# Kinetics, Catalysis, and Mechanism of Isomerization of *N*-[(Benzotriazol-1-yl)methyl]anilines into the Benzotriazol-2-yl Derivatives

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## Abstract

The $^1$H NMR technique was applied for the measurement of the isomerization rates of *N*-ethyl-*N*-[(benzotriazol-1-yl)methyl]aniline (**4**) and 4-butyl-*N*-[(benzotriazol-1-yl)methyl]aniline (**7**) to the corresponding benzotriazol-2-yl isomers in dioxane-$d_8$ at 35°C. The rate constants obtained for pure dioxane-$d_8$ were 1.62 and 0.28 $h^{-1}$ for **4** and **7**, respectively. For both compounds, addition to acetic acid to the dioxane solutions accelerated the isomerizations whereas addition of triethylamine retarded it strongly. Addition of water slowed the isomerization of **4** but accelerated that of **7**: the different effects operating in the two cases are discussed and rationalized. © 1995 John Wiley & Sons, Inc.

## Introduction

Linsay-Smith and Sadd [1] first showed that *N*-(*N'*,*N'*-disubstituted aminomethyl)-benzotriazole derivatives exist in solution as an equilibrium mixture of the corresponding 1-(*N'*,*N'*-disubstituted-aminomethyl)- (**1**) and 2-(*N'*,*N'*-disubstituted-aminomethyl) benzotriazoles (**2**) (Chart 1). They found that while the 1-isomer normally predominates, the position of this equilibrium depends strongly both on the polarity of the solvent and on the substrate structure. Thus, as the polarity of the medium increases, so does the amount of isomer **1** relative to isomer **2**, whereas increased bulkiness in the *N*-aminomethyl substituents favors 2-substitution.

Later, one of our research groups demonstrated [2] by X-ray analysis, solid-state NMR, and IR that several *N*-(dialkylaminomethyl)benzotriazoles exist solely in the 1-substituted form (**1**) in the crystalline phase. However, the same compounds exist as an equilibrium mixture of isomers **1** and **2** in the liquid, melt, solution, and argon matrix phases. Isomers **1** and **2** equilibrate by an intermolecular mechanism (as proven by cross-over experiments), and with characteristics consistent with a dissociative pathway to immonium ions and a benzotriazolide anion. The subsequent alternative modes of recombination of these two species furnishes equilibrium mixtures of **1** and **2** in which isomer **1** always predominates.

Subsequently [3], we calculated the equilibrium constants (K, defined as [**1**]/[**2**]) and the associated free energies for the equilibria, and the free energies of activation for the isomerization process, of a series of 1- (**1**) and 2-(*N*,*N*-dialkylaminoalkyl)benzotriazoles (**2**) from their variable temperature $^1$H NMR

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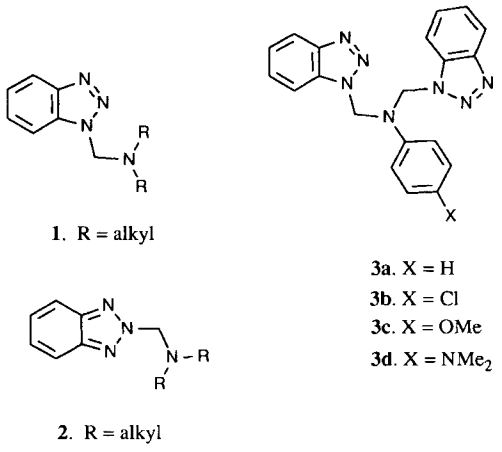



Chart 1

spectra. The free energy of activation for the 1- to 2-benzotriazolyl rearrangement of the title compounds is greatly dependent on the degree of stabilization provided to either of the intermediate ions (immonium cation and benzotriazolide anion): the greater such stabilization, the lower the value of $\Delta G^{\#}$. In terms of the extent of isomerization, the bulkier the dialkylaminoalkyl (or -aryl) substituent, the more abundant the isomer **2**, which in extreme cases becomes the predominant component, as shown by values of K less than 1 and $\Delta G^0$ greater than zero. The presence of a methyl group at the C-4 and/or C-7 positions of the benzotriazole ring strongly disfavors substitution on the adjacent nitrogen atom(s). These ring substituent steric interactions favor the 2-isomer while increasing solvent polarity favors the 1-isomer [4].

