THE CHEMISTRY OF N-SUBSTITUTED BENZOTRIAZOLES. PART 18. A STUDY OF THE INFLUENCE OF STRUCTURE ON THE 1- TO 2-(N,N-DIALKYLAMINOALKYL)BENZOTRIAZOLE EQUILIBRIUM

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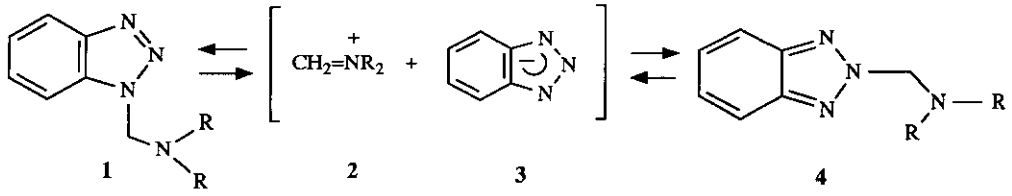
Dedicated with admiration and affection, to Derek Barton on his 70th birthday.

Abstract- The equilibrium constants, the associated free energies for the equilibria, and the free energies of activation for the isomerization process of a series of 1- and 2-(N,N-dialkylaminoalkyl)benzotriazoles of types (8)-(11) were calculated from the variable temperature ^{1}H-nmr spectra. Trends in the magnitudes of these energies and equilibrium constants are correlated with the molecular structure.

N-(N',N'-Dialkylaminomethyl)benzotriazoles exist in solution as equilibrium mixtures of the benzotriazol-1-yl (**1**) and benzotriazol-2-yl (**4**) isomers (Scheme 1), as was first established a decade ago.[1] In Part VII of this series,[2] we reported on mechanistic studies which proved, by cross-over experiments, that this (**1**) to (**4**) interconversion proceeded intermolecularly. The responsible dissociative process is convincingly rationalized as the formation of intermediate iminium cations (**2**) and the benzotriazole anion (**3**) (Scheme 1): there is considerable independent chemical evidence for the existence of (**2**).[3]



Scheme 1

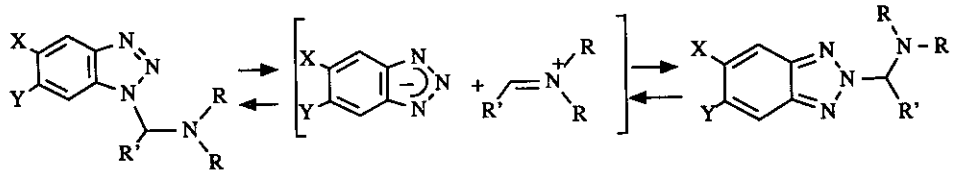
The present paper reports a study of the ^{1}H-nmr spectra of a series of benzotriazole adducts at variable temperatures, and provides estimates of the $\Delta G^{\ddagger}$ values for the isomerisation process. We discuss the parameters affecting the rates and equilibrium positions of the dissociation processes as a function of the molecular structure. In particular, we examine series of compounds with the objective of evaluating the effects of the following features [see generalized structures (**5**)-(**7**), Scheme 2]:

(a) The electron withdrawing or donating character of both α-substituents in the iminium ion intermediate (R') and in the benzotriazole benzene ring (X, Y).

(b) The nature of the N-substituent R, in correlation with the basicity of the corresponding amine.

(c) The steric effects of R and R′.

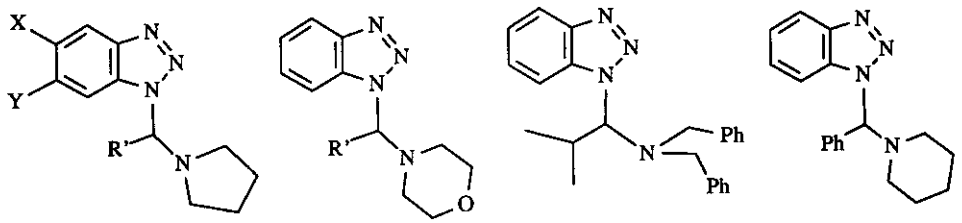
(d) The influence of the solvent on the magnitude of ΔG° and $\Delta G^{\ddagger}$.



5 **3** **6** **7**

Scheme 2

To acquire a more quantitative picture of how the relative energy levels of the 1- and 2- isomers can be changed by electronic factors, we prepared compounds (**8a-e**), (**9a-e**), (**10**) and (**11**) (Scheme 3). For adducts (**5**, R′ ≠ H) the energy barriers of the equilibrium (**5**) to (**7**) (Scheme 2) should be lower than in the case of (**1**) to (**4**) interconversion: the R′ group will generally stabilise the intermediate iminium ion (**6**) compared to ion (**2**). If the benzotriazole group carries an electron withdrawing substituent (X and/or Y), it will become a better leaving group thus again facilitating the dissociation.



8 **9** **10** **11**

	X	Y	R′
a	H	H	H
b	NO_2	H	H
c	Cl	H	H
d	Me	Me	H
e	H	H	Pr^i

	R′
a	H
b	C_6H_5
c	4-NO_2-C_6H_4
d	4-MeO-C_6H_4
e	Pr^i

Scheme 3

Preparation of compounds.- A recent publication from our group[3] describes the preparation of compounds (**8e**), (**9b-e**), (**10**) and (**11**) from benzotriazole, an aldehyde and a secondary amine by azeotropic removal of water

in benzene. In the work quoted, some of the compounds were used for further reactions without isolation. We now describe the isolation of (**9c-e**) in a pure state (see experimental); it is important to note that for most of these compounds the ^{1}H- and ^{13}C-nmr spectra near or at room temperature are much affected by peak coalescense broadening, especially when examined in deuterated chloroform solution. This can give the incorrect impression that the compounds are not pure.

