An NMR Study of the Kinetics of 1,4-N,N′-Migration of the Acyl Group Vinylogs on Aromatic 1,2-Diamines

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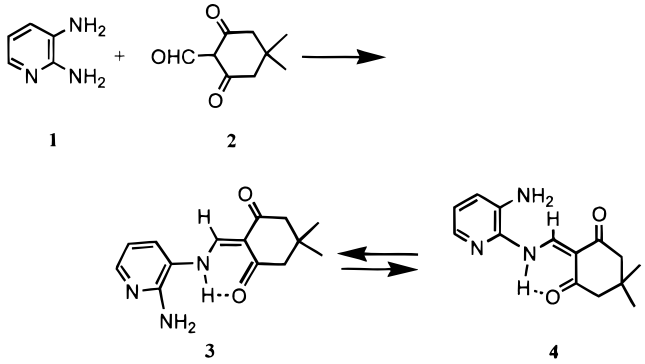
As part of our continuing studies of the reactions of aromatic 1,2-diamines with 2-acyl-1,3-cyclandiones,[1−3] the reactions of 2,3-diaminopyridine were attempted with 2-acyl-1,3-cyclohexanediones to produce pyrido[2,3-*b*][1,4]-benzodiazapine derivatives. This class of compounds have been shown to exhibit a wide range of biological activity.[4−6]

Specifically, 2,3-diaminopyridine (**1**) and 2-formyldimedone (**2**) were used to synthesize 2-(2-amino-3-pyridylaminomethylene)- (**3**) and 2-(3-amino-2-pyridylaminomethylene)-5,5-dimethyl-1,3-cyclohexanedione (**4**).[1−3] Both



compounds were separated from the reaction mixture by chromatography and structurally characterized by IR and NMR spectroscopy. They were shown to be rigid amino vinyl ketones having a $^3J(H,H)_{CH-NH} \approx 12-13$ Hz, stabilized with an intramolecular hydrogen bond of the type N−H···O = δ (NH ≈ 12−13 ppm).

Although the two isomers are stable in the solid state, upon dissolving either individual isomer in $CDCl_3$ or DMSO-d_6, it begins to convert to the other one and the process continues until an equilibrium mixture of **3** and **4** is reached. The process, an intramolecular transamination, is much more rapid in DMSO-d_6 than in $CDCl_3$ and can be followed by ^{1}H NMR spectroscopy. In Figure 1, the spectrum of **3** immediately after dissolving in DMSO-d_6 indicates only one isomer. After a given amount of time, a second resonance signal for each proton from the other isomer, **4**, appears and continues to grow until a ratio of 1 to 1.3 (**3** to **4**) is observed at 303.1 K.

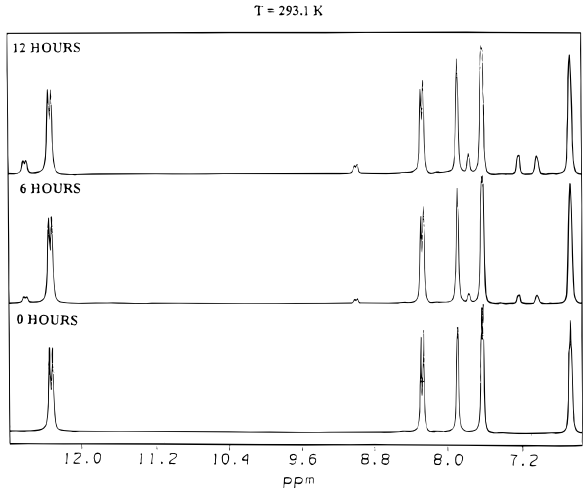


Figure 1. The 400 MHz ^{1}H NMR spectrum of **3** as a function of time at 293.1 K.

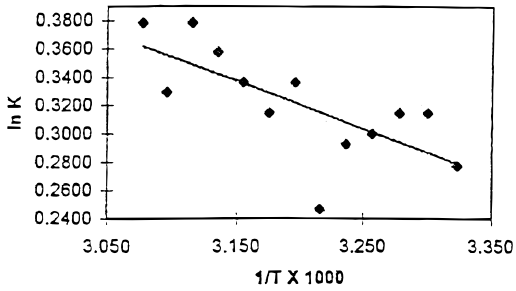


Figure 2. Van't Hoff plot of ln *K* vs 1/*T*.