While equilibration in the simple compounds discussed thus far is so fast that separation of the individual 1-*N* and 2-*N* isomers is not possible, this circumstance is not always observed, however. Thus, the individual isomers of the *N,N-bis*(benzotriazolylmethyl)arylamines (**3**) (Chart 1) are relatively stable at room temperature in solution [5]. Substituents on the aniline ring of the *N,N-bis*(benzotriazoylmethyl)-anilines strongly influence the interconversion rates of the individual isomers. Thus, no isomerization was observed when solutions of the aniline (**3a**) and 4-chloroaniline (**3b**) derivatives in chloroform were stored at 25°C for several weeks, whereas fast equilibration (within hours) occurred in chloroform solutions of the 4-anisidine (**3c**) and 4-dimethylaminoaniline (**3d**) derivatives. The isomers in these last two series undergo relatively fast equilibration (days at 20°C) even in the solid state.

To gain a better understanding of the isomerization process, kinetic measurements were performed on two 1-(arylaminomethyl)benzotriazoles and the results obtained are presented below.

## Results and Discussion

*Reaction Conditions. Influence of the Structure*

Two model compounds, *N*-ethyl-*N*-[(benzotriazol-1-yl)methyl]aniline (**4**) and 4-butyl-*N*-[(benzotriazol-1-yl)methyl]aniline (**7**) were chosen for investigation. The ethyl group

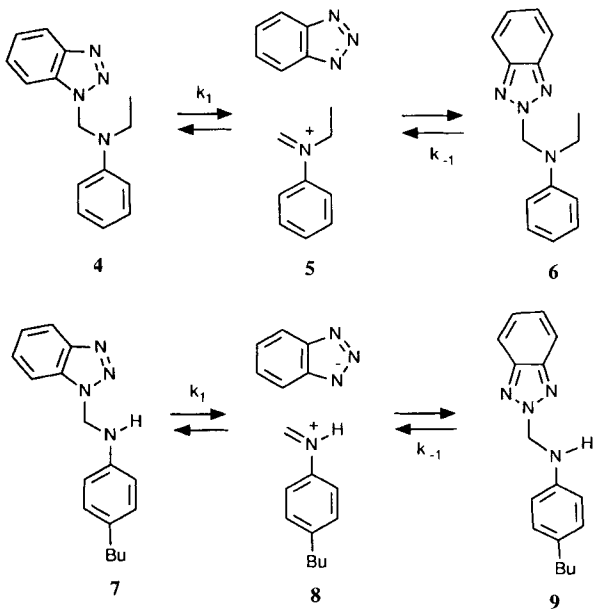
of the former and the butyl group of the latter model were introduced to increase solubility of these compounds.

According to our isomerization model, ionization of the Bt-$CH_2$N bond in **4** leads to benzotriazolide anion ($Bt^-$) and immonium cation **5** (Scheme I). The ion pair thus obtained can recombine back to the benzotriazol-1-yl isomer (**4**) or to the benzotriazol-2-yl derivative (**6**). The total molecular energy for the ionic pair of $Bt^-$ and immonium cation **5** will be much higher than the energy of either of the nonionic forms, **4** and **6**. This additional energy of the transition state (barrier to isomerization) showed a dependency on the polarity of the solvent: with strong solvatation effect and comparably lower energy of **5** in polar solvents. Dioxane-$d_8$ used in most of the experiments is a solvent of medium polarity, relatively inert chemically, and as obtained was free of impurities which might affect the isomerization. In some initial attempts, rapid isomerization in deuteriochloroform was observed. Less polar inert solvents (benzene) could not be used because of low solubility of the investigated compounds **4** and **7**. Dilute (1%) solutions of **4** and **7** were used to prevent association of the molecules.

The first investigations proved that isomerization of **4** was much faster than **7**. This is in accordance with expectations since cation **5** derived from *N*-ethylaniline is more stable than cation **8** derived from 4-butylaniline; cf, *N*,*N*-diethylaniline (p*Ka* 6.6) and *N*-ethyl-*p*-toluidine (p*Ka* 4.9) [6]. At room temperature, isomerization of **7** appeared to be inconveniently slow for monitoring by NMR. On the other hand, at 50°C, isomerization of **4** was too rapid to be followed by NMR measurements. To make direct comparison of both reactions, a compromise was achieved at temperature 35°C.