Characterisation of compounds (8)-(11) and assignment of the ^{1}H- and ^{13}C-nmr spectra. - Compounds (**8b,e**) and (**9d**) were best characterised by low temperature ^{1}H-nmr in a solvent where a large dispersion of chemical shifts was observed and peaks due to the individual isomers could readily be detected (Tables 1a,b). All ^{13}C-nmr spectra were recorded in chloroform-d. Low temperature spectra were obtained in cases where broad peaks were observed at room temperature [(**8b,e**), (**11**), Table 2]. Although most 1-substituted benzotriazoles show a typical pattern in the ^{1}H-nmr spectrum[4,5] (two doublets and two triplets for H-4, H-7, H-5 and H-6, respectively), in some cases the picture is less characteristic. However, all show an easily recognisable pattern consisting of six signals in the ^{13}C-nmr spectrum.[6,7] The 2-substituted isomers, because of symmetry, show just three peaks in the ^{13}C-nmr[6,7] and an AA'BB' pattern in the ^{1}H-nmr spectrum.[4,8] All the compounds unsubstituted in the benzo ring of benzotriazole are simple binary mixtures of the 1- and 2-isomers and show both patterns in the ^{1}H- and the ^{13}C-nmr spectra. The ^{13}C-nmr spectra are easier to interpret than the ^{1}H-nmr spectra, where frequently considerable overlapping of some benzotriazole protons by signals of R and R' resulted in complex multiplets. However, assignment was achieved in most cases (Tables 1a,b and 2) using literature information.[5,6]

Two structural features in some of the compounds caused increased complexity in the spectra, and in these cases additional experiments were carried out to aid the complete assignment:-

(a) Substitution on the 5-carbon atom of the benzotriazole ring without equivalent substitution at the 6-position (**8b, 8c**), resulted in the generation of three interconverting 1-, 2- and 3-isomers. Chloroform-d solutions of N-[(5-nitrobenzotriazolyl)methyl]pyrrolidine (**8b**) contained the 1-isomer as the major component with the 2- and 3-isomers in equal amounts (at -25°C, [1-]:[2-]:[3-] = 44:28:28). The complete assignment of the ^{1}H- and ^{13}C-nmr spectra of this adduct was achieved by the independent preparation and separation of 1-methyl-, 2-methyl- and 3-methyl-5-nitrobenzotriazole,[9] recording their spectra in the same solvent, and comparing them to those of (**8b**) (Tables 1a,b and 2). In the case of the chloro compound (**8c**), the populations of the three isomers were all significantly different, (20°C, $CDCl_3$, [1-]:[2-]:[3-] = 45:23:32) thus enabling assignment of the ^{13}C-nmr spectrum. A two dimensional ^{1}H-^{13}C correlation spectrum (HETCOR), and li-te-rature[10] nmr spectra of N-methyl-5-chlorobenzotriazoles, then led to the assignment of the ^{1}H-nmr spectrum of (**8b**).

(b) The existence of an asymmetric carbon (when R′ ≠ H) caused chemical shift non-equivalency to protons in CMe_2 and in CH_2 groups up to three bonds away. Adduct (**10**) contained only two isomers, however both the benzylic CH_2 and the two methyl groups resonated at different frequencies for each of the two isomers. A proton-proton correlation spectrum (COSY), unraveled the assignment for this molecule and for the similar molecules (**8e**) and (**9e**).

Table 1a. ^{1}H-Nmr chemical shifts of 1-isomers of compounds **8-11**[a] at a single temperature (below coalescence).

No.	Sol.[b]	T(°C)	-NR_2	R′	CH	Benzotriazole
8b	C	-25	2.78(br s, 4 H)	-[c]	5.76(s[d])	9.04(d[e,f]), 8.46(dd[e,f,g])
			1.80(br s, 4 H)			7.88(d[e,g])
8c	C	+21	2.74(br m, 4 H)	-[c]	5.54(s[d])	7.65(d[e,f]), 7.31(d[e,g,h])
			1.73(m, 4 H)			7.96(d[e,g])
8e	T	-20	2.85(m[d]), 2.18(m[i,d])	3.01(m[e]),1.06(d[h,i])	4.92(d[e,j])	7.99(d[e,k])·7.02(m[i,l])
			1.30(m, 4 H)	0.44(d[h,i,k])		
9a	C	+21	3.65(t,[m] 4 H))	-[c]	5.41(s[d])	8.05(d[e,k]), 7.62(d[e,k]),
			2.74(t,[m] 4 H)			7.48(dd[k,n]), 7.37(m[l])
9b	B	+21	3.42(m,[l] 4 H)	7.05(m,[l] 5 H)	6.45(s[e])	8.03(dd[e,k,n]), 7.26(m[i,o])
			2.29(m,[l] 4 H)			
9c	A	+21	3.77(m,[l] 4 H)	8.22(d[d,k,l])	6.79(s[e])	8.13(dd[e,k,n])
			2.64(m,[l] 4 H)	7.63(d[d,k])		7.52-7.35(m[l,o])
9d	A	-20	3.70(m,[l] 4 H)	7.35(d[g,f]), 6.89(d[g,f])	6.71(s[e])	8.07(d[e,k]), 7.68(d[e,k])
			2.51(br s,[l] 4 H)	3.57(s[j])		7.50-7.32 (m[l,o])
9e	C	+21	3.68(2m[l], 4 H)	3.08(2q[e,j])	5.01(d[e,j])	8.08(dd[k,n]), 7.59(d[e,k])
			2.60(m,[l] 4 H)	1.20(d[i,k])		7.45(td[k,n]), 7.37(m[l])
				0.63(d[i,k])		
10	T	+21	7.30(d[k]), 7.12(m[l])	2.95(2m,[l] C*H*Me_2)	5.01(d[e,j])	8.03(d[e,k]), 6.90(t[h,l])
			4.13(d[d,p])	1.16(d[i,h])		
			3.07(d[d,p])	0.32(d[i,h])		
11	T	+21	2.80-2.25(m,[l] 4 H)	7.25-7.60(m,[l] 8 H)	6.61(s[e])	8.02(m[e,k])
			1.40(br s,[l] 4 H)			7.25-7.00(m[l,o])
			1.20-1.00(m[d,l])			

