Kinetics of Cyclization of 2-(N-β-Bromoethyl)-amino-5-substituted Benzophenones into 1,4-Benzodiazepines

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The overall pseudo-first order cyclization rates of 2-N-β-bromoethylamino-5-substituted benzophenones 1—3 into 1,4-benzodiazepines 7—9, determined in 60/o ethanolic ammonia at 100°C, 115°C, and 125°C respectively, were found to range between 1.0 × 10⁻⁴ and 8.33 × 10⁻⁴ s⁻¹ for 1, between 1.6 × 10⁻⁴ and 5.83 × 10⁻⁴ s⁻¹ for 2 and between 6.66 × 10⁻⁵ and 3.16 × 10⁻⁴ s⁻¹ for 3. Rate values calculated from the rising concentrations of cyclization products 7—9 were lower indicating the formation of stable intermediates. It is assumed that these are protonated aziridine derivatives 4—6, since compounds 4 and 5 were identified as intermediates by TLC and GLC. The formation rate for the model compound 2-amino-5-chlorobenzophenone imine was found to be only 5.8 × 10⁻⁷ s⁻¹ at 125°C, which eliminates imine (C=NH) derivatives of 1—3 as possible intermediates. The ammonolysis rates of 3-phenylpropylbromide between 110°C and 125°C, were found to range from 1.5 × 10⁻⁴ to 4.16 × 10⁻⁴ s⁻¹. These values revealed that the β-participation of the N(2)-atom, being a relatively rapid equilibrium, does not enhance the overall cyclization rate. The following parameters characterize the overall cyclization process: ΔH⁺ = 50.0 ± 4.0 kJ mol⁻¹ and ΔS⁺ = 156 ± 5 J mol⁻¹ K⁻¹ for 1, ΔH⁺ = 89.9 ± 4.0 kJ mol⁻¹ K⁻¹ for 2, ΔH⁺ = 75.3 ± 4.0 kJ mol⁻¹ and ΔS⁺ = 69 ± 4 J mol⁻¹ K⁻¹ for 3.

INTRODUCTION

2-Deoxy-1,4-benzodiazepines belong to an important class of the central nervous system (CNS) active compounds²-⁸. In previous papers¹⁻⁴, we gave stereochemical evidence for β-participation of vinylogous amide nitrogen during the cyclization of N-substituted 2-aminobenzophenone into these heterocycles (Scheme 1).

High regioselectivity in the ring opening of the intermediary aziridinium ion was observed. The retention of configuration in products B revealed the front side attack of ammonia on the intermediary ion pair. Another possibility
of the intramolecular front side attack by the intermediary formed ketimine according to Scheme 2, was proposed\textsuperscript{5}, however. In order to further clarify the cyclization pathway, we undertook a kinetic study, and in this paper we describe some results of this investigation.
The kinetic scheme of the main steps during the ammonolysis and cyclization of 2-N-β-bromoethyl-5-substituted benzophenones is shown in Scheme 3.

A full kinetic solution of such a multistep scheme requires a number of independent data on the concentrations of all involved species yielding the rates of particular steps by a sophisticated mathematical treatment. Our main aims were, however, the following:

- to determine the overall cyclization rates of compound A(1–3),
- to determine possible intermediates during the cyclization A → D.
- to determine the rate of formation of benzophenonimines of the corresponding N-unsubstituted benzophenones.

Thus, a simplified picture of the above scheme, based on some previous quantitative experimental results, turned to be satisfactory.

The relation \( k_4 \gg k_2, k_3 \) is based on our earlier experience that the cyclization rate of 2-(N-α-aminoacyl)-amino-5-chlorobenzophenones at ambient temperature is very high, presumably much higher than any of the processes measured in this work. Moreover, compounds C were not identified under any experimental condition used, which indicates their undetectably low steady-state concentration caused by high \( k_4 \).