*Effect of Moisture*

Unexpectedly, when in one instance commercial dioxane-$d_8$ was used directly to kinetic measurements, without storage over molecular sieves, isomerization of




Scheme I

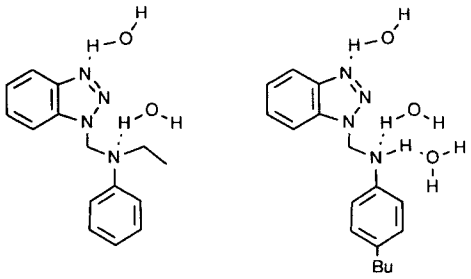
compound **4** appeared to be much slower. Careful examination of the $^1H$ NMR spectrum revealed an additional singlet at $\delta$ 2.30 which was later found to belong to water; addition of a small amount of water resulted in an increase of its intensity and a downfield shift to $\delta$ 2.60. This turned our attention to moisture and to other possible impurities in the investigated systems which might affect the isomerization.

As can be seen in Table I, water dramatically reduced the isomerization rate of **4** (about 12 times, run 3). A quite different influence of water was observed on the rate of isomerization of compound **7**; an approximately five times increase in the rate was found in run 12. These data suggest that the mechanisms of water interaction with molecule **4** and **7** are quite different.

To consider the influence of water on isomerization of **4** and **7** we have to distinguish the sites in the molecules with the strongest interaction with water. In the molecule of **4**, two places of attack of water molecules seem to be the most probable: the N-3 atom of benzotriazole and the aniline nitrogen atom (Chart 2). The N-3 position of 1H-benzotriazole is known to be the basic site [7]. Because the benzotriazole system becomes an electron acceptor and the aniline nitrogen atom becomes the electron donor in the ionization process (Scheme I), decreasing the electron density in the benzotriazole system and increasing the electron density on the aniline nitrogen atom would help the ionization. In this light, it is clear that the first of these interactions with water (with N-3) should accelerate the isomerization whereas the second, decreasing electron density on the aniline nitrogen atom, should have a retarding effect. In reality, the interactions have to compete and, as the experimental data show, hydrogen bonding to the aniline atom has the predominant influence. It is clear that the basicity of the aniline nitrogen (p*Ka* of *N*,*N*-diethylaniline 6.6 [6]) is higher from that of the benzotriazole N-3 (p*Ka* 1.6 [8]).

TABLE I. Kinetic data for isomerizations of **4** and **7** at 35°C in dioxane-$d_8$.

| Run | Reagents | $k_1 + k_{-1}(h^{-1})$ | $\frac{k_{-1}}{k_1}$ | $k_1(h^{-1})$ | r | s ($h^{-1}$) |
|---|---|---|---|---|---|---|
| 1 | **4** | 1.62 | 2.16 | 0.512 | 0.996 | 0.061 |
| 2 | **4** + $H_2O$ (1 : 0.3) | 1.41 | 2.16 | 0.446 | 0.987 | 0.081 |
| 3 | **4** + $H_2O$ (1 : 1.9) | 0.137 | 2.16 | 0.043 | 0.949 | 0.028 |
| 4 | **4** + $H_2O$ (1 : 6.6) | 0.273 | 2.16 | 0.086 | 0.994 | 0.025 |
| 5 | **4** + $Et_3N$ (1 : 0.2) | 0.114 | 2.14 | 0.053 | 0.960 | 0.039 |
| 6 | **4** + $CH_3COOH$ (1 : 1) | 14.4 | 2.01 | 4.79 | 0.975 | 0.340 |
| 7 | **4** + PhNHEt | 0.165 | 2.27 | 0.050 | 0.962 | 0.067 |
| 8 | **4** + BtH (1 : 0.5) | 0.138 | 4.52 | 0.025 | 0.966 | 0.064 |
| 9 | **7** | 0.28 | 2.70 | 0.078 | 0.984 | 0.065 |
| 10 | **7** + $H_2O$ (1 : 0.96) | 0.310 | 2.77 | 0.082 | 0.996 | 0.026 |
| 11 | **7** + $H_2O$ (1 : 1.34) | 0.773 | 2.65 | 0.212 | 0.994 | 0.086 |
| 12 | **7** + $H_2O$ (1 : 2.6) | 1.45 | 2.70 | 0.392 | 0.962 | 0.418 |
| 13 | **7** + $H_2O$ (1 : 4) | 1.48 | 2.88 | 0.381 | 0.933 | 0.474 |
| 14 | **7** + $Et_3N$ | 0.060 | 2.68 | 0.016 | 0.984 | 0.017 |
| 15 | **7** + $CH_3COOH$ | 0.56 | 2.45 | 0.162 | 0.971 | 0.161 |
| 16 | **7** + 4-$BuNH_2$ + $H_2O$ (1 : 0.4 : 1.0) | 0.188 | 2.69 | 0.051 | 0.978 | 0.048 |
| 17 | **7** + BtH + $H_2O$ (1 : 0.5 : 1.4) | 0.171 | 3.50 | 0.038 | 0.982 | 0.036 |
| 18 | **7** + $(CH_2O)_n$ + $H_2O$ (1 : 1 : 1) | 1.27 | 2.61 | 0.352 | 0.982 | 0.239 |