[a] The complete proton spectra of **8a** and **8d** are reported in ref. 2. [b] C = $CDCl_3$; T = toluene-d_8; B = benzene-d_6; A = CD_3CN. [c] R′ = H. [d] 2 H. [e] 1 H. [f] J_m = 2 Hz. [g] J_o = 9 Hz. [h] J = 6.5 Hz. [i] 3 H. [j] J = 10 Hz. [k] J_o = 8 Hz. [l] Overlaps partially with corresponding signals of the other isomer. [m] J = 5 Hz. [n] J_o = 1 Hz. [o] Superimposed signals from benzotriazole, R′ or both. [p] J = 14 Hz.

Table 1b. ^{1}H-Nmr chemical shifts[a] of 2- and 3-isomers of compounds **8-11**[b] at a single temperature (below coalescence).

No.	Sol.[c]	T(°C)	-NR_2	R′	CH	Benzotriazole
			2-isomers			
8b	C	-25	2.87(br s), 1.80(s)	-[d]	5.85(s)	8.94(d[e]), 8.32(dd[e,f]) 8.08(d[f])
8c	C	+21	2.85(br m), 1.73(m)	-[d]	5.68(s)	7.87(d[e]), 7.82(d[e,f]) 7.31(d[f])
8e	T	-20	2.56(2 m), 1.30(m)	3.02(m) 1.04(d[g]), 0.56(d[g])	5.38(d[h])	7.87(m[j]), 7.20(m[i,k])
9a	C	+21	3.65(t[i,l]), 2.74(t[i,l])	-[d]	5.53(s)	7.88(m[j]), 7.37(m[i,k])
9b	B	+21	3.44(m[i]), 2.69(m[i]) 2.30 (m[m])	7.05[m]	6.78(s)	7.89(m[j]), 7.26(m[m,k])
9c	C	+21	3.77(m[m]) 2.64(m), 2.85(m)	8.21(d[i]) 7.52-7.35(m[i])	6.85(s)	7.93(m[j]) 7.52-7.35(m[i,k,m])
9d	A	-20	3.7(m), 2.51(br m)	7.50-7.32(m[i,n]) 3.77(s)	6.79(s)	7.93(m[j]),7.50-7.32(m[i,k])
9e	C	+21	3.68(m[i]), 2.6(m[i])	2.97(dq[g,h]) 1.20(d[g]) 0.67(d[g])	5.10(d[h])	7.90(m[j]), 7.37(m[i,k])
10	T	+21	4.17(d[n]) 3.17(d[n])	2.95(m[m]) 1.07(d,[g] Me) 0.39(d,[g] Me)	5.31(d[h])	7.92(m[j]) 7.22-7.06(m[i,k,m])
11	T	+21	2.80-2.25(m[i]) 1.40(br s[i]) 1.20-1.00(m[i])	7.25-7.00(m[i])	6.86(s)	7.25-7.00(m[i,j,k,m])
			3-isomers			
8b	C	-25	2.78(br s[i]), 1.80(s[i])	-[d]	5.78(s)	8.71(d[e]), 8.28(dd[e,f]) 8.25(d[f])
8c	C	+22	2.74(br m[i]), 1.73(m[i])	-[d]	5.57(s)	8.02(d[e]), 7.43(dd[e,f]) 7.59(d[f])

[a] The number of hydrogens under a certain peak is the same as in the corresponding column of Table 1a. [b] The complete proton spectra of **8a** and **8d** are reported in ref. 2. [c] C = $CDCl_3$; T = toluene-d_8; B = benzene-d_6; A = CD_3CN. [d] R′ = H. [e] J_m = 2 Hz. [f] J_o = 9 Hz. [g] J = 6.5 Hz. [h] J = 10 Hz. [i] Overlaps partially with corresponding signals of the other isomer. [j] AA′ multiplet, app. J = 3 Hz. [k] BB′ multiplet, app. J = 3 Hz. [l] J_m = 5 Hz. [m] Superimposed signals from benzotriazole, R′ or both. [n] J = 14 Hz.

Table 2. ^{13}C-Nmr chemical shifts of compounds 8-11[a] at a single temperature (below coalescence) in $CDCl_3$

