Studies on the Thermal Isomerization of *N*-Arylmethylbenzotriazoles

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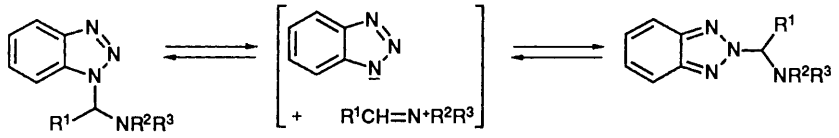
The thermal isomerizations of *N*-benzyl-, *N*-diarylmethyl- and *N*-trityl-benzotriazole, and of *N*-[bis-(4-methoxyphenyl)methyl]- and *N*-trityl-5,6-dimethylbenzotriazole under nitrogen have been investigated. In all these cases, the N-1 isomer predominates over the N-2 isomer at thermodynamic equilibrium, to an extent which depends on the steric bulk of the *N*-substituent. The rate of attainment of equilibrium depends on the electronic effects of the substituents, both in the benzotriazole ring and in the migrating group. These results, in conjunction with a cross-over experiment, support a mechanism involving a heterolytic N–C bond cleavage followed by an intermolecular rearrangement.

N-(*N*′,*N*′-Dialkylaminomethyl)benzotriazoles **1** usually exist in the crystalline state solely as the N-1 isomers, but in solution they form equilibrium mixtures of the N-1 and N-2 isomers (Scheme 1).[1,2] The interconversion of these N-1 and N-2 isomers proceeds intermolecularly by a dissociation–recombination mechanism (Scheme 1).[2] While most *N*-(*N*′,*N*′-dialkylaminomethyl)benzotriazoles **1** undergo rapid equilibration in solution, for the corresponding sulphur **2**[3] or oxygen **3**[4] analogues, the N-1 and N-2 isomers interconvert less rapidly and can be separated, as can some *N*-aryl derivatives.[5] The higher energy barriers for these interconversions are ascribable to the lower stability of the positively charged sulphur, oxygen and nitrogen intermediates ($R^1CH{=}S^+R^2$, $R^1CH{=}O^+R^2$ and $R^1CH{=}N^+R^2Ar$) compared with $R^1CH{=}N^+R^2R^3$. Recent studies[6] have shown that, in several solvents, mixtures of benzotriazole and carbonyl compounds exist in equilibrium with their isomeric N-1 and N-2 adducts, in which the N-1 adducts, in general, predominate over their N-2 isomers.



1

2 X = S
3 X = O

Scheme 1.

We report here our results on the thermal isomerization of several *N*-benzyl-, *N*-diarylmethyl- and *N*-trityl-benzotriazoles **4–11** in the absence of solvent. These compounds were chosen for the isomerization study to assess the effects of (i) the steric bulk of the migrating groups and (ii) their ability to stabilize ionic or radical intermediates that may arise during the isomerization process.

Results and Discussion

Preparation of N-*Substituted Benzotriazoles.*—*N*-[Bis-(4-dimethylaminophenyl)methyl]- **6**, *N*-[bis-(4-methoxyphenyl)-methyl]-**7**, *N*-[bis-(4-chlorophenyl)methyl]-benzotriazole **8** and *N*-[bis-(4-methoxyphenyl)methyl]-5,6-dimethyl-benzotriazole **10**, were prepared by the reaction of benzotriazole with the corresponding diarylmethanols in benzene in the presence of a catalytic amount of toluene-*p*-sulphonic acid (PTSA) with azeotropic removal of water. The other *N*-substituted benzotriazoles studied **4**, **5**, **9** and **11** were prepared by the alkylation of benzotriazole, or of 5,6-dimethylbenzotriazole, with the corresponding arylmethyl chloride in benzene in the presence of solid potassium hydroxide and polyethylene glycol. Benzotriazole derivatives were obtained in this way, in general, as mixtures of N-1 and N-2 isomers. *N*-Benzylbenzotriazole **4**, *N*-(diphenylmethyl)benzotriazole **5**, and *N*-tritylbenzotriazole **9** were previously prepared by the alkylation of benzotriazole employing a phase-transfer catalyst (KOH and a tetrabutylammonium salt).[7] Data for compounds **4–11** are presented in Table 1.