The total rate constants \( k \) were calculated as for the pseudo-first order reaction. The results are presented in Tables I—III where two constants, i.e. those obtained by following the disappearance of A, or those obtained by following the enhancement of concentration of D are presented. The difference
### TABLE I
Cyclization Rates of 2-N-β-Bromoethylamino-benzophenone (1) into 1,4-Benzodiazepine 7

<table>
<thead>
<tr>
<th>$t/°C$</th>
<th>$k \times 10^5$/s$^{-1}$</th>
<th>$k \times 10^5$/s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.60 ± 0.45$^b$</td>
<td>3.67 ± 0.22$^b$</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>11.76 ± 1.20$^c$</td>
<td>3.58 ± 0.40$^c$</td>
</tr>
<tr>
<td>10.98 ± 0.43$^d$</td>
<td>2.57 ± 0.43$^d$</td>
<td></td>
</tr>
<tr>
<td>37.22 ± 1.05$^b$</td>
<td>9.23 ± 0.63$^b$</td>
<td></td>
</tr>
<tr>
<td>115</td>
<td>44.67 ± 2.28$^c$</td>
<td>9.75 ± 1.28$^c$</td>
</tr>
<tr>
<td>41.48 ± 2.55$^d$</td>
<td>6.78 ± 0.73$^d$</td>
<td></td>
</tr>
<tr>
<td>76.05 ± 2.83$^b$</td>
<td>17.58 ± 0.85$^b$</td>
<td></td>
</tr>
<tr>
<td>125</td>
<td>88.55 ± 4.22$^c$</td>
<td>18.77 ± 1.66$^c$</td>
</tr>
<tr>
<td>84.63 ± 11.52$^d$</td>
<td>14.63 ± 1.33$^d$</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Rates determined following disappearance of starting 1;
$^b$ Calculated retaining one parameter ($k$);
$^c$ Calculated retaining two parameters ($k$ and $c_A$);
$^d$ Calculated retaining three parameters ($k$, $c_{A_0}$ and $c_D$);
$^e$ Rates determined following appearance of 1,4-benzodiazepine 7.

### TABLE II
Cyclization Rates of 2-N-β-Bromoethylamino-5-chlorobenzophenone (2) into 1,4-Benzodiazepine 8

<table>
<thead>
<tr>
<th>$t/°C$</th>
<th>$k \times 10^5$/s$^{-1}$</th>
<th>$k \times 10^5$/s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.03 ± 0.87$^b$</td>
<td>14.67 ± 1.55$^b$</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>19.87 ± 1.40$^c$</td>
<td>10.13 ± 1.43$^c$</td>
</tr>
<tr>
<td>17.01 ± 1.52$^d$</td>
<td>7.60 ± 1.73$^d$</td>
<td></td>
</tr>
<tr>
<td>35.35 ± 1.00$^b$</td>
<td>21.47 ± 0.72$^b$</td>
<td></td>
</tr>
<tr>
<td>115</td>
<td>38.72 ± 1.67$^c$</td>
<td>22.90 ± 1.47$^c$</td>
</tr>
<tr>
<td>39.25 ± 2.15$^d$</td>
<td>22.48 ± 1.92$^d$</td>
<td></td>
</tr>
<tr>
<td>51.43 ± 2.27$^b$</td>
<td>22.97 ± 1.53$^b$</td>
<td></td>
</tr>
<tr>
<td>125</td>
<td>59.80 ± 3.33$^c$</td>
<td>28.23 ± 3.53$^c$</td>
</tr>
<tr>
<td>58.57 ± 4.38$^d$</td>
<td>13.30 ± 2.88$^d$</td>
<td></td>
</tr>
</tbody>
</table>

Subscripts a–e have the same meaning as in the Table I.