No	Tem. (°C)	-NR_2	R′	CH	Benzotriazole
			1-isomers		
8b	-25	49.9, 23.4	-[b]	65.5	144.4,[c] 144.2,[c] 136.4,[c] 122.8, 116.9, 110.7
8c	+20	49.9, 23.4	-[b]	65.1	145.8,[c] 133.2,[c] 129.1,[c] 124.5, 120.1, 109.4
8e[f]	-48	47.1, 22.7	30.5, 19.8, 19.0	81.3	144.5, 134.4, 126.9, 123.5, 119.2, 109.7
9a	+20	66.2, 50.1	-[b]	68.9	145.5, 133.5, 127.2, 123.6, 119.4, 109.6
9b	+20	66.3, 49.6	134.6, 128.4	82.4	145.7, 132.7, 126.9, 123.5, 119.6, 111.1
			128.1, 127.2		
9c	+20	66.5, 49.7	142.3, 141.9	81.1	145.8, 133.0, 127.8, 124.2, 120.1, 110.5
			128.7, 123.6		
9d	+20	66.4, 49.7	159.4, 127.6	82.4	145.6, 132.5, 127.1, 123.8, 119.5, 111.4
			113.7, 54.8		
9e	+20	66.6, 48.8	28.4, 19.7, 19.0	85.5	145.0, 134.4, 127.2, 123.7, 119.6, 109.7
10	+20	138.7, 128.9	30.4, 29.6, 19.4	80.1	144.9, 135.1, 126.9, 123.7, 119.7, 109.8
		128.5, 127.3, 53.4			
11	-20	50.1, 25.4, 23.5	134.9, 128.1	82.8	145.4, 132.8, 126.6, 123.4, 119.2, 111.5
			128.0, 127.0		
			2-isomers		
8b	-25	50.1, 23.7	-[b]	73.3	120.5,[d,e] 119.4, 118.8
8c	+20	48.9, 23.7	-[b]	72.4	145.8,[c] 133.2,[c] 129.1,[c] 127.0, 119.0, 116.8
8e[f]	-48	46.4, 22.9	30.5, 19.4,19.0	88.7	142.8, 125.8, 117.8
9a	+20	66.4, 59.8	-[b]	76.7	143.8, 126.2, 117.7
9b	+20	66.6, 48.6	135.0, 128.4	88.2	143.5, 126.1, 118.1
			128.2, 127.2		
9c	+20	66.6, 48.6	147.9, 128.7, 123.4	87.2	143.9, 126.8, 118.3
9d	+20	66.1, 48.8	159.4, 126.6	88.1	142.0, 125.2, 114.6
			113.9, 54.8		
9e	+20	66.8, 48.3	28.4, 19.1, 18.9	92.3	143.3, 125.9, 118.0
10	+20	138.8, 128.5	30.4, 20.0, 19.3	87.3	143.5, 126.0, 118.4
		128.3, 127.3, 53.3			
11	-20	49.4, 25.4, 23.5	134.9, 128.1	89.0	143.3, 125.9, 117.9
			128.0, 127.0		
			3-isomers		
8b	-25	49.0, 23.4	-[b]	65.9	120.5,[d,e] 116.4, 107.4
8c	+20	49.8, 23.4	-[b]	65.1	143.8[c] 134.0,[c] 132.1, 127.7, 118.4, 110.6

[a] The complete ^{13}C-nmr spectra of 8a and 8d are reported in ref. 2. [b] R′ = H. [c] Unambiguous assignment of the quaternary carbon atoms was not possible, thus the reported peaks could be due to the other isomer. [d] Assignments can be interchanged between corresponding carbon atoms of the 3-isomer. [e] The quaternary atoms were not detected. [f] The assignment was aided by an INEPT spectrum at -48°C which distinguishes between 1°, 2°, and 3° carbon atoms.

Calculation of equilibrium constants (K) and free energies(ΔG°) for isomerisation.- The equlibrium constants were measured for each compound in several solvents at the temperatures specified in Table 3. The free energies of the isomerisation processes were then calculated from $\Delta G° = -RT\ln K$, where $K = P_1/P_2$; P_1 and P_2 are the populations of the 1- and 2-isomers, respectively, measured from integration of the peaks in the aromatic and/or the aliphatic NCH(R')N regions of the ^{1}H-nmr spectra. Positions 1 and 3 of the benzotriazole ring are degenerate [except for adducts (**8b**) and (**8c**)], and this was taken into account when calculating P_1. For adducts (**8b**) and (**8c**), when separation of the signals allowed, in addition to K, $K' = P_3/P_2$ and $K'' = P_1/P_3$ could also be calculated. The values so obtained are collected in Table 3 (see also footnotes). A negative ΔG° value indicates that the 1-isomer is more stable than the 2-isomer, while a positive ΔG° shows the reverse. In general, in solutions of compounds of type (**1**) [R' = H, i.e (**8a**)-(**8d**) and (**9a**)], the 1-isomer is the most thermodynamically favored component in the mixture (see Table 3). Adducts of type (**5**) (R' ≠H), either show little preference toward either isomer in a common nmr solvent [e.g (**9b**) in $CDBr_3$)], or, in extreme cases of steric hindrance, the 2-isomer becomes the most stable [e.g. (**10**) in $CDBr_3$)], where K is less than 1 and ΔG° > 0. Increasing solvent polarity can move the equilibrium toward the 1-isomer, as will be discussed next.

Effect of the solvent.- Polar solvents have been shown[1,2] to favor the 1-isomer in solutions of compounds of type (**1**). Dipole moment measurements[11] indicate that (somewhat surprisingly) simple 1-substituted benzotriazoles are more polar than their 2-substituted isomers. Here we observe a similar effect. For example, the ΔG° value of (**10**) indicates that the 1-isomer becomes more favored on going from toluene (μ = 0.36 D)[12] to bromoform (μ = 0.99 D), to chloroform (μ = 1.01 D), to acetonitrile (μ = 3.92 D). Marked effects are observed in CD_3CN solutions of (**8a**)-(**8d**) and (**9b**), where the 1-isomer increases in each case to more than 83 % in the equilibrium mixture. Compound (**9e**) exemplifies a case where the solvent determines which isomer will predominate in solution (2-isomer in toluene-d_8; 1-isomer in CD_3CN).

Effect of R, R', X, and Y. - Increased bulk of R' results in increased amounts of the 2-isomer in the equilibrium mixture. This is reflected by a decrease in the magnitude of K in acetonitrile on going, for example, from (**9a**) to (**9e**). When R' is a phenyl- or p-substituted phenyl group, the equilibrium constant is near unity, meaning that no actual preference is expressed for any of the two isomers. The results in Table 3 indicate that the *peri*-interactions (buttressing between H-7 and the aminoalkyl substituent) are very important[5] in the 1-isomer. This was further demonstrated by a different experiment: the ^{1}H-nmr spectrum of the pyrrolidine-isobutyraldehyde adduct (**8e**) in toluene-d_8, showed that the signals of H-7 and $(Pr^i)_2C$ *HN* in the 1-isomer became broad and moved toward each other as the temperature was lowered from –20°C to –80°C. Restricted rotation about the Bt-C(R')NR_2 bond was evidently responsible for this phenomenon, which was observed only for the 1-isomer. The electron withdrawing or electron releasing nature of the substituents R and R' does not

seem to have any noticeable effect, since the magnitude of ΔG° remains the same (within experimental error) in (**9b**) and (**9c**) in acetonitrile, while the differences observed for (**8e**), (**9e**) and (**10**) in toluene, would rather be attributed to steric effects. Similarly, substitution on the benzotriazole ring by X and Y shows little effect in the observed values of K and ΔG°.

