effect has been corrected for incomplete labeling. Results of nitrogen isotope effect measurements are given in Table I.

In the case of triazine nitrogens the isotopic composition of the product 5 stays practically unchanged throughout the reaction (Table I). We have calculated the isotope effect of these nitrogens by converting eq 4 into the form

$$\ln [1 + \delta_{20}/1000 - f(1 + \delta_{pf}/1000)] = \frac{1}{^{15}k} \ln (1 - f) + \ln (1 + \delta_{20}/1000) \quad (6)$$

If a preliminary value for δ_{20} is assumed, the isotope effect can be calculated from the linear regression analysis as the inverse of the slope of the left-hand-side expression of eq 6 vs $\ln (1 - f)$. Furthermore, the intercept leads to a revised value for δ_{20}. If this last value is different from the preliminary value it can be used instead and the analysis repeated until agreement between the assumed and resulting values is reached. The triazine nitrogens kinetic isotope effect resulting from this regression analysis is $^{15}k = 0.999\,94 \pm 0.000\,02$.

Discussion

The magnitude of a kinetic isotope effect on a single-step reaction depends on two principal factors.[5] The first one is associated with the difference in frequencies of crossing the energetic barrier of isotopic species. This factor invariably favors the "lighter" isotopomer. The second factor reflects changes in bonding around the isotopic atom. It is larger than unity when bonds to the isotopic atom are weaker in the transition state than in the ground state. Thus, an isotope effect on a reaction in which a bond to the isotopic atom is being broken should be larger than unity. When bonds to the isotopic atom are stronger in the transition state than in the reactants, then the second factor is smaller than unity, and the corresponding isotope effect should be small or inverse due to the partial cancellation of the two factors. We have recently demonstrated the usefulness of nitrogen kinetic isotope effects of an incoming group in predicting the structure of the transition state[6] for the reaction of *N,N*-dimethyl-*p*-toluidine with methyl iodide.

Table I. ^{15}N Isotope Effect of Nitrogen Atoms of Aniline and Triazine

f	$\delta_5(^{15}N)^a$	$\delta_3(^{15}N)$	$\delta_4(^{15}N)$	aniline ^{15}k
0		−6.461		
0.15		−7.242		0.9952[c]
	−7.608		−3.350	0.9966[d]
0.55		−10.857		0.9945[c]
	−7.756		−5.843	0.9990[d]
0.82	−7.785			
mean	≈1.0[b]			0.9963 ± 0.0010

[a] Each δ value is an average from two measurements. [b] See Results for discussion of the analysis of the triazine nitrogen isotope effect. [c] Calculated from eq 5. [d] Calculated from eq 4.

If the reaction were to proceed in one step, a normal primary kinetic isotope effect should be expected for the aniline nitrogen and a significant isotope effect should be seen[6] for aniline-d_2. Neither of this predictions agrees with the observed values, e.g., inverse nitrogen and small deuterium isotope effects, and we conclude, therefore, that the one-step mechanism can be eliminated.

Thus, the reaction proceeds through a tetrahedral intermediate as depicted in eq 3. The magnitudes of isotope effects for this mechanism reflect isotope effects on individual steps as well as relative rates of formation and decomposition of the tetrahedral intermediate (eq 7)

$$^{15}k = \frac{^{15}k_3{}^{15}k_1/^{15}k_2 + {}^{15}k_1k_3/k_2}{1 + k_3/k_2} \quad (7)$$

where superscripts refer to the nitrogen isotope and subscripts refer to steps as numbered in eq 3. The same equation holds for the deuterium isotope effect.

The limiting values for the observed isotope effect described by eq 7 are $^{15}k_3{}^{15}k_1/^{15}k_2$ when k_3/k_2 approaches 0 and $^{15}k_1$ when k_3/k_2 approaches infinity. The first case corresponds to rate-controlling decomposition of the intermediate (forward reaction of the intermediate being much slower than the reverse reaction) while the second corresponds to rate-controlling formation of the intermediate.