### TABLE III
Cyclization Rates of 2-N-β-Bromoethylamino-5-nitrobenzophenone (3) into 1,4-Benzodiazepine 9

<table>
<thead>
<tr>
<th>$t/°C$</th>
<th>$k \times 10^5$/s$^{-1}$</th>
<th>$k \times 10^5$/s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.50 ± 0.08$^b$</td>
<td>5.13 ± 0.23$^b$</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>6.55 ± 0.15$^c$</td>
<td>5.00 ± 0.30$^c$</td>
</tr>
<tr>
<td>6.47 ± 0.20$^d$</td>
<td>5.87 ± 0.52$^d$</td>
<td></td>
</tr>
<tr>
<td>16.43 ± 0.40$^b$</td>
<td>12.65 ± 0.70$^b$</td>
<td></td>
</tr>
<tr>
<td>115</td>
<td>15.45 ± 0.68$^c$</td>
<td>11.42 ± 1.08$^c$</td>
</tr>
<tr>
<td>16.77 ± 0.63$^d$</td>
<td>13.07 ± 1.15$^d$</td>
<td></td>
</tr>
<tr>
<td>31.03 ± 0.68$^b$</td>
<td>22.43 ± 1.10$^b$</td>
<td></td>
</tr>
<tr>
<td>125</td>
<td>29.85 ± 1.18$^c$</td>
<td>20.63 ± 1.88$^c$</td>
</tr>
<tr>
<td>31.00 ± 1.60$^d$</td>
<td>24.33 ± 2.12$^d$</td>
<td></td>
</tr>
</tbody>
</table>

Subscripts a–e have the same meaning as in the Table I.
in the values for $k$ obtained by following these two components clearly reveals formation of some stable intermediates.

\[
\begin{align*}
1 & \quad 2 & \quad 3 & \quad X & \quad H & \quad Cl & \quad NO_2 \\
4 & \quad 5 & \quad 6 & \quad X & \quad H & \quad Cl & \quad NO_2 \\
7 & \quad 8 & \quad 9 & \quad X & \quad H & \quad Cl & \quad NO_2
\end{align*}
\]

It turns out that these intermediates are aziridinium ions, i.e. protonated compounds 4—6. They were identified by TLC, as free bases during the cyclization of compounds 1 and 2. Since the high basicity of aziridine nitrogen is nearly unaffected on $N$-substitution, it could be proposed that protonated aziridines are real substrates for the nucleophilic ring (re)opening by bromide ion or ammonia. Figure 1 illustrates concentration changes of substrate 1, of intermediary aziridine derivatives 4, and of the product of cyclization 7.

During the cyclization of 3, the intermediary aziridinium compound 6 could not be detected, Figure 2 shows the absorption dependence of 3 at various temperature.

As already mentioned, other expected intermediates might be the corresponding ketimines of compounds 1—3, as shown in Scheme 2. We were able, however, neither to identify them by TLC nor to determine their formation rate. Therefore the rate of formation of the model 2-amino-5-chloro-benzophenone-imine was determined. At 100°C and 115°C the reaction was too slow for
reproducible measurements, while at 125 °C \( k \) was determined to be \( 3.5 \times 10^{-3} \) min\(^{-1}\). Thus ketimine formation seems to be at least \( 10^3 \) times slower than the rate of the overall process of cyclization for 2-N-\( \beta \)-bromoethyl-derivative 2. All attempts to isolate this ketimine failed, however, since it hydrolysed on standing on silicagel plates, or during chromatography on silicagel column, or during attempted crystallizations. In kinetic experiments it was quantitatively determined as benzophenone, after TLC separation from unreacted benzophenone, and subsequent hydrolysis.

Although we had thus kinetically confirmed \( \beta \)-participation postulated earlier\(^4\), it remained open if it actually contributes to the enhancement of the overall cyclization rate. Therefore a parallel study of the ammonolysis rate of the simple model compound, 3-phenylpropylbromide, was undertaken. The results are given in Table IV.

<p>| TABLE IV |
| Ammonolysis Rates of 3-Phenyl-propylbromide |</p>
<table>
<thead>
<tr>
<th>( t/\degree C )</th>
<th>( k \times 10^3/s^{-1} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>14.73 ± 0.82(^b)  14.65 ± 0.66(^c)</td>
</tr>
<tr>
<td>115</td>
<td>15.52 ± 2.82(^b)  16.55 ± 2.08(^c)</td>
</tr>
<tr>
<td>125</td>
<td>17.67 ± 3.13(^b)  18.75 ± 2.32(^c)</td>
</tr>
</tbody>
</table>

Subscripts a–e have the same meaning as in the Table I.

