89. Diazotisation Mechanism of Heteroaromatic Amines

Diazotisation of 2-Aminothiazole as an Equilibrium

by **Heinz Diener, Bilge Güleç, Peter Skrabal,** and **Heinrich Zollinger***

Technisch-Chemisches Laboratorium, Eidgenössische Technische Hochschule (ETH), CH-8092 Zürich

(6.II.89)

The rate of diazotisation of 2-aminothiazole was measured in 65 to 75% (*w*/*w*) aqueous H_2SO_4. The kinetic solvent isotope effect of the diazotisation in 72% D_2SO_4/D_2O was determined ($k_H/k_D = 5.8 \pm 0.2$). These data are consistent with a mechanism in which the 2-aminothiazole, protonated at the ring N-atom, but not at the NH_2 group, is attacked by the NO^+ ion. The reaction does not go to completion, but to an equilibrium. The equilibrium concentration of the diazonium ion was determined in 30, 50, 70, and 90% (*w*/*w*) H_2SO_4 at three initial concentrations of reagents (0.001, 0.01, and 0.1M). The final concentrations of the reagents and the diazonium ion are consistent with a reversible process. This is the first diazotisation for which quantitative evidence for equilibration has been found. In the very large range of acidities used ($H_0 = -1.73$ to -9.01), it was not possible to calculate meaningful equilibrium constants that are independent of the acidity.

Introduction. – Diazotisation of five- and six-membered heteroaromatic amines has been investigated for many years, according to *Butler*'s 1975 review [1] mainly for preparative reasons. It is surprising that kinetic investigations of diazotisation of heteroaromatic amines have been carried out with six-membered ring compounds, *e.g.* aminopyridines [2] and 3-aminoquinoline [3], but not with the more important five-membered heteroaromatic amines. Also, there is qualitative information on the reverse reaction of heteroaromatic diazonium ions to the corresponding amines [4] [5] available, *e.g.* the observation by *Štěrba* and coworkers [5] that 5-phenyl-1,3,4-thiadiazole-2-diazonium ion is transformed into 2-amino-5-phenyl-1,3,4-thiadiazole in aqueous mineral acid. However, this did not stimulate quantitative investigation of such equilibria.

We decided, therefore, to measure rate and equilibrium constants of the reaction *heteroaromatic amine + nitrous acid ⇄ diazonium ion* as a function of reagent concentration and of acidity in H_2SO_4/H_2O mixtures. As amine, we chose 2-aminothiazole.

Results. – All diazotisations discussed here were carried out in H_2SO_4/H_2O mixtures at 20°. For equilibrium and kinetic measurements, 30 to 90% (*w*/*w*) and 65 to 75% (*w*/*w*) H_2SO_4 was used, respectively.

In heteroaromatic amines containing at least one N-atom in the 5-membered heteroring, the basicity of the ring N-atom is much greater than that of the NH_2 group. For the conjugate acid of 2-aminothiazole, one finds $pK_{a2} = 5.28$ [6]. The ^{13}C- and ^{15}N-NMR spectra of 2-aminothiazole in 90% H_2SO_4 show that under these conditions significant protonation of the amino N-atom is very unlikely [7]. To confirm these results, we measured ^1H-decoupled and ^1H-coupled ^{15}N-NMR spectra of the amine in 96% H_2SO_4 and CF_3SO_3H (H_0 *ca.* -9 and -13 [8], respectively). In both solvents, the observed chemical shifts are in agreement with the published data [7]. In addition, even at these higher acidities, the coupling constants $^1J(^{15}N,H)$ (*ca.* 97 Hz) of the ring N-atom and the narrow *singuletts* of the NH_2 group indicate protonation of the ring N-atom only and fast proton exchange (on the

NMR time scale) at the unprotonated NH_2 group. Therefore, to a first approximation, diprotonation of 2-aminothiazole can be neglected. The pK_{a1} value seems to be < -7[1]). Consequently, our kinetic and equilibrium measurements were carried out over a range of solvent acidities in which the dominant equilibrium form is the monocation.