We can estimate these limiting values of the nitrogen isotope effect on the basis of data available in the literature. The $^{15}k_1$ isotope effect involves formation of a new N–C bond. Kinetic nitrogen isotope effects for similar processes in S_N2-type reactions have been measured.[6,7] On the basis of these data $^{15}k_1$ can be expected to be in the range 1.000–1.004 (a mean value of 1.002 will be used). The equilibrium nitrogen isotope effect on the similar process, leading from $-NH_2$ to $-^+NH_2-$, has been found[8] to be $^{15}K = 0.979$, and this value can be used as a good estimation of the equilibrium isotope effect on the first step ($^{15}k_1/^{15}k_2$). The second step involves fast proton transfer and departure of the triazine moiety. Thus, $^{15}k_3$ should be slightly less than 1.017, as a small inverse nitrogen isotope effect can be expected due to the sp^3 to sp^2 rehybridization of the central carbon atom.[9] We will use 1.013 in further discussions. The limiting values are, therefore, 0.991 for rate-limiting decomposition of the intermediate and 1.002 for rate-determining formation. The observed nitrogen isotope effect of 0.996 lies in between these two limiting values, indicating that both processes contribute to the reaction rate. From eq 7 the partitioning factor $k_3/k_2 =$

(7) Kurz, J. L.; Seif El-Nasr, M. M. *J. Am. Chem. Soc.* **1982**, *104*, 5823.
(8) Hermes, J. D.; Weiss, P. M.; Cleland, W. W. *Biochemistry* **1985**, *24*, 2959.
(9) O'Leary, M. H.; Urberg, M.; Young, A. P. *Biochemistry* **1974**, *13*, 2077.

0.83 can be calculated on the basis of the above nitrogen isotope effects.

The above conclusion is also supported by the deuterium isotope effect, although the quantitative analysis is difficult because of the lack of appropriate model data. Both $^{15}k_1/^{15}k_2$ and $^{15}k_1$ should be small secondary effects, probably slightly inverse due to the stiffer N-H bonds in $-^{+}NH_2-$ than in $-NH_2$. The isotope effect on k_3 should be large, as this step involves proton transfer. Thus, one would expect a small inverse isotope effect if the formation of the intermediate is rate determining and a large normal isotope effect if the decomposition is rate determining. These conclusions are supported by the observed isotope effects for ammonolysis of benzoates[10] and acetates[11] in D_2O: 0.8 and 1.0 for the uncatalyzed reactions, which proceed with rate-determining formation of the intermediate, and 1.6 and 1.5 for the catalyzed reactions, which proceed with rate-determining decomposition of the intermediate. Our observed deuterium isotope effect of 1.29 is intermediary and agrees well with the partitioning factor k_3/k_2 of about unity.

In conclusion, we find our results on kinetic isotope effects indicative of the stepwise reaction with the formation of a tetrahedral intermediate and its decomposition being nearly equally rate limiting. This is an interesting finding, since decomposition of the intermediate is usually assumed to control the overall reaction rate in analogous reactions.[12,13]

Registry No. 1, 3140-73-6; 2, 91889-76-8; 3, 6625-74-7; 4, 6625-74-7; Nitrogen-15, 14390-96-6; deuterium, 7782-39-0.

(10) Kirsch, J. F.; Kline, A. *J. Am. Chem. Soc.* **1969**, *91*, 1841.
(11) Jencks, W. P.; Carriuolo, J. *J. Am. Chem. Soc.* **1960**, *82*, 675.
(12) Kemp, D. S.; Choong, S.-L. H.; Pekaar, J. *J. Org. Chem.* **1974**, *39*, 3841.
(13) Kemp, D. S.; Choong, S.-L. H.; Pekaar, J. *Tetrahedron* **1974**, *30*, 3955.

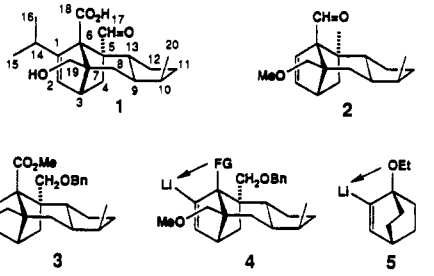
Oxazoline-Directed Metalation of Unactivated Norbornenyl Olefinic CH: Application to an Attempted Synthesis of the Diterpenoid Mold Metabolite Sordaricin

Lewis N. Mander* and Ralph P. Robinson[1]

Research School of Chemistry, Australian National University, GPO Box 4, Canberra, A.C.T. 2061, Australia

Received April 2, 1991

Heteroatom-directed ortho metalation of aromatic compounds is a highly developed technique,[2] but there are very few examples of the analogous deprotonation of unactivated vinyl compounds.[3,4] Having recently established efficient synthetic routes to the tetracyclic aldehyde **2** and ester **3**[5] as part of a project to elucidate the biogenesis of the unusual diterpenoid sordaricin (**1**),[6] we speculated about whether the unactivated norbornenyl double bond in **3** could be regioselectively deprotonated at C(1) with



1 **2** **3** **4** **5**

activation and direction by an appropriate derivative of the bridgehead carboxy group (cf. structure **4**). A metalation of this kind could then be expected to allow the selective introduction of the isopropyl group and facilitate a direct conversion of **3** into **1**.