These data revealed that only at 115 °C and 125 °C the overall cyclization rate for compounds 1—3 was somewhat higher than the rate of ammonolysis of the model compound. At 100 °C, however, only the most reactive compound 3
exhibited a higher cyclization rate than ammonolysis of 3-phenyl-propyl-bromide. Thus, no significant enhancement of the overall cyclization rate by β-participation has been found, which is presumably a consequence of the rapid equilibrium established on β-participation. The subsequent nucleophilic attack by ammonia should be the rate determining step.

Temperature dependent rate determinations (see Figure 3) allowed the calculation of thermodynamic parameters given in the Table V.

![Figure 3. Temperature dependence of overall cyclization rates of the compounds 1–3.](image)

<table>
<thead>
<tr>
<th>TABLE V</th>
<th>Thermodynamic Parameters for Overall Cyclization Rates of the Compounds 1–3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\Delta H^\pm \times 10^4$ /J mol$^{-1}$</td>
</tr>
<tr>
<td>1</td>
<td>4.77 ± 0.2$^a$</td>
</tr>
<tr>
<td></td>
<td>5.15 ± 0.08$^b$</td>
</tr>
<tr>
<td></td>
<td>5.48 ± 0.54$^c$</td>
</tr>
<tr>
<td>2</td>
<td>9.29 ± 0.54$^a$</td>
</tr>
<tr>
<td></td>
<td>8.95 ± 0.58$^b$</td>
</tr>
<tr>
<td></td>
<td>9.21 ± 0.46$^c$</td>
</tr>
<tr>
<td>3</td>
<td>7.62 ± 0.25$^a$</td>
</tr>
<tr>
<td></td>
<td>7.57 ± 0.54$^b$</td>
</tr>
<tr>
<td></td>
<td>7.49 ± 0.08$^c$</td>
</tr>
</tbody>
</table>

$^a$ Values obtained from kinetic data using one, $^b$-two, and $^c$-three variables.
Since the activation parameters actually relate to a composite process, they should be considered with caution, consequently, we prefer to draw no conclusions therefrom.

**Conclusion**

From the results described above the following conclusions may be drawn:

(a) β-Participation of the N(2)-atom takes place during cyclization of compounds 1—3. It gives rise to the formation of stable intermediates, protonated forms of 4—6, which could be identified as free bases. In two cases their formation could also be followed quantitatively.

(b) The overall cyclization rate is not significantly enhanced by β-participation, which represents a fast equilibrium. The ammonolysis of the model compound 3-phenyl-propylbromide exhibits approximately the same rate as the cyclization of 1—3.

(c) The rate determining step in the cyclization is nucleophilic attack of ammonia on the intermediary aziridinium derivatives of 4—6.

(d) The rate of the ketimine formation of 2-amino-5-chloro-benzophenone is about $10^3$ times lower than the overall cyclization rate. This result eliminates ketimine as intermediate in the »front side« ring opening of the intermediary aziridinium derivatives 4—6. It confirms the earlier proposed¹⁴ bimolecular »front side« attack of ammonia on aziridinium derivatives, resulting in the retention of the configuration during the recyclization of some chiral compounds.

**Experimental**

All mp.'s were determined on a Kofler microheating stage (Boetius), uncorrected values are given. 3-Phenyl-propylbromide was prepared starting from cinnamic acid (Fluka puriss.) which was reduced with 10% Pd/C in 90% ethanol (quantitative yield), and esterified in ethanol saturated with hydrogen chloride (78% yield of ester bp 135—140 °C/20—22 mm Hg)*. This ester was reduced with LiAlH₄ in ether using a standard procedure¹⁰, giving 3-phenyl-propanol (bp 125—128 °C/8 mm Hg, lit.¹¹ bp 119 °C/12 mm Hg) in 96% yield. This alcohol was brominated in nitromethane using PB₃ in great excess. 3-Phenyl-propylbromide was obtained in 75% yield after dilution with water, extraction with ether and, after drying and evaporation of the solvent, distillation at 68—72 °C/16 mm Hg (lit.¹² bp 110 °C/12 mm Hg). NMR (CCl₄) = δ in ppm: 2.10 (s, 2 H), 2.72 (t, 2 H), 3.26 (t, 2 H), 7.1 (s, 5 H).