The equilibrium measurements are based on concentration measurements of the diazonium ion ($\lambda_{max} = 320$ nm; no other compound in the systems absorbs at this wavelength). All equilibrations were accomplished with equal initial concentrations of 2-aminothiazole and $NOHSO_4$. As expected, the equilibrium depends on the concentration of the reagents and on solvent composition as shown in *Table 1*[2]).

Table 1. *Equilibrium Concentration of Diazonium Ion, in % of the Initial Concentrations of the Reagents* $[RNH_2]_0 = [NOHSO_4]_0$ *and in Dependence of the Concentration of* H_2SO_4 (at 20°)

$[RNH_2]_0$ [mol·dm^{-3}]	H_2SO_4[a])			
	30% (–1.73)	50% (–3.30)	70% (–5.82)	90% (–9.01)
0.001	–	–	8.3 (±0.3)	–
0.01	45.8	60.0	52.1 (±2.3)	27.5
0.1	–	–	89 (± 3)	–

[a]) Acidity functions H_0 in parentheses [10].

The equilibrium concentrations of the diazonium ion given in *Table 1* are *measured* concentrations given as a percentage of the initial concentrations of 2-aminothiazole. These percentages are *lower* limits of the equilibrium concentrations because diazotisation of 2-aminothiazole is accompanied by some irreversible decomposition of the diazonium ion.

For the *kinetics* of the diazotisation of 2-aminothiazole, we used *Letort*'s method of initial rates [11], because the reaction does not lead to 100% conversion into the diazonium ion. The reaction rate constants k_H and k_D in *Table 2* were obtained spectrophotometrically by measuring the increase in the absorption of the diazonium ion at 320 nm. The values calculated for the reaction order with respect to the two reagents in *Eqn. 1* are, within experimental error, equal to 1. The rate dependence on h_0[3]) is based on measurements in 65, 70, 72, and 75% H_2SO_4 *(Table 2)*.

$$v = k_H [RNH_2]^{0.87} \cdot [HNO_2]^{0.93} \cdot h_0^{-0.70} \qquad (1)$$

In addition, the rate of diazotisation was measured in 72% D_2SO_4/D_2O (*Table 2*). A kinetic isotope effect $k_H/k_D = 5.8$ (±0.2) was obtained.

---

[1]) It has to be emphasized that pK_{a1} is defined with respect to the H_+ acidity function. However, H_+ is not known for 96% H_2SO_4 and for CF_3SO_3H. The value < -7 is based on an extrapolation of the H_+ scale, which has been measured only up to 82% H_2SO_4 ($H_+ = -5.62$ [9]).

[2]) In this paper, R stands for the thiazole ring and $H\overset{+}{R}$ for the thiazole ring protonated at the heterocyclic N-atom. Numbers in parentheses are total concentrations, including all possible acid/base equilibrium forms. Brackets are used for concentrations of the acid/base equilibrium form given. Subscripts 0 and ∞ refer to initial and equilibrium concentrations, respectively.

[3]) $\log h_0 = -H_0$.

Table 2. *Rate Constants (k) for Diazotisation of 2-Aminothiazole in Aqueous H_2SO_4* (20.0 ± 0.1°)

% (*w*/*w*) H_2SO_4	H_0 (D_0)[a]	k[b]) [$dm^3 \cdot mol^{-1} \cdot s^{-1}$]
65	−5.06	2.65 (±0.12) 10^{-1}
70	−5.82	8.37 (±0.14) 10^{-2}
72	−6.15	5.37 (±0.09) 10^{-2}
75	−6.64	2.50 (±0.18) 10^{-2}
72[c])	(−6.47)	9.26 (±0.22) 10^{-3}

[a]) H_0 from [10], D_0 from [12].