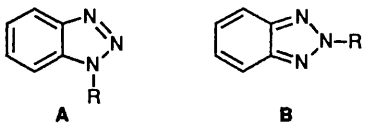
The mixtures of N-1 and N-2 isomers of the above compounds were separated by flash column chromatography. The *N*-diphenylmethylbenzotriazole **5** prepared as described above was obtained solely in the N-1 isomeric form **5a**. Hence, the N-2 isomer **5b** was obtained by thermal isomerization of the N-1 isomer at 250 °C for 8 h under nitrogen, followed by flash column chromatographic separation.

^1H *and* ^{13}C *NMR Spectra.*—The ^1H and ^{13}C NMR chemical shifts of the N-1 isomers **4A–11A** and those of the N-2 isomers **4B–11B** are listed in Tables 2 and 3. Many of the proton signals of the benzotriazole rings in compounds **4–11** could be assigned readily by employing the usual techniques (spin decoupling, HETCOR and comparison with other benzotriazole derivatives), but a few signals overlapped with the intense signals

Table 1. Preparation of *N*-(arylmethyl)benzotriazoles.

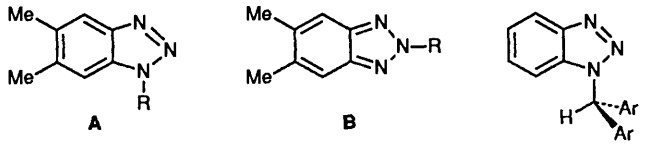
Compound							Calc. (%)			Found (%)		
No.	N-Subst.	N-Position	5,6-Subst.	Yield (%)	M.p./°C	Formula	C	H	N	C	H	N
4	CH_2Ph	N-1	H	65	114–116[a]							
		N-2		27	oil[b]							
5	$CHPh_2$	N-1	H	70	154–55[c]							
		N-2			87–88	$C_{19}H_{15}N_5$	79.98	5.30	14.73	80.3	5.3	14.8
6	$CH(C_6H_4NMe_2\text{-}4)_2$	N-1	H	58	159–161	$C_{23}H_{25}N_5$	74.36	6.78	18.85	74.6	7.0	18.8
		N-2		27	136–138					74.05	6.9	18.6
7	$CH(C_6H_4OMe\text{-}4)_2$	N-1	H	60	103–105	$C_{21}H_{19}N_3O_2$	73.03	5.54	12.17	73.3	5.5	12.2
		N-2		30	74–76					72.6	5.4	12.1
8	$CH(C_6H_4Cl\text{-}4)_2$	N-1	H	32	104–105	$C_{19}H_{13}Cl_2N_3$	64.42	3.70	11.86	64.3	3.6	11.9
		N-2		43	137–139					64.25	3.4	11.9
9	CPh_3	N-1	H	49	218–220[d]							
		N-2		29	196–198	$C_{25}H_{19}N_3$	83.08	5.30	11.63	82.9	5.3	11.7
10	$CH(C_6H_4OMe\text{-}4)_2$	N-1	Me	60	75–77	$C_{23}H_{23}N_3O_2$	73.97	6.21	11.25	73.8	6.25	11.25
		N-2		24	99–100					73.9	6.15	11.1
11	CPh_3	N-1	Me	42	218–220	$C_{27}H_{23}N_3$	83.26	5.95	10.79	83.1	5.9	10.8
		N-2		40	214–216					82.8	6.0	10.8

[a] Lit.,[7] 114–117 °C. [b] Lit.,[7] oil. [c] Lit.,[7] 149–151 °C. [d] Lit.,[7] 214–216 °C.



A **B**

4 R = CH_2Ph
5 R = $CHPh_2$
6 R = $CH(C_6H_4NMe_2\text{-}p)_2$
7 R = $CH(C_6H_4OMe\text{-}p)_2$
8 R = $CH(C_6H_4Cl\text{-}p)_2$
9 R = CPh_3



A **B**

10 R = $CH(C_6H_4OMe\text{-}p)_2$
11 R = CPh_3

12

of the aryl groups. The 7-H signals of the N-1 isomers of tritylbenzotriazoles, **9A** and **11A**, appear far upfield at δ 6.43 and 6.11, respectively, compared with those of the N-1 isomers of diarylmethylbenzotriazoles (at δ 7.10–7.21). This suggests that the 1-(diarylmethyl)benzotriazoles adopt predominantly the conformations **12** in which the aryl rings orient themselves away from the 7-H protons, because of steric interference. However, the 7-H proton in compound **9A** or **11A** necessarily has to be in the shielding zone of one of the phenyl rings and hence its signal is shifted upfield. It follows that the 1-tritylbenzotriazoles **9A** and **11A** are more sterically crowded than the 1-(diarylmethyl)benzotriazoles **5A–8A** and **10A**.