Variable temperature nmr spectral study: Calculation of free energies of activation ($\Delta G^{\ddagger}$).- The temperatures at which the characteristic proton resonances of the 1- and 2-isomers coalesce were measured. Specifically, the signals of the methylene groups, located between the amino and the benzotriazole nitrogen atoms, of the two isomers were monitored for compounds (**8a-d**) and (**9a**). The corresponding methinic proton signals were monitored for compounds (**8e**), (**9b-e**), (**10**) and (**11**). The range of temperatures within which coalescence occurred was visually estimated from the lineshape of the signals under observation (Table 3). Approximate free energies of activation were calculated using the simplified equation,[13]

$$\Delta G^{\ddagger} = RT_c[22.96 + \ln(T_c/\delta\nu)]$$

where T_c is in °K and $\delta\nu$ the chemical shift difference of the two separate peaks in the slow exchange region. The error in T_c is $^{\mp}2$ to $^{\mp}3$°C, and this corresponds to $^{\mp}0.1$ to $^{\mp}0.2$ kcal/mole in $\Delta G^{\ddagger}$. The isomerisation process is intermolecular[2] and the populations of the isomers are unequal in most cases studied, therefore additional error is introduced in the calculations.[13] However, since only approximate $\Delta G^{\ddagger}$ values are desired for the evaluation of the relative ease of isomerization of the compounds, the free energies of activation listed in Table 3 are satisfactory. The $\Delta G^{\ddagger}$ values for all compounds [adjusted for (**8e**) and (**10**)] are those for the 2- to 1- conversion process. In deuterated toluene, for most of the compounds coalescence did not occur below the boiling point. Bromoform (bp 150°C) was then used in which the $\Delta G^{\ddagger}$ values were generally lower. Finally, in cases were the proton resonances under observation were not well resolved or were obscured by other signals in the above solvents, [e.g (**9c,d**)], deuterated acetonitrile was used successfully but this could not be extended to all molecules: the amount of the 2- isomer in (**8a-d**) and (**9a**) in CD_3CN was very small, resulting in weak proton resonances, and therefore unacceptable errors in the measurement of T_c.

Effect of the solvent.- The nature of the solvent also affects the magnitude of $\Delta G^{\ddagger}$ just as it affects that of ΔG°. Table 3 distinctively shows that the energy barrier is highest in toluene next in bromoform, and lowest in acetonitrile [e.g. (**8b**), (**9b**)]. A polar solvent solvates the ion pair [(**3**) + (**6**), Scheme 2] more than the individual isomers, thus providing additional stabilisation and lowering the energy difference between the ion pair and either of the isomers.

Effect of R'.- The results in Table 3 clearly show that the free energy of activation is lower when resonance stabilisation is provided to the intermediate (**6**) through the substituent R', compared to the unsubstituted cases.

Table 3. Equilibrium constants and free energies of activation for the isomerization of benzotriazolylalkyl-N,N-dialkylamines.

						Equilibrium			Kinetics	
No	NR_2[a]	R′	X	Y	Solvent	T[b] (°C)	K[c]	ΔG° (kcal/mole)	T_c[d] °C)	$\Delta G^{\ddagger}$[e] (kcal/mol)
8a	Pyr	H	H	H	$CDBr_3$	+22	1.6	-0.25	85	18.2
					CD_3CN	+22	6.2	-1.05		
8b	Pyr	H	NO_2	H	Toluene-d_8	+21	1.7[f]	-0.30	105	18.0
					$CDCl_3$	-25	2.5[g]	-0.45	32	15.4
					CD_3CN	-48	5.6[h]	-0.75		
8c	Pyr	H	Cl	H	$CDBr_3$	+21	–[i]	–[i]	66	17.0
					$CDCl_3$	+21	2.0[j]	-0.40		
					CD_3CN	-20	6.4[k]	-0.95[j]		
8d	Pyr	H	Me	Me	$CDBr_3$	+23	1.7	-0.30	98	18.7
					CD_3CN	+22	4.9	-0.95		
8e	Pyr	Pr^i	H	H	Toluene-d_8	-40	0.4	+0.40	48	15.6
					CD_3CN	–[i]		–[i]		
9a	Mor	H	H	H	$CDBr_3$	+22	1.8	-0.35	86	18.3
					CD_3CN	+23	5.6	-1.00		
9b	Mor	Ph	H	H	$CDBr_3$	+23	1.2	-0.10	62	17.7
					CD_3CN	+20	2.5	-0.55	63	16.9
9c	Mor	4-NO_2-C_6H_4	H	H	CD_3CN	+20	2.5	-0.55	83	18.6
9d	Mor	4-MeO-C_6H_4	H	H	CD_3CN	-20	2.7	-0.50	35	15.7
9e	Mor	Pr^i	H	H	Toluene-d_8	+25	0.4	+0.55		
			H	H	$CDCl_3$	+21	0.5	+0.40		
					CD_3CN	+23	1.1	-0.05	35	16.1
10	Dib	Pr^i	H	H	CD_3CN	+22	0.9	+0.05		
					$CDBr_3$	+22	0.7	+0.20	75	17.9
					$CDCl_3$	+22	0.8	+0.15		
					Toluene-d_8	+25	0.4	+0.55		
11	Pip	Ph	H	H	Toluene-d_8	+21	1.1	-0.05	73	16.8
					CD_3CN		–[i]	–[i]		