[b]) Standard deviations in parentheses.

[c]) D_2SO_4/D_2O (98% isotope purity).

Discussion. – 1. *Equilibria.* The results at three initial concentrations in 70% H_2SO_4 *(Table 1)* provide good evidence for our claim that this diazotisation does not go to completion, but leads to an equilibrium. If the concentration ratios $[RN_2^+]_\infty/[RNH_2]_\infty = r$ are calculated from the percentages of $[RN_2^+]_\infty$ in 70% H_2SO_4, $r/[RNH_2]_o(r - 1)$ is expected to be a constant c, which is independent of the initial concentration of reagents $[RNH_2]_o$. The result for the three levels of $[RNH_2]_o$ = 0.001, 0.01, and 0.10M is c = 90.5 (±1.6), 106.7 (±5.1), and 85.1 (±15.9). Considering the low accuracy of the equilibrium measurements, which is due to the competing irreversible decomposition of the diazonium salt and of the $NOHSO_4$ (see *Bayliss* and *Watts* [13]), we think that the almost equality of the three values of c allows to assume that this diazotisation reaction leads to an equilibrium.

We tried to calculate the equilibrium constant *K* for this diazotisation on the basis of the equilibrium concentrations of the diazonium ion, the amine, and the nitrosating reagent in the range 30–70% H_2SO_4, but failed for the following reasons:

a) The concentrations of H_2SO_4 cover a range of almost $10^{7.3}$ in acidity as shown by the H_0 values in *Table 1*: H_0 (30%) = −1.73, H_0 (90%) = −9.01 [10].

b) The overall equilibrium system includes protonation/deprotonations for which different acidity functions have to be applied: H_0 and H_+ for the two equilibria of RNH_2, H_R for $NOHSO_4$ equilibrium, as shown by *Seel* and *Winkler* [14], and *Bayliss et al.* [15][4]).

c) In addition, the overall equilibrium includes an N–N bond formation/dissociation and a dehydration/hydration of a $N\overset{+}{O}H_2$ group. No acidity functions for such processes have been determined so far.

d) We tried a completely pragmatic approach, and checked, if 9 different 'reasonable' overall equilibrium equations, such as *Eqns. 2* and *3*, yielded equilibrium constants which are independent of acidity. This approach failed, last not least because neither activities nor concentrations of H_3O^+ and H_2O have been determined for the whole range of 30 to 90% H_2SO_4 [17].

$$RNH_2 + NO^+ \leftrightarrows RN_2^+ + H_2O \qquad (2)$$

$$H\overset{+}{R}NH_2 + NO^+ \leftrightarrows RN_2^+ + H_3O^+ \qquad (3)$$

Accordingly, there seems to be no way to calculate an equilibrium constant for diazotisation in 30–90% H_2SO_4/H_2O systems, including *Cox* and *Yates'* excess acidity method [16] [18]. This is unfortunate, because it precludes a convincing explanation for the fact that, until now, only diazotisations of beteroaromatic amines containing a ring N-atom in α-position to the NH_2 group were found (qualitatively) to be reversible. Also, no evidence has been reported that diazotisation of aromatic amines in aqueous systems is reversible[5]). *Ernst* [20] recently examined this possibility by investigating the diazotisation of very weakly basic anilines (*e.g.* 2-bromo-4,6-dinitroanilinium ion, pK_a = −6.69 [10]). No indication for reversibility was found. It is difficult to compare

---

[4]) This subject has been frequently reviewed, most recently by *Cox* and *Yates* [16]. H_R is the acidity function for the protonation/dehydration equilibrium of triarylcarbinols (see [16]).