**Kinetics**

All UV kinetic measurements were performed on Varian Techtron Mod. 635 UV-VIS spectrophotometer using 1 cm silica-grade cells. Samples were prepared by weighing 25.0 mg of the substrate, and dissolving them into 25.0 ml of 6% ethanolic solution of ammonia. This solution was divided into 15 ampoules, which were sealed under ice-water cooling. They were thermostated at reaction temperature using a block-thermostat BT-3, Grant Co., Cambridge, England. The reaction temperature was maintained within ± 0.2 °C. Quenching of the reaction was performed by cooling the samples in an ice bath. TLC's were performed on silicagel plates F254 (Merck), 20 × 20 cm. The separation of the components was performed using benzen-cyclohexane-ethanol (50 : 50 : 10, eluation system A), or the same solvents in the ratio 50 : 50 : 20 (eluation system B). In the first system, separation of the starting compounds 1—3 ($R_f \sim 0.8$) from intermediate aziridines 4—6 ($R_f \sim 0.4$) was achieved,

* 1 mm Hg $\approx$ 133.322 Pa
while 1,4-benzodiazepines remained on the start. In the second system, 1,4-benzo-
diazepines 7—9 moved up $R_f \sim 0.2$, while all other compounds moved with the front
of the solvent mixture.

Chromatographic plates (20 × 20 cm) were divided into 8 vertical segments 15 mm
wide. Within these segments, 50 µl of the solution from the ampoule was spotted on
line 2 cm up from the edge of the plate. After elution with system A, zones con-
taining starting compounds 1—3, and aziridines 4—6 were identified under a UV$_{254}$
lamp, then scratched off from the plate and transferred into a centrifuge glass (10 ml
volume) which contained 5 ml of ethanol. The stopped glass was shaken on the
shaker at 80 cycles per minute for 10 min. Then it was centrifuged at 5000 revolutions
per second, the ethanolic supernatant transferred into a UV cell and extinctions at
particular wavelengths (385 nm for 1, 240 nm for 2 and 365 nm for 3) were measured.
For the first and last sample, the whole spectra between 300—450 nm were run.

Thereafter, the same TLC plate was eluated with system B, the zone of the
1,4-benzodiazepines identified and scratched off. It was transferred into a tube
containing 5.0 ml 0.1 molar HCl, then shaken and the centrifugation was performed
as described above. The extinctions were measured at 245 nm for 1, 440 nm for 2, and
365 nm for 3.

The obtained $\varepsilon_{\text{max}}$ values vs. time were used for calculating the pseudo-first
order rate constants by iterative nonlinear regression using the least-square method.
All attempts to determine the overall cyclization constants by UV spectrophotometry
following the concentrations of the various components during cyclization without
separation failed, although the maxima of all components were well separated. The measured $\varepsilon_{\text{max}}$ vs. time values did not allow calculations of $k$'s with more than 20%
confidence (reliability).

Negative results were also obtained using GLC as a kinetical tool. Using Chromo-
sorb 6 coated with 2%/Dexyl, a GC 300 (Pye Unicam, Analys) column was prepared
according to the literature. Samples (1 µl) from the ampoules were injected directly
into the chromatograph, and separation was achieved at 200 °C for the cyclization
of 1, at 215 °C for the cyclization of 2, and at 230 °C for the cyclization of 3. The
injection block temperature was always 260 °C, the carrier gas, argon, had a flow rate
50 ml/min, and area 450 ml/min. Good separation of the peaks was achieved, as
shown in the Figure 4. Quantitative evaluation of the peaks was impossible, however,
because of the concomitant decomposition of the compounds in the column.

![Figure 4. A. Gas chromatogram of the mixture of the compounds 1, 4 and 7. B. Gas chromatogram of the mixture of the compounds 2, 5 and 8.](image-url)
Argentometric Titration of free bromide ions was used for the kinetics of ammonolysis of 3-phenyl-propylbromide. Titrations were performed using a TTT 2 titrator (Radiometer, Copenhagen) equipped with an ABU 13 automatic burette, and a SBR 2c recorder. A pair of electrodes Hg-HgSO₄/Ag-AgCl was used. The sample was pipetted from the ampoule, and acetonitrile (4 ml), and 2.5% nitric acid (10 ml) were added. The titration was then performed using 0.01 molar AgNO₃. The consumed reagent (ml) was plotted vs. time, and the k's of ammonolysis were calculated as described above. This method was not used for the determination of the kinetics of the bromine displacement in compounds 1-3, since no reproducible titrations could be obtained. Some interaction of silver ions with the benzophenone moiety might be assumed.