Isomerization Studies.—All the isomerizations were carried out under nitrogen by heating pure dry samples of either N-1 isomers **4A–11A** or N-2 isomers **4B–11B** (the solid samples liquified at the temperatures used). All compounds, except **4A**, **4B**, **5B**, **8A** and **8B** where no change could be detected, underwent clean isomerization to afford mixtures of the N-1 and N-2 isomers at 175–250 °C. In some cases, heating of the samples at high temperature for a long time resulted in significant decomposition. The results of the isomerizations are presented in Table 4.

The ratios of N-1 to N-2 isomers in the isomeric mixtures were estimated from the relative intensities of the proton signals of the isomers. That these isomerizations reach thermodynamic equilibria is evident from the almost identical ratios of N-1 to N-2 isomers obtained by heating either the N-1 or N-2 isomers, except in the case of compounds which showed no isomerization or very low rates of isomerization. In the case of the N-2 isomer **5B**, no isomerization was observed at 250 °C. However, this compound underwent isomerization in the presence of a catalytic amount of anhydrous zinc chloride to afford an N-1 to N-2 ratio of 84:16, which confirms the predominance of the N-1 isomer in the equilibrium mixture.

Equilibrium Positions.—The data listed in Table 4 reveal that both the *N*-(diarylmethyl)- and *N*-trityl-benzotriazoles show preference towards the N-1 isomers at equilibrium. However, the amounts of the N-2 isomer in the *N*-tritylbenzotriazoles **9** and **11** were found to be more than those in *N*-(diarylmethyl)-benzotriazoles **5–8** and **10**, suggesting that the increased bulk of the *N*-substituent increases the proportion of the N-2 isomers at equilibrium.

The substituents present in the 4-position of the phenyl ring (or the methyl groups at the 5- and 6-position of the benzotriazole) in the *N*-(diphenylmethyl)benzotriazoles have little effect on the equilibrium isomeric ratios. Similarly, both the *N*-tritylbenzotriazole pairs **9** and **11** afforded almost the same ratio of the N-1 to N-2 isomers. These results suggest that the electronic effects of the substituents had no significant effect on the positions of these equilibria, as found in the study on the reversible formation of N-1 and N-2 adducts between benzotriazole and carbonyl compounds.[6]

Rates of Equilibration.—The substituents have an enormous influence over the rates of attainment of equilibrium of these compounds. *N*-Benzyl- **4** and *N*-[bis-(4-chlorophenyl)methyl]-benzotriazole **8** did not undergo isomerization at a detectable rate at 250 °C. The 1-isomer of *N*-(diphenylmethyl)benzotriazole, compound **5A**, underwent isomerization only slowly at 250 °C, while *N*-[bis-(4-dimethylaminophenyl)methyl]- **6** and *N*-[bis-(4-methoxyphenyl)methyl]-benzotriazole **7** reached equilibrium in ≤5 min at 215 °C. Compound **6A** underwent

Table 2. The ^{1}H NMR shifts for *N*-arylmethylbenzotriazoles.

Compound	4-H	5-H	6-H	7-H	–CH–	R
4 (N-1)	8.04	*a*	*a*	*a*	5.81	7.40–7.20
(N-2)	7.85	7.34	7.34	7.85	5.85	7.40, 7.31
5 (N-1)	8.06	*a*	*a*	7.10	7.39	7.42–7.17
(N-2)	7.88	7.32[b]	7.32[b]	7.88	*a*	7.38–7.27
6 (N-1)	8.03	7.26	7.26	7.12	7.25	7.06, 6.63, 2.88
(N-2)	7.85	7.30	7.30	7.85	7.21	7.18, 6.65, 2.87
7 (N-1)	8.05	7.29[b]	7.29[b]	7.12[b]	7.29[b]	7.12, 6.84, 3.75
(N-2)	7.87	7.33	7.33	7.87	7.28	7.22, 6.86, 3.74
8 (N-1)	8.08	*a*	*a*	*a*	7.27	7.40–7.28
(N-2)	7.87	7.37	7.37	7.87	7.28	7.32, 7.20
9 (N-1)	8.05	*a*	7.06	6.43		7.32–7.10
(N-2)	7.87	7.32	7.32	7.87		7.32–7.16
10 (N-1)	7.78			7.21	6.91	7.12, 6.86, 3.76, 2.34, 2.27
(N-2)	7.60			7.60	7.21	7.19, 6.84, 3.75, 2.35
11 (N-1)	7.78			6.11		7.28, 7.17, 2.30, 2.06
(N-2)	7.61			7.61		7.28, 7.18, 2.35

[a] These signals overlap with aryl signals. [b] Approximate values.