The equilibrium constant, $K = [\mathbf{4}]/[\mathbf{3}]$, increases slightly with increasing temperature (Figure 2). From the Van't Hoft plot, the $\Delta H°$ for the reaction is 4 kJ/mol ± 1 kJ/mol. The $\Delta S°$ for the reaction is 12 J/(mol K) ± 2 J/(mol K). At 303.1 K, the $\Delta G°$ for the reaction is −0.7 kJ/mol ± 0.2 kJ/mol.

In Figure 3, the initial region of the plot of the natural logarithm of the spectral intensity versus time is shown. Since only 5−10% of **3** has been converted and the back reaction is still negligible, the decrease is exponential and a plot of ln *I* vs *t* for the first-order rate process yields a straight line. The rate constants as a function of temperature were calculated from the initial linear portions of the curves and are summarized in Table 1. An Arrhenius plot of these data yielded a straight line (Figure 4) and an activation energy of 70 kJ/mol ± 4 kJ/mol as well as an ln A of 17 ± 1 in DMSO-d_6. Substitution of the vinyl proton by a methyl group blocks the migration. The transamination is catalyzed by OH^- where the increase in the reaction rate constant is linear with $[OH^-]$.

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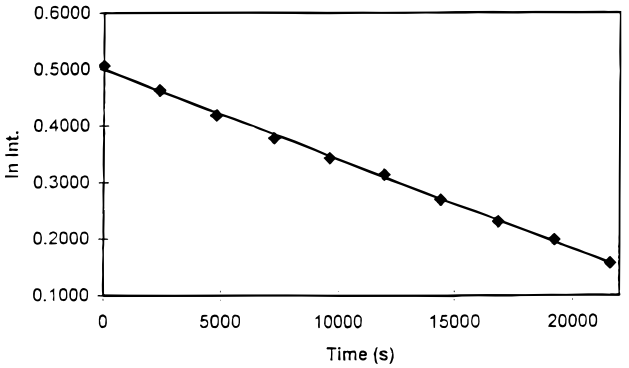


Figure 3. A plot of ln *I* vs *t* for the **3** isomer at 303.1 K.

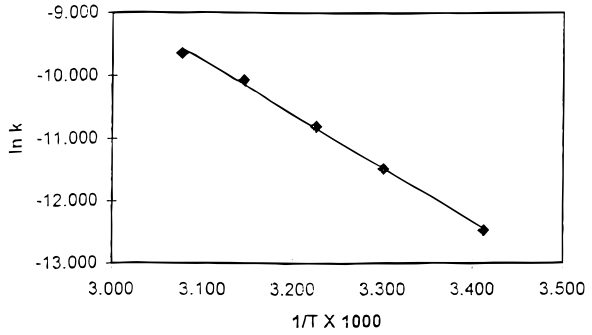
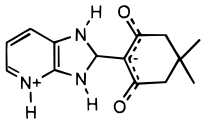


Figure 4. Arrhenius plot of ln *k* vs 1/*T*.

Table 1. Rate Constants for Migration in DMSO-d_6 at Various Temperatures

T (K)	*k* (1/s)	ln *k* (1/s)
293	3.85E−06	−12.467
303	1.031E−05	−11.483
310	2.028E−05	−10.806
318	4.222E−05	−10.073
325	6.514E−05	−9.639

One proposed intermediate for this rearrangement is structure **5**, but the exact mechanism has yet to be confirmed. Deprotonation of the proposed intermediate by base is consistent with the observed catalysis by OH^-.



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The N substituent of 1,2-diaminopyridine in compounds **3** and **4** can be considered as a vinylog of the acyl group, thus the process, an intramolecular transamination, may qualify as the first example of 1,4-N,N′-migration of acyl group vinylogs.