Kinetics of formation of 2-amino-5-chlorobenzophenone-imine was determined using same reaction conditions (125 °C in the thermostat, ampoulation in 60/o ethanolic ammonia) as for the cyclization procedures. After applying 10 µl of the reaction solution to TLC immediate eluation with dry benzene was performed. The zone of benzophenone-imine (Rf ~ 0.2) could then be quantitatively hydrolyzed back to the starting benzophenone by leaving the plate standing overnight, or by spraying it with 0.1 molar HCl. It was then scratched off, shaken and centrifuged with 5.0 ml of ethanole. 2-Amino-5-chlorobenzophenone was quantitatively determined at 238 nm.

Acknowledgement. — The authors are indebted to Dr. B. Ruščić for his valuable help in developing computer programs and rate constant calculations.

REFERENCES AND NOTES

5. See footnote in the ref 1 page 133.

SAŽETAK

Kinetika ciklizacije 2-(N-β'-brometil)-amino-5-supstituiranih benzothenona u 1,4-benzodiazepine

J. Kuftinec, L. Klasic, F. Kajfež, M. Mihačić, E. Decorte i V. Sunjić

Određene su brzine za ukupnu reakciju ciklizacije pseudo-prvog reda 2-(N-β'-brometil)-amino-5-supstituiranih benzothenona 1—3 u 1,4-benzodiazepine 7—9 u 6/o etanolnom amonijaku kod 100 °C, 115 °C i 125 °C, i nađeno je da leže između 1.0 × 10⁻³ s⁻¹ i 8.33 × 10⁻⁴ s⁻¹ za spoj 1, 1.6 × 10⁻⁴ s⁻¹ i 5.8 × 10⁻⁵ s⁻¹ za spoj 2, te 6.66 × 10⁻⁵ s⁻¹ i 3.16 × 10⁻⁴ s⁻¹ za spoj 3. Niže vrijednosti za brzine reakcije dobivene su kada su bile izračunate iz porasta koncentracije produkta ciklizacije 7—9, što upućuje na nastajanje stabilnih intermedijara. To su protonirani aizrinski derivati 4—6, a spojevi 4 i 5 su identificirani kao intermedijari koristeći kromatografiju na tankom sloju i plinsku kro-
matografiju. Brzina nastajanja imina modelnog spoja 2-amino-5-klor-benzofenona bila je kod 125 °C $5.8 \times 10^{-7}$ s$^{-1}$, što je eliminiralo taj spoj kao mogući intermedijar. Brzina amonolize drugoga modelnog spoja, 3-fenil-propilbromida, određena između 110 °C i 125 °C, iznosila je od $1.5 \times 10^{-4}$ s$^{-1}$ do $4.16 \times 10^{-4}$ s$^{-1}$. Te vrijednosti pokazuju da β-participacija atoma N(2), budući da je to brzo ravnotežna reakcija, ne povećava brzinu ukupne reakcije. Slijedeći termodinamički parametri karakteriziraju ovu reakciju ciklizacije: $\Delta H^\circ = (50.0 \pm 4.0)$ kJ mol$^{-1}$, $\Delta S^\circ = (-156 \pm 5)$ J mol$^{-1}$ K$^{-1}$ za spoj 1, $\Delta H^\circ = (89.0 \pm 4.0)$ kJ mol$^{-1}$, $\Delta S^\circ = (-41 \pm 4)$ J mol$^{-1}$ K$^{-1}$ za spoj 2, $\Delta H^\circ = (73.5 \pm 4.0)$ kJ mol$^{-1}$, $\Delta S^\circ = (89 \pm 4)$ J mol$^{-1}$ K$^{-1}$ za spoj 3.

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