Table 3. The ^{13}C NMR shifts for *N*-benzotriazolyl derivatives.

Compound	Isomer	C-3a	C-4	C-5	C-6	C-7	C-7a	R
4	N-1	146.3	119.9	123.9	127.4	109.7	132.8	134.7, 128.9, 128.4, 127.5, 52.2
	N-2	144.6	118.1	126.3	126.3	118.1	144.6	134.7, 128.8, 128.6, 128.3, 60.3
5	N-1	146.3	120.1	123.8	127.3	110.5	133.0	137.6, 128.7, 128.4, 128.3, 67.0
	N-2	144.3	118.4	126.4	126.4	118.4	144.3	138.2, 128.6, 128.4, 128.4, 74.0
6	N-1	146.2	119.7	123.4	126.7	111.1	132.8	150.0, 128.9, 125.7, 112.0, 66.6, 40.2
	N-2	144.1	118.2	125.8	125.8	118.2	144.1	150.1, 129.1, 126.4, 112.0, 73.6, 40.3
7	N-1	146.3	120.0	123.8	127.2	110.7	132.9	159.4, 130.1, 129.4, 114.1, 66.2, 55.2
	N-2	144.2	118.3	126.2	126.2	118.3	144.2	159.4, 130.6, 129.5, 113.9, 73.1, 55.1
8	N-1	146.2	120.3	124.1	127.7	110.0	132.7	135.8, 134.6, 129.5, 129.0, 65.5
	N-2	144.4	118.3	126.7	126.7	118.3	144.4	136.3, 134.6, 129.7, 128.9, 72.5
9	N-1	146.3	119.9	123.5	126.6	113.6	134.2	141.3, 130.0, 127.8, 127.8, 76.6
	N-2	143.5	118.7	126.4	126.4	118.7	143.5	142.5, 130.4, 127.9, 127.5, 84.2
10	N-1	145.5	119.0	133.5[a]	137.3	109.9	131.9[a]	159.3, 130.3, 129.3, 113.9, 65.8, 55.1, 20.9, 20.2
	N-2	143.6	116.7	136.6	136.6	116.7	143.6	159.3, 130.9, 129.5, 113.8, 72.7, 55.1, 20.8
11	N-1	145.7	119.0	133.3[a]	136.8	113.0	133.4[a]	141.6, 130.2, 127.8, 127.8, 78.7, 20.8, 20.2
	N-2	143.0	117.1	136.8	136.8	117.1	143.0	142.7, 130.3, 127.8, 127.5, 83.7, 20.9

[a] These assignments may be reversed within a row.

isomerization much faster than did compound **7A**, as is evident from the ratio of N-1 to N-2 isomers obtained at 175 °C after 5 min (**6A**: 74:26; **7A**: 97:3).

The *N*-tritylbenzotriazoles **9A** and **9B** underwent isomerization at 250 °C in ≤5 min to reach thermodynamic equilibrium. The presence of methyl groups at the 5- and 6-position of the benzotriazole derivatives (*viz.*, **10** and **11**) diminished their reactivity as was evident from the fact that these compounds took more time (>5 min) to reach equilibrium (under similar conditions) than the corresponding compounds without the methyl groups, compounds **7** and **9**. The above observations lead to the following orders of rate of attainment of equilibrium: (i) **6** > **7** > **10** > **5** > **8** > **4** and (ii) **9** > **11**.

Cross-over Experiment.—An isomerization experiment carried out on a mixture of 1-tritylbenzotriazole **9A** and 1-[bis-(4-methoxyphenyl)methyl]-5,6-dimethylbenzotriazole **10A** afforded a mixture of products whose ^{13}C NMR spectrum unambiguously revealed the formation of the cross-over products **7A** and **11A**. From this, it is clear that the isomerization proceeds *via* an intermolecular rearrangement *via* N–C bond cleavage.

Mechanism.—These isomerizations could proceed through a stepwise mechanism *via* a homolytic or heterolytic C–N bond cleavage involving radical or ionic intermediates, respectively, since a concerted mechanism involving a three-membered cyclic transition state is ruled out by the results of the cross-over experiment.