[5]) There is some evidence, however, for the reversibility of aromatic diazotisation in MeOH [19].

numerically the basicity of the NH_2 group in this aniline derivative with that of 2-aminothiazolium ion ($pK_{a1} < -7$), because they are based on two different acidity functions, *i.e.* H_0 and H_+, respectively. Nevertheless, $pK_{a1} < -7$ for the conjugate acid of 2-aminothiazolium ion indicates that this NH_2 group is considerably less basic. For the nitrosation step in the mechanism of diazotisation, it is, however, not the basicity, but the nucleophilicity of the NH_2 group which determines, if the reverse reaction is detectable. In this respect, semiquantitative studies on the reversibility of the diazotisation of other heteroaromatic amines and comparisons of the nucleophilicities of aromatic and heteroaromatic amines might be helpful.

2. *Kinetics and Reaction Mechanism.* We compare the dependence of the diazotisation kinetics of 2-aminothiazole on acidity (*Table 2* and *Eqn. 1*, rate proportional to $h_0^{-0.70}$) with that found by *Challis* and *Ridd* [21] for the diazotisation of aniline, *p*-toluidine, and *p*-nitroaniline in the same range of H_2SO_4/H_2O mixtures. In those reactions, the dependence on h_0 is $10^{-2.4}$.

Challis and *Ridd* explained their results as being due to a rapid nitrosation equilibrium of the anilinium ion, followed by a slow and rate-limiting proton loss from the protonated nitrosamine (*Eqns. 4–6*[6]) [21] [22]. In other words, the rate-determining part of such diazotisations includes *two* proton transfers – a conclusion that is consistent with the rate dependence on h_0, which is $10^{-2.4}$ in H_2SO_4 and $10^{-2.1}$ in $HClO_4$. This explanation is supported by a large solvent isotope effect in D_2O: $k_H/k_D = 10$ [21].

$$Ar{-}NH_3^+ + NO^+ \twoheadrightarrow Ar{-}\overset{+}{N}H_2NO + H^+ \qquad (4)$$

$$Ar{-}\overset{+}{N}H_2NO \xrightarrow[\text{slow}]{} Ar{-}NHNO + H^+ \qquad (5)$$

$$Ar{-}NHNO \underset{\text{fast}}{\twoheadrightarrow} Ar{-}N_2^+ \qquad (6)$$

In our case, the deuterium isotope effect $k_H/k_D = 5.8\ (\pm 0.2)$ is significantly lower than that for the diazotisation of aniline: the rate dependence on h_0 and the isotope effect indicate strongly that in the rate-determining part of the 2-aminothiazole diazotisation only *one* proton transfer is involved[7][8]). It is likely, therefore, that the aminothiazolium ion $H\overset{+}{R}NH_2$ is nitrosated. The modification of *Ridd*'s mechanism that we published recently [24] is not relevant for 2-aminothiazole, because it is not the NH_3^+ ion which is nitrosated.

We thank Prof. *E. Buncel*, Queen's University, Kingston, Canada, Prof. *E. Heilbronner*, University of Basle, Prof. *A. R. Katritzky*, University of Florida, Gainsville, and Dr. *M. D. Ravenscroft*, postdoctoral fellow at ETH Zurich (1982–85), for helpful discussions.

---

[6] Double arrows indicate more than one mechanistic step for the given reaction.

[7] The result that the powers of h_0 in the kinetic equations used by *Challis* and *Ridd* for aromatic amines and by us for 2-aminothiazole are not −2.00 and −1.00, but slightly different, is well known, because acidity functions are based on equilibria and not on kinetics.

[8] As the diazotisation rates of aniline and 2-aminothiazole are dependent on acidity, the calculation of k_D should be based on D_0. We did not do that, because our isotope effect measurement had to be compared with that of *Challis* and *Ridd* for aniline. The fact that their isotope effect is clearly larger than ours is the only relevant result for our mechanistic interpretation. D_0 for D_2SO_4/D_2O was measured by *Högfeldt* and *Bigeleisen* [23] and by *Wyatt* and coworkers [12].