4 7

Chart 2

In a molecule of **7**, apart of the two effects described above, an additional interaction, with the amino hydrogen atom should be taken into the consideration. In this case, removal of the proton would dramatically increase the electron density on the nitrogen atom and hence increase the ability of the molecule to ionize. Strong increase of the isomerization rate of **7** in the presence of water (Table I) indicates that the interaction with the N—H hydrogen is predominant.

*Influence of Acids, Bases, and the Starting Materials*

Addition of 50% molar equivalent amounts of *p*-toluenesulfonic acid to solutions of **4** and **7** caused very rapid isomerization in both cases; the spectra recorded after about 5 min showed the samples had already reached equilibrium. Investigation of such fast reactions was not possible by our NMR technique. Zinc bromide also caused almost immediate changes in the samples; in this case, the NMR spectra showed in addition to **4** and **6**, or **7** and **9**, the presence of several unidentified new compounds (or zinc complexes). Even a relatively weak acid, acetic acid, caused a dramatic increase in the isomerization rate of **4** (9 times) and a more modest increase in the rate of **7** (1.9 times).

All types of the intermolecular interactions depicted above for water seem to be active also in the case of acids. However in this case, the dominant interaction is probably with the benzotriazole N-3 atom activating the molecules for ionization. The less hindered aniline nitrogen atom in **7** also may facilitate to some degree hydrogen bonding to this atom which stabilizes the molecule and as a result, the isomerization rate of **7** is less affected than that of **4**. The third type interaction of **7**, that with the aniline hydrogen atom, is probably unimportant as the acids are themselves stronger proton donors.

Triethylamine used as a base showed in both cases (runs 5 and 14) strong retarding effect on the isomerization. Such an influence may be in binding traces of active proton donors present in the solution. To rule out the influence of trace amounts of the starting materials, the isomerizations were carried out in the presence of benzotriazole (runs 8 and 17) and the constituent amines (runs 7 and 16). In all these cases, the isomerization proceeded more slowly than for the pure compounds **4** and **7**.

*The Equilibrium Constants*

As can be seen in Table I, the equilibrium constants, or the ratio between $k_1$ and $k_{-1}$, directly obtained from the measurements of concentrations of **4** and **7** after prolonged

storage at 35°C, does not depend significantly on substances added to the solution. For **4**, it was always around 2.16 and **7** around 2.70. The only exception is benzotriazole, which increased the equilibrium constant of **4** to 4.52, perhaps as a result of strong hydrogen bonding between benzotriazole anion and benzotriazole.

## Conclusion

Isomerization of compound **4** is 6.6 times faster than isomerization of **7**. Acetic acid present in the solution accelerates dramatically the isomerization of both compounds whereas triethylamine has a retarding effect. Water slows remarkably the isomerization of **4** but increases the isomerization rate of compound **7**, this different behavior is rationalized in terms of two different sites in these molecules where the predominant interaction with water occurs. Free benzotriazole decreases the isomerization rates of **4** and **7**. The presence of parent anilines retards the equilibration of both **4** and **7**.