The large dependence of the reactivity on the electronic effects of the substituents favours an ionic rather than a free-radical mechanism. It is interesting to note that these isomerizations proceed *via* ionic intermediates, although no solvent is present to facilitate the ionization process. Presumably, in the liquid state, the highly polar molecules of the benzotriazole derivatives help to lower the activation energy of the dissociation process.

Experimental

M.p.s were determined with a Thomas–Hoover capillary melting point apparatus and are uncorrected. The ^{1}H NMR spectra were taken in $CDCl_3$ at 300 MHz on a VXR-300 (FT-mode) spectrometer with tetramethylsilane as internal reference. The ^{13}C NMR spectra at 75 MHz were obtained on the same instrument with $CDCl_3$ as solvent and internal lock. Microanalyses were conducted on a Calo-Erba-1106 instrument under the supervision of Dr. D. Powell. 5,6-Dimethylbenzo-

Table 4. Results of isomerization of compounds **4**–**11**.

Compound (isomer)	T/°C	t/h	N-1:N-2
4 (N-1)	250	5	100:0[a]
(N-2)	250	7	0:100[a]
5 (N-1)	250	3	88:12
	250	8	72:28
(N-2)	250	8	0:100[a]
	215	5	84:16[b]
6 (N-1)	175	0.08	74:26
	215	0.08	77:23[c]
(N-2)	215	0.08	75:25
7 (N-1)	175	0.08	97:3
	215	0.08	75:25
	250	0.08	71:29
(N-2)	215	3	72:28
8 (N-1)	215	7	100:0[a]
(N-2)	215	10	0:100[a]
9 (N-1)	215	0.5	58:42
	250	0.08	59:41
(N-2)	215	3	60:40
	250	0.08	61:39
10 (N-1)	250	0.08	74:26
	250	0.5	69:31
(N-2)	250	0.5	68:32
11 (N-1)	250	0.08	66:34
	250	0.5	55:45
(N-2)	250	0.08	27:73
	250	0.5	56:44

[a] No isomerization detected by NMR spectroscopy. [b] In the presence of a catalytic amount of anhyd. $ZnCl_2$. [c] Only approximate because of some decomposition.

triazole was prepared from 1,2-diamino-5,6-dimethylbenzene as described in the literature, m.p. 156–157 °C (lit.,[8] 157.5 °C).

General Methods for the Preparation of N-(*Arylmethyl*)*benzotriazoles.—Method A, from halides.* A mixture of benzotriazole (30 mmol), the arylmethyl chloride (30 mmol), polyethylene glycol (average MW 600, 2 cm^3) and KOH (30 mmol) was stirred under reflux in benzene (100 cm^3) for 4 h. The reaction mixture in benzene was washed successively with hydrochloric acid (1M; 50 cm^3) and water. The aqueous layer was extracted with chloroform (2 × 30 cm^3), and the benzene and chloroform solutions were combined and dried over $MgSO_4$. Removal of the solvent and recrystallization afforded a solid consisting of a mixture of the N-1 and N-2 benzotriazolyl isomers in all cases except for *N*-diphenylmethylbenzotriazole **5**, wherein only the N-1 isomer was obtained.

Method B, from benzhydrol. A mixture of benzotriazole (9.0 g, 75 mmol), bis-(4-substituted phenyl)methanol (75 mmol), and a catalytic amount of PTSA monohydrate was stirred and refluxed for 8 h in benzene (200 cm^3). Water formed during the reaction was removed azeotropically by means of a Dean–Stark trap. The reaction mixture was washed with aq. K_2CO_3 to remove PTSA, and the organic layer was dried with $MgSO_4$. Evaporation of the solvent and recrystallization afforded mixtures of the N-1 and N-2 benzotriazolyl isomers.

The mixtures of N-1 and N-2 benzotriazolyl isomers obtained in the above methods were separated by flash column chromatography on silica gel (230–400 mesh) with CH_2Cl_2 or hexane–CH_2Cl_2–$CHCl_3$ as eluant.

Isomerization Procedure.—All the isomerizations were carried out under nitrogen with dry, pure N-1 or N-2 isomeric samples. Each sample (~60–100 mg) of compounds **4**–**11** were heated, separately, at the temperature and for the time shown in Table 4. The products were cooled rapidly, dissolved in $CDCl_3$ and their spectra recorded.

Cross-over Experiment.—Finely powdered pure N-1 isomeric samples of compounds **9** and **10** (75 mg each) were mixed well and heated at 250 °C for 30 min under nitrogen. The sample was then cooled and the spectrum recorded.

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