Experimental Part

Syntheses. 2-Aminothiazole was obtained by a modification of the method of *Traumann*, *i.e.* by cyclocondensation of chloroacetaldehyde with thiourea [25]. Instead of 1,2-dichloroethyl ethyl ether, 436 g (0.35 mol) of chloroacetaldehyde dimethyl acetal (*Fluka, purum* 98%) and a trace of TsOH was added to a soln. of 22.84 g (0.30 mol) thiourea in 270 ml of H_2O and refluxed until the acetal disappeared. The mixture was neutralised with 12 g of NaOH, evaporated under vacuum, extracted four times with Et_2O and the product recrystallized twice from CH_2Cl_2: 11.1 g (37%). M.p. 88.5–89.5° ([25]: 90°).

Kinetic Measurements. All kinetic runs were made at 20.0 ± 0.1°. The calculated amount of 2-aminothiazole was dissolved in 5 ml of aq. H_2SO_4 of the respective concentration (*w/w*) at 0°. The reaction was started by addition of $NOHSO_4$, obtained by the method of *Fierz-David* and *Blangey* [26]. After exactly 1 min, ice cooling was replaced by a water bath maintained at 20.0 ± 0.1°. Visible decomposition was never observed by this procedure. After 4 min, an aliquot was transferred to a 0.01-cm UV cell. The extinction at 320 nm (maximum of the thiazole-2-diazonium ion) was measured after 5 min. Initial concentrations of 2-aminothiazole and $NOHSO_4$ varied in the range of 0.01–0.04M; the ratio of the two reagents varied from 1:4 to 4:1. H_2SO_4 concentrations are given in *Table 2*. Details of experiments and their evaluation have been already published [27a].

The experiments for the determination of the kinetic isotope effect were carried out in D_2SO_4/D_2O, made from 1.50 g D_2SO_4 96% (*Ciba-Geigy*, 98% isotopic purity) and 0.50 g D_2O (99%).

Dediazoniation of Thiazole-2-diazonium Ion. We determined dediazoniation rates at 30, 50, 70, and 90% H_2SO_4. The rates were measured spectrophotometrically in 30, 50, 70, and 90% H_2SO_4 at 20.0 ± 0.1° by following the decrease of the maximum of the diazonium ion at 320 nm as discussed above. They are the same within a factor of 2.4 (highest in 30% H_2SO_4, lowest in 90% H_2SO_4). Details are described in [27b].

Equilibrium Measurements. Equilibria were determined by measuring the extinction of the thiazole-2-diazonium-ion absorption at 320 nm in reagent solns. which were prepared as for the kinetic experiments. In 30–70% H_2SO_4, the equilibrium is attained within *ca.* 1 h, but in 90% H_2SO_4 only after 4 days. Therefore, dediazoniation has some influence. The concentrations of the diazonium ion (see *Table 1*) are, therefore, lower limits.

The true equilibria are a little higher in 30 to 70% H_2SO_4. They may be significantly higher in 90% H_2SO_4 due to the long reaction time (4 days) necessary to reach equilibrium.

^{15}N-NMR spectra were run on a *Bruker AM 300-WB* spectrometer, in 10-mm tubes with field stabilization and refencing with the help of a $D_2O/^{15}NH_4{}^{15}NO_3$ capillary.

REFERENCES

[1] R.N. Butler, *Chem. Rev.* **1975**, *75*, 241.

[2] E. Kalatzis, *J. Chem. Soc. (B)* **1967**, 277; E. Kalatzis, C. Mastrokalos, *J. Chem. Soc., Perkin Trans. 2* **1974**, 498, *ibid.* **1983**, 53.

[3] C. Bravo, A. Castro, E. Iglesias, J.R. Leis, M.E. Peña, *Bull. Soc. Chim. Fr.* **1987**, 572.