[a] Pyr = pyrrolidine; Mor = morpholine; Dib = Dibenzylamine; Pip = Piperidine. [b] Temperature at which the equilibrium constant was measured. [c] $K = P_1/P_2$, where P_1 and P_2 are the populations of the 1- and 2- isomers, respectively (estimated error ±0.2). [d] ± 2°C. [e] ±0.1-0.2 kcal/mole. [f] Corresponds to $K = [P_1+P_3]/P_2$ since the signals of the 1- and 3-isomers overlapped. [g] $K' = P_3/P_2 = 1.0$, with $\Delta G° = 0$, and $K'' = P_1/P_3 = 2.5$ with $\Delta G° = -0.45$ kcal/mole, where P_3 = the population of the 3-isomer. [h] $K' = P_3/P_2 = 2.3$ with $\Delta G° = -0.35$ kcal/mole, and $K'' = P_1/P_3 = 3.0$ with $\Delta G° = -0.5$ kcal/mole. [i] The signals were not well separated ($\delta\nu = 0.03$ ppm) to allow reliable measurement of K. [j] $K' = P_3/P_2 = 1.4 = K''$ with $\Delta G° = -0.20$ kcal/mole. [k] $K' = P_3/P_2 = 5.5$ with $\Delta G° = -0.85$ kcal/mole and $K'' = P_1/P_3 = 1.3$ with $\Delta G° = -0.15$ kcal/mole.

Specifically, in acetonitrile, the order of decreasing $\Delta G^{\ddagger}$ values is (**9c**) > (**9b**) > (**9d**). Strong stabilisation to the electron deficient iminic carbon is also provided by isopropyl substituents, as indicated in the case of (**8a**) *vs* (**8e**), and to a lesser extent, (**9a**) *vs* (**9e**).

Effect of substituents in the benzotriazole ring.- The electron withdrawing nitro substituent of (**8b**) stabilises the negative charge developed on anion (**3**), and therefore facilitates N-C bond dissociation leading to recombination on the N-2 atom of benzotriazole. On the other hand, the electron donating methyl groups of (**8d**) have the opposite effect, raising the energy barrier to a relatively high value. The 5-chloro substituted and the ring unsubstituted compounds have intermediate effects. The calculated $\Delta G^{\ddagger}$ values in $CDCBr_3$ are therefore classified in order of decreasing magnitude, as follows: (**8d**) > (**8a**) > (**8c**) > (**8b**). Compound (**8b**) in $CDBr_3$ is very near coalescence at room temperature, so the $\Delta G^{\ddagger}$ in this solvent could not be measured (the solvent freezes at +8.3°C), but the corresponding value in chloroform suggests it will be less than 15.4 kcal/mol.

Effect of the nature of secondary amine.- The availability of the lone pair of electrons on the amino nitrogen for donation to the adjacent electron deficient carbon in (**6**), plays a significant role in determining the height of the barrier. This is best illustrated in the compounds bearing the isopropyl substituent, where a significant amount of positive charge could be developed. We then observe, in order of decreasing $\Delta G^{\ddagger}$ magnitude, (**9b**) > (**11**) and (**10**) > (**8e**). This order correlates inversely with the pK_a values[14] of the corresponding secondary amines. Thus, pK_a[(morpholine) = 8.49] < pK_a[(piperidine) = 11.20] and pK_a[(dibenzylamine) = 8.52] < pK_a[(pyrrolidine) = 11.30]. The benzotriazole adducts of morpholine and dibenzylamine are consequently more easily isolable and stable compounds than the adducts of pyrrolidine or piperidine, most of which are readily hydrolysed oils or low melting solids.[3]

Conclusions. 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 (**3**) or (**6**): the greater the stabilization the lower the energy barrier. The greater the polarity of the solvent the lower the value of $\Delta G^{\ddagger}$. Finally the bulkier the dialkyaminoalkyl (or aryl) substituent, the more abundant the 2-isomer, which in extreme cases becomes the predominant component, as shown by values of K less than 1 and $\Delta G° > 0$. The chemical reactivity of the compounds studied is thus tailored according to the appropriate substitution. Compounds for which $\Delta G^{\ddagger}$ has low values react rapidly and cleanly with weak nucleophiles such as amines and thiols with concurrent removal of benzotriazole.[15] Compounds having high $\Delta G^{\ddagger}$ values are much less reactive toward the same nucleophiles. Results demonstrating the synthetic significance of the present paper will be published in due course.

Table 4. ^{1}H-Nmr chemical shifts of compounds (8a-e), (9a-e), (10), (11)[a] at a single temperature (above coalescence)