## Experimental

### *Materials*

Isomerically pure 4-butyl-*N*-[(benzotriazol-1-yl)methyl]aniline (**7**) and *N*-ethyl-*N*-[(benzotriazol-1-yl)methyl]aniline (**4**) were obtained by careful fractional crystallization from toluene. Highly isotopically pure dioxane-$d_8$ (99.5%), needed for the reactions in diluted solutions, was purchased from Aldrich. To keep the solvent dry, it was stored under nitrogen over molecular sieves (4A) at room temperature for 2 to 10 days. It was found that longer storage of the solvent (over 1 month) over molecular sieves can affect the rates; some chemicals from the molecular sieves could be eluted to the solvent or some changes of the solvent could be catalyzed by molecular sieves.

### *Measurements*

In a typical run, a sample of **4** (5.0 mg, 0.020 mmol) was dissolved in an NMR tube in dioxane-$d_8$ (0.44 ml, 495 mg) under a protective atmosphere of dry $N_2$ and immediately placed in an NMR probe (VXR-300 instrument) preheated to 35°C. From this point ($t = 0$), after every 10 min time interval, $^1$H NMR spectrum (32 transients) was taken with expansion of the 7.60–8.20 ppm region. The dioxane-$d_7$ singlet at $\delta$ 3.53 ppm was used as a reference. For every measurement, the integrals of the one proton multiplet of **4** at $\delta$ 8.01 and the two proton multiplet of **6** at $\delta$ 7.82 were made three times, with individual adjustment of the integral curve each time. A mean value of these integrations was used for the rate calculations. The reaction was followed by the NMR measurements until the concentration of **4** reached a level of less than 3% different from that of the equilibrium (about four lifetimes).

For the other experiments with **4**, the appropriate amounts of additional reagents (catalysts) were added to the solutions of **4** in dioxane-$d_8$ described above using a microsyringe (for liquids). In the case of benzotriazole, both solids were mixed in an NMR tube and dissolved in dioxane-$d_8$ as above and not the benzotriazolyl but the ethyl triplets at $\delta$ 1.13 (**4**) and $\delta$ 1.21 (**6**) were integrated.

The experiments with compound **7** were carried out similarly to those with **4**. However, to keep the same molar concentration, larger samples of **7** (5.6 mg, 0.020 mmol) were used for the same amount of dioxane-$d_8$ (0.44 ml, 495 mg).

*Processing the Experimental Data*

The integrated rate eq. [9] for a reversible reaction of compound A can be presented as below:

$$\ln\frac{C_A - C_A^e}{C_A^0 - C_A^e} = -(k_1 + k_{-1})t$$

The parameter $C_A$ represents concentration of $A$ at the moment $t$. The parameters $C_A^0$ and $C_A^e$ are the initial concentration and the concentration at the equilibrium point, respectively. Application of a Linear Least-Squares Regression program allowed for direct computing of the rate constant $(k_1 + k_{-1})$, the correlation coefficient (r) and the standard deviation (s) for every set of the experimental data (Table I).

## Bibliography

[1] J.R.L. Smith and J.S. Sadd, *J. Chem. Soc., Perkin Trans. 1,* 1181, (1975).
[2] A.R. Katritzky, K. Yannakopoulou, W. Kuzmierkiewicz, J.M. Aurrecoechea, G.J. Palenik, A.E. Koziol and M. Szczesniak, *J. Chem. Soc., Perkin Trans. 1,* 2673 (1987).
[3] A.R. Katritzky and K. Yannakopoulou, *Hetercocycles,* **28,** 1121 (1989).
[4] A.R. Katritzky, A. Jozwiak, F. Saczewski, and K. Yannakopoulou, *J. Phys. Org. Chem.,* **3,** 289 (1990).
[5] A.R. Katritzky, S. Rachwal and J. Wu, *Can. J. Chem.,* **68,** 446 (1990).
[6] R.P. Bell and J.W. Bayles, *J. Chem. Soc.,* 1518 (1952).
[7] cf. A.R. Katritzky, *Handbook of Heterocyclic Chemistry,* Pergamon Press, Oxford, New York, 1985, pp. 300–302.
[8] A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.,* 2240 (1948).
[9] K.A. Connors, *Chemical Kinetics. The Study of Reaction Rates in Solution,* VCH Publishers, Inc., New York, 1990.

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