[4] J. Goerdeler, K. Deselaers, *Chem. Ber.* **1958**, *91*, 1025; V. Chmátal, V. Štěrba, *Collect. Czech. Chem. Commun.* **1967**, *32*, 2679; R.N. Butler, T.M. Lambe, J.C. Tobin, F.L. Scott, *J. Chem. Soc., Perkin Trans. 1* **1973**, 1357; H. Diener, H. Zollinger, *Can. J. Chem.* **1986**, *64*, 1102.

[5] J. Kaválec, K. Janák, V. Štěrba, *Collect. Czech. Chem. Commun.* **1979**, *44*, 3102.

[6] R. Barone, M. Chanon, R. Gallo, *Chem. Heterocycl. Compounds* **1979**, *34/II*, 9.

[7] G. Tóth, B. Podányi, *J. Chem. Soc., Perkin Trans. 2* **1984**, 91.

[8] R.D. Howells, J.B. McCown, *Chem. Rev.* **1977**, *77*, 69.

[9] P. Vetešník, J. Bielavský, M. Večeřa, *Collect. Czech. Chem. Commun.* **1968**, *33*, 1687.

[10] C.D. Johnson, A.R. Katritzky, S.A. Shapiro, *J. Am. Chem. Soc.* **1969**, *91*, 6654.

[11] M. Letort, *J. Chem. Phys.* **1937**, *34*, 206; *Bull. Chem. Soc. Fr.* **1942**, 1; see K.J. Laidler, 'Chemical Kinetics', 2nd edn., McGraw-Hill, New York, 1965, p. 16.

[12] J. Sierra, M. Ojeda, P.A.H. Wyatt, *J. Chem. Soc. (B)* **1970**, 1570.

[13] N.S. Bayliss, D.W. Watts, *Aust. J. Chem.* **1963**, *16*, 927.

[14] F. Seel, R. Winkler, *Z. Phys. Chem.* **1960**, *25*, 217.

[15] N.S. Bayliss, R. Dingle, D.W. Watts, R.J. Wilkie, *Aust. J. Chem.* **1963**, *16*, 933.

[16] R.A. Cox, K. Yates, *Can. J. Chem.* **1983**, *61*, 2225.

[17] W. F. Giauque, E. W. Hornung, J. E. Kunzler, T. R. Rubin, *J. Am. Chem. Soc.* **1960**, *82*, 62; E. B. Robertson, H. B. Dunford, *ibid.* **1964**, *86*, 5080; C. W. F. Kort, H. Cerfontain, *Rec. Trav. Chim. Pays-Bas* **1968**, *87*, 24.

[18] R. A. Cox, K. Yates, *J. Am. Chem. Soc.* **1978**, *100*, 3861.

[19] A. Woppmann, H. Sofer, *Monatsh. Chem.* **1972**, *103*, 163.

[20] Th. Ernst, 'Beiträge zur Kinetik der Diazotierung schwach basischer Aniline mit Nitrosylschwefelsäure', Ph. D. thesis No. 8348, ETH Zürich, 1987.

[21] B. C. Challis, J. H. Ridd, *Proc. Chem. Soc.* **1960**, 245.

[22] E. C. R. de Fabrizio, E. Kalatzis, J. H. Ridd, *J. Chem. Soc. (B)* **1966**, 533.

[23] E. Högfeldt, J. Bigeleisen, *J. Am. Chem. Soc.* **1960**, *82*, 15.

[24] H. Zollinger, *Helv. Chim. Acta* **1988**, *71*, 1661.

[25] V. Traumann, *Liebigs Ann. Chem.* **1888**, *249*, 15.

[26] H. E. Fierz-David, L. Blangey, 'Grundlegende Operationen der Farbenchemie', 5th edn., Springer Verlag, Wien, 1943, p. 236.

[27] H. Diener, 'Fünfgliedrige heterocyclische Amine: Mechanismus der Diazotierung und Reaktivität der Diazoniumverbindungen'. Ph. D. thesis No. 7693, ETH Zürich, 1984; a) p. 98–104; b) p. 58 and 106.