No	Solv.	Temp. (°C)	-NR_2	R′	CH	Benzotriazole
8a	$CDBr_3$	110	2.8 (br s, 4 H)	-[b]	5.6 (s, 2 H)	8.1-7.7 (br m, 4 H)
			1.7 (br s, 4 H)			
8b	$CDCl_3$	45	1.7 (br s, 4 H)	-[b]	5.8 (br s)	9.1-7.7
			2.7 (br s, 4 H)		(2 H)	(v. br m, 4 H)
8c[c]	$CDBr_3$	84	2.8 (br s, 4 H)	-[b]	5.7 (s, 2 H)	8.0-7.4 (br m)
			1.7 (br s, 4 H)			(4 H)
8d[d]	$CDBr_3$	110	2.8 (br s, 4 H)	-[b]	5.5 (s, 2 H)	7.8-7.3 (v. br m, 2 H)
			1.7 (br s, 4 H)			2.4 (br s, 3 H, Me)
8e	tol-d_8	70	2.9-2.7(m, 4 H)	1.0	5.3 (d, 1 H)	7.8 (br s, 2 H)
			1.4 (s, 4 H)	(m, 7 H)	(J = 10 Hz)	7.2-7.1 (m, 2 H)
9a	$CDBr_3$	110	3.6 (br s, 4 H)	-[b]	5.4 (s, 2 H)	8.7 (v br s, 2 H)
			2.7 (br s, 4 H)			7.4 (s, 2 H)
9b	$CDBr_3$	90	3.9 (br s, 1 H)	-[g]	6.7 (s, 1 H)	7.9 (br m, 3 H)[f]
			3.7 (br s, 3 H)			7.5-7.3 (m, 6 H)
			3.2 (br s, 1 H)			
			2.6 (br s, 3 H)			
9c[h]	$CDBr_3$	110	4.1 (br s,1 H)	-[g]	6.8 (br s)	9.5 (v br s, 1 H)
			3.8 (br s, 3 H)		(1 H)	8.2-7.2 (m, 7 H)
			3.2 (br s, 1 H)			
			2.8 (br s, 3 H)			
9d	CD_3CN	60	3.7 (m, 4 H)	6.8[g]	6.7	9.9 (s, 1 H)
			2.5 (br m, 3 H)	(d, 2 H)	(s, 1 H)	8.6 (br s, 1 H)
			2.8 (br s, 1 H)	3.7 (s, 3 H)		8.0-7.7 (m, 1 H)
						7.5-7.3 (br m, 2 H)
9e	CD_3CN	50	3.6 (m, 4 H)	3.0(m, 1 H)	5.1 (d, 1 H)	8.2-7.7 (m, 2 H)
			2.6 (m, 4 H)	1.2 (m, 6 H)	(J = 10 Hz)	7.6-7.3 (m, 2 H)
10	$CDBr_3$	90	4.2 (br m, 2 H)[g]	3.1 (br m)	5.3	7.9 (v. br s, 3 H)
			3.3 (br m, 2 H)	(1 H)	(br s, 1 H)	7.3 (br m, 6 H)
				1.2 (m, 3 H)		
				0.5 (m, 3 H)		
11	tol-d_8	90	2.3 (br m, 4 H)	6.8 (m, 5 H)	6.4 (s, 1 H)	7.5 (v. br s, 4 H)
			1.2 (m, 4 H)			
			0.9 (m, 2 H)			

[a] Many peaks did not become entirely sharp, even at several degrees above coalescence. [b] R′ = H. [c] Some decomposition must have occurred as evidenced by additional aliphatic peaks. [d] In addition, δ 3.4 (br m), 2.0 (br m), probably due to free pyrrolidine. [e] The $CHMe_2$ signal is hidden under broad peaks. [f] In addition, δ 10.30 (v. br, 1 H). [g] Phenyl protons come together with benzotriazole protons. [h] The spectrum was recorded in $CDBr_3$, since bp (CD_3CN) = 82°C and T_c = 84°C in CD_3CN.

EXPERIMENTAL

Proton nmr spectra were recorded on a Varian VXR 300 MHz instrument using TMS as the internal chemical shift reference and as the standard peak for linewidth comparisons. The samples were solutions of 50-70 mg of compound in 0.5 ml of solvent in 5 mm nmr tubes. The temperature was raised in 10°C increments, allowing at least 10 min for equilibration at each setting. *High temperature calibration* of the instrument with an ethylene glycol, standard sample, showed that the set and actual temperatures were in agreement within ±1°C. Variable temperature measurements were repeated twice and equilibrium constant values were the average of at least three measurements. Deuterated solvents were purchased from MSD Isotopes (toluene-d_8, $CDCl_3$, CD_3CN, C_6D_6) and Chemalog ($CDBr_3$) and were used directly. Carbon-13 nmr spectra were recorded on either a JEOL-FX 100 or a Varian XL 200 or a Varian VXR 300 instruments. Two-dimensional spectra were recorded on the Varian VXR 300 instrument using the standard software for COSY and HETCOR pulse sequences provided by Varian.

The preparation of the following compounds has been reported in previous papers from this lab: *N-[(benzotriazol-N-yl)methyl]pyrrolidine* (**8a**),[3] *N-[α-(benzotriazol-N-yl)-β-methyl)propyl]pyrrolidine* (**8e**),[3] *N-[α-(benzotriazol-N-yl)phenylmethyl]piperidine* (**11**),[3] *N-[α-(benzotriazol-N-yl)phenylmethyl]morpholine* (**9b**),[3] *N-[(5,6-dimethylbenzotriazol-N-yl)methyl]pyrrolidine* (**8d**)[2], and *N-[α-(benzotriazol-N-yl)-β-methylpropyl]dibenzylamine* (**10**).[3] A literature method[16] was adopted for preparation of *N-[Benzotriazol-N-yl)methyl]morpholine* (**9a**) (mp 108-109.5°C; lit.[16] mp 104-105°C).

N-[(5-Nitrobenzotriazol-N-yl)methyl]pyrrolidine (**8b**). - It was prepared from 5-nitrobenzotriazole (5.42 g, 0.033 mol), pyrrolidine (0.038 mol , 3.1 ml), and 37% aq. formaldehyde (0.04 mol , 3.4 ml) in methanol (50 ml) according to the standard literature methods.[1,16] The compound was at first obtained as an oil, which then solidified gradually after stirring with diethyl ether in a dry ice/acetone bath, it then crystallised from diethyl ether as a yellow solid (7.22 g, 89%), mp 76-78°C (Found, C, 53.01; H, 5.14; N, 28.21%. $C_{11}H_{13}N_5O_2$ requires, C, 53.44; H, 5.30; N, 28.32 %).

N-[(5-Chlorobenzotriazol-N-yl)methyl]pyrrolidine (**8c**) was prepared as (**8b**), using the same molar amounts of the required starting materials. The oily residue obtained after evaporation of the solvent soon started crystallising. It was recrystallised from diethyl ether/hexane (7/1, v/v). An off-white solid was collected (5.75 g, 71 %), mp 58-60°C (Found, C, 55.57; H, 5.40; N, 23.82 %. $C_{11}H_{13}ClN_4$ requires, C, 55.82; H, 5.54; N, 23.67 %).