Experimental Section

General Procedure. To 5 mmol of **1** dissolved in 15 mL of ethanol was added 5 mmol of **2** dissolved in 15 mL of ethanol, and the mixture was allowed to stand at either 20 °C for 24 h or 78 °C for 10 min. A mixture of **3** and **4** was obtained in a yield of 4.78 g (96%). A 1.15-g aliquot of the mixture was applied to 35−70 mp Aeros Silica gel with a pore diameter of 6 nm and eluted with ethyl acetate−toluene (7:3). After removal of the solvent, 0.39 g of **4**, $R_f = 0.47$, and 0.62 g of **3**, $R_f = 0.08$, were obtained.

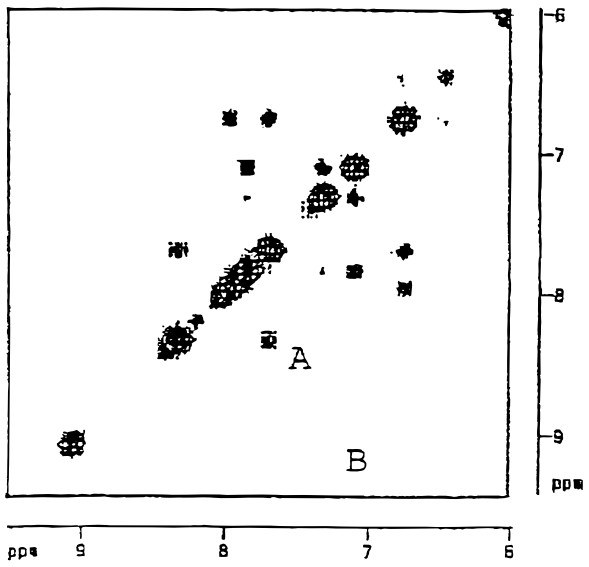

Figure 5. NOESY spectrum of a mixture of **3** and **4** in DMSO-d_6. A: Cross-peak between the vinyl proton and the 4-H of the pyridine ring of **3**. B: Region where the expected cross-peak between the vinyl proton and the 4-H proton of the pyridine was not observed.

Instrumentation. The ^{1}H NMR spectrum were run on either a Bruker AM-360 or AMX 400 WB spectrometer. The natural abundance ^{13}C and ^{15}N NMR spectra were obtained on Bruker AM-360 spectrometer at frequencies 90.5 and 36.51 MHz, respectively. The ^{15}N−^{1}H coupling constants were measured from ^{1}H NMR spectra using HMQC pulse sequence. For calculating the delays in HMQC sequences, a $^1J(^{15}N, ^1H) = 90$ Hz coupling constant was used. The NOESY spectra were obtained using a mixing time of 500 ms. The two isomers can be differentiated by the presence of a cross-peak in the NOESY spectrum of **3** between the vinyl proton and the 4-H of the pyridine ring which is not observed in the NOESY spectrum of **4** (Figure 5). The kinetic data were obtained at a spectrometer frequency of 400.13 MHz using a multiple ZG program with a fixed delay time (20−60 min) between acquisitions. The spectral intensity was taken as the peak height in the absolute intensity mode since the line width did not vary with time. The sample was prepared immediately before use by dissolving in DMSO-d_6 (Sigma, 100% D). This procedure usually took a minute, and the mixing time was not included in the time used for kinetic analysis. The temperature was maintained to ±0.1 K using a B−VT 1000 variable-temperature unit. For the catalytic experiments, increments of 2.5 μL of 0.10 M NaOH in H_2O were added to the sample prior to spectral acquisition. The IR spectra were obtained on a Specord-75 IR spectrometer.