The preparation of the alkenyllithium **5** by reaction of the parent alkene with *tert*-butyllithium[7] appeared to provide an encouraging precedent for obtaining the metalated ether **4** (FG = CH_2OCH_2OMe), but we were unable to detect any reaction of this kind, possibly because the inductive effect of the alkoxy function in this substrate is attenuated by an additional intervening carbon atom.[8] However, the oxazoline derivative **6** could be successfully lithiated by *n*-butyllithium at C(1) as demonstrated by deuteration to give **7** (Scheme I).[9]

Application of the metalation-based strategy to the synthesis of sordaricin (**1**) from the intermediate **3** was then explored as outlined in Scheme II. Ester **3** was very resistant to hydrolysis, but the oxazoline **8** could be obtained in an overall yield of 73% by heating **3** in a mixture of 2-amino-2-methylpropan-2-ol and its potassium salt at 140 °C and treating the amide with thionyl chloride. A significant amount of acid was also formed in the first step and was converted to amide in the usual way via the acyl chloride. Lithiation of oxazoline **8** proceeded as smoothly as for **6**, but attempts to effect the direct introduction of an isopropyl group[10] were not productive and it was necessary to resort to a progressive elaboration of this group. Thus, acylation of **9** with methyl chloroformate followed by in situ reaction with methyllithium afforded carbinol **10**.[11] Although simple dehydration was unsuccessful, treatment with HBr gave the cyclic ether **11**, which was readily converted by LDA into the isopropenyl derivative **12**. Selective hydrogenation of the more exposed double bond in this product could only be accomplished with a rhodium catalyst,[12] but unfortunately, concomitant satu-

(1) Present address: Pfizer Inc., Central Research Division, Eastern Point Road, Groton, CT 06340.
(2) Gschwend, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1-360. Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306-311. Beak, P.; Meyers, A. J. *Acc. Chem. Res.* **1986**, *19*, 356-361. Narasimhan, N. S.; Mali, R. S. *Top. Curr. Chem.* **1987**, *138*, 63-47. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879-933.
(3) Klumpp, G. W. *Rec Trav. Chim.* **1986**, *105*, 1-21.
(4) Cuvigny, T.; Julia, M.; Rolando, C. *J. Chem. Soc., Chem. Commun.* **1984**, 8.
(5) Robinson, R. P.; Mander, L. N. *J. Org. Chem.* **1991**, *56*, 3595-3601.
(6) Vasella, A. T. Ph.D. Dissertation, Eidgenossischen Technischen Hochschule, Zurich, 1972.
(7) Grootveld, H. H. Ph.D. Thesis, Vrije University, 1973. Reported in ref 3.
(8) Furber, M. Unpublished results. Metalation of the corresponding carbinol, methyl ester, and carboxylic acid was also attempted. Cf. Eaton, P. E.; Lee, C. H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016-8018.
(9) The oxazoline function was chosen because it had been established as one of the more effective activating groups[2] and has a relatively low steric demand. TMEDA was employed as an activating ligand in early metalation experiments, but did not appear to affect the outcome.
(10) In an exploratory investigation, the isopropyl group was introduced into a simple norbornenyl oxazoline analogue of **8**, i.e., 2-[bicyclo[2.2.1]hept-2'-en-1'-yl]-4,4-dimethyloxazoline, by bromination of the lithiated derivative followed by a coupling reaction of the resulting vinyl bromide with isopropyl zinc chloride catalyzed by dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II): Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.*, **1984**, *106*, 158-163. Although the 1-bromo derivative of **8** was readily prepared, the coupling reaction failed on this substrate, presumably because of steric hindrance.
(11) The intermediate **9** could be converted directly into **10** by treatment with acetone, but in only ca. 25% yield, presumably because of competing enolization.
(12) Hydrogenation of **12** over platinum black, for example, afforded mainly the isopropylidene derivative (retention of benzyl). The use of 10% palladium on carbon similarly afforded largely the isopropylidene product, but with hydrogenolysis of the benzyl group as well. Variable results were obtained with soluble hydrogenation catalysts.

0022-3263/91/1956-5718$02.50/0