Compounds. 2-(2-Amino-3-pyridylaminomethylene)-5,5-dimethyl-1,3-cyclohexanedione: pale yellow solid, mp 136−137 °C; IR (KBr) 3320, 3164, 1668, 1620, 1568; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.08 (6H, s, $2CH_3$), 2.40 (2H, s, CH_2), 2.44 (2H, s, CH_2), 4.88 (2H, br s, NH_2), 6.77 (1H, dd, $^3J = 4.9$ and 7.9 Hz, Py), 7.45 (1H, dd, $^3J = 7.9$, $^4J = 1.5$ Hz, Py), 8.01 (1H, dd, $^3J = 4.9$, $^4J = 1.5$ Hz, Py), 8.44 (1H, d, $^3J = 12.8$ Hz, =CH−), 12.74 (1H, d, $^3J = 12.8$ Hz, NH); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.01 (6H, s, $2CH_3$), 2.33 (2H, s, CH_2), 2.4 (2H, s, CH_2), 5.97 (2H, br s, NH_2), 6.77 (1H, dd, $^3J = 4.9$ and 7.8 Hz, Py), 7.64 (1H, dd, $^3J = 7.8$, $^4J = 1.4$ Hz, Py), 7.91 (^{1}H,dd, $^3J = 4.9$, $^4J = 1.4$ Hz, Py), 8.29 (1H, d, $^3J = 13.1$ Hz, =CH−), 12.35 (1H, d, $^3J = 13.1$, NH); ^{13}C NMR (90.5 MHz, DMSO-d_6) δ 28.04 (CH_3), 30.7, 50.7 (CH_2), 51.9 (CH_2), 109.1, 113.7, 121.2, 127.6, 145.8, 152.2 (=CH−), 194.6 (C=O), 198.4 (C=O); ^{15}N NMR (36.5 MHz, $CDCl_3$) $^1J(^{15}N, ^1H) = 90.3$ Hz, $^1J(^{15}N, ^1H) = 83.7$ Hz.

2-(3-Amino-2-pyridylaminomethylene)-5,5-dimethyl-1,3,-cyclohexanedione: pale yellow solid, mp 135−136 °C IR (KBr) δ 3382, 3340, 1670, 1636, 1594, 1550; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.08 (6H, s, $2CH_3$), 2.42 (2H, s, CH_2), 2.46 (2H, s, CH_2), 3.69 (2H, br s, NH_2), 6.98 (1H, dd, $^3J = 4.6$ and 7.9 Hz, Py), 7.11 (1H, dd, $^3J = 7.9$, $^4J = 1.5$ Hz, Py), 7.91 (1H, dd, $^3J = 4.6$, $^4J =$

1.5 Hz, Py), 9.26 (1H, d, ^3J = 12.5 Hz, =CH−), 13.16 (1H, d, ^3J = 12.5 Hz, NH); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.01 (6H, s, $2CH_3$), 2.37 (2H, s, CH_2), 2.44 (2H, s, CH_2), 5.22 (2H, br s, NH_2), 7.04 (1H, dd, ^3J = 4.6 and 7.8 Hz, Py), 7.27 (1H, dd, ^3J = 7.8, ^4J = 1.4 Hz, Py), 7.79 (1H, dd, ^3J = 4.8, ^4J = 1.4 Hz, Py), 9.02 (1H, d, ^3J = 12.6 Hz, =CH−), 12.62 (1H, d, ^3J = 12.6, NH); ^{13}C NMR (90.5 MHz, DMSO) δ 22.9 (CH_3), 30.6, 50.72 (CH_2), 51.0 (CH_2), 109.1, 121.9, 125.4, 134.1, 137.4, 138.8, 147.1 (=CH−), 195.3 (C=O), 198.9 (C=O); ^{15}N NMR (36.5 MHz, $CDCl_3$) $^1J(^{15}N, ^1H)$ = 89.9 Hz (NH), $^1J(^{15}N, ^1H)$ = 78.5 Hz.

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Additions and Corrections

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Michael A. Calter, T. Keith Hollis, Larry E. Overman,* Joseph Ziller, and G. Greg Zipp. First Enantioselective Catalyst for the Rearrangement of Allylic Imidates to Allylic Amides.

Page 1449, Scheme 1. The following correction to Scheme 1 should be made: **b**: $R^1 = CH_2OTBDPS$, $R^3 =$ *n*-Bu, $R^4 = CCl_3$, $R^5 = H$.

The rearrangement of **1b** is described in Mehmandoust, M.; Petit, Y.; Larchevêque, M. *Tetrahedron Lett.* **1992**, *33*, 4313.

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