N-[α-(Benzotriazol-N-yl)arylmethyl)morpholines (**9c**)-(**9e**).- *Benzotriazole* (7.942 g, 0.0667 mole) and morpholine (1 equiv., 5.8 ml) were stirred in dry benzene (50 ml) and then the aldehyde (1 equiv.) was added. The mixture was heated under reflux in a Dean-Stark apparatus, until (1-5 days) the theoretically calculated amount of

water had been collected (1.2 ml). *N-[α-(Benzotriazol-N-yl)-α-(4-nitrophenyl)methyl]morpholine* (**9c**) was obtained as a hard yellowish solid (21.5 g, 96%), which was recrystallised from 95% ethanol, mp 145-148°C. (Found, C, 60.35; H, 5.03; N, 20.50 %. $C_{17}H_{17}N_5O_3$ requires, C, 60.17; H, 5.05; N, 20.64 %). *N-[α-(Benzotriazol-N-yl)-α-(4-methoxyphenyl)methyl]morpholine* (**9d**) was a low melting solid (mp less than 20°C), which could not be purified (remained as a very viscous oil) and was characterised by ^{1}H- and ^{13}C-nmr at -20°C (see Tables 1 and 3). *N-[α-(Benzotriazol-N-yl)-β-methylpropyl]morpholine* (**9e**) was obtained initially as an oil which solidified when treated with diethyl ether in a dry ice acetone bath (11.2 g. 65%), mp 101-103°C. (Found, C, 64.89; H, 8.20; N, 21.79 %. $C_{14}H_{20}N_4O$ requires, C, 64.59; H, 7.74, N, 21.52 %).

Methylation of 5-nitrobenzotriazole.- 5-Nitrobenzotriazole (0.5 g, 0.03 mol) was dissolved in aq. 2N NaOH (25 ml) and water (10 ml) was added to achieve a clear solution. Dimethyl sulphate (10 g, 0.076 mol) was added and a yellow precipitate appeared. The suspension was stirred at room temperature for 0.5 h and at 0°C for 1.5 h, then the solid was filtered, washed with water and air dried. The crude solid contained three products, as indicated by tlc (eluted with a mixture of hexane/diethyl ether, 1/1, v/v). A portion of the crude solid (0.25 g) was placed on a silica gel column and eluted with hexane/diethyl ether (8:2, 7:3, 6:4, 5:5, 2:8, v/v), and then diethyl ether (recovery 0.20 g, 80 %). The following compounds were collected as fractions (in order of elution: *2-methyl-5-nitro-benzotriazole* (R_f = 0.62, 0.094 g, 46 %, mp 180-184°C, lit.[10] mp 187°C); δ_H (300 MHz, $CDCl_3$) 8.87 (dd, J_m = 2 Hz, J_p = 0.7 Hz, H-4), 8.24 (dd, J_o = 9 Hz, J_m = 2 Hz, H-6), 7.98 (dd, J_o = 9 Hz, J_p = 0.7 Hz, H-7), 4.61 (3 H, s, Me); δ_C (75 MHz, $CDCl_3$) 146.6 (C-3a 0r C-5, small br), 143.0 (C-7a), 120.7 (C-6), 119.1 (C-7), 116.0 (C-4), 44.0 (Me); *3-methyl-5-nitrobenzotriazole* (R_f = 0.37, 0.048 g, 24 %, mp 154-157°C (lit.[9] does not report isolation of this compound)(Found, C; 48.53, H; 4.67, N; 30.80 %. $C_7H_6N_4O_2$ requires, C, 47.19; H, 3.39; N, 31.45 %); δ_H (300 MHz, $CDCl_3$), 8.55 (d, J_m = 2 Hz, H-4), 8.27 (dd, J_o = 9 Hz, J_m = 2 Hz, H-6), 8.18 (d, J_o = 9 Hz, H-7), 4.45 (s, 3 H, CH_3); *1-methyl-5-nitrobenzotriazole* (R_f = 0.19, 0.06 g, 30 %, mp 160-162°C, lit.[10] mp 163°C); δ_H (300 MHz, $CDCl_3$) 8.99 (d, J_m = 2 Hz, H-4), 8.42 (dd, J_o = 9 Hz, J_m = 2 Hz, H-6), 7.69 (d, J_o = 9 Hz, H-7), 4.41 (3 H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 144.9 (C-3a or C-5, small br) 136.0 (C-7a), 122.4 (C-5), 117.2 (C-3), 109.0 (C-7), 34.70 (Me).

REFERENCES

1 J. R. Lindsay Smith and J. S. Sadd, *J. Chem. Soc., Perkin Trans.1*, 1975, 1181.

2 A. R. Katritzky, K. Yannakopoulou, W. Kuzmierkiewicz, J. M. Aurrecoechea, G. J. Palenik, A. E. Koziol, M. Szczesniak, and R. Skarjune, Part VII, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2673.

3 A. R. Katritzky, K. Yannakopoulou, P. Lue, D. Rasala, and L. Urodgí, *J. Chem. Soc., Perkin Trans. 1*, in press.

4 A. J. Boulton, P. J. Halls, and A. R. Katritzky, *Org. Magn. Res.*, 1969, **1**, 311.

5 M. H. Palmer, R. H. Findlay, S. M. F. Kennedy, and P. S. McIntyre, *J. Chem. Soc., Perkin Trans. 2*, 1975, 1695.

6 L. Avila, J. Elguero, S. Julia, and J. M. del Mazo, *Heterocycles*, 1983, **20**, 1787.

7 M. Begtrup, J. Elguero, R. Faure, P. Camps, C. Estopa, D. Ilavsky, A. Fruchier, C. Marzin, and J. de Mendoza, *Magn. Res. Chem.*, 1988, **26**, 134.

8 H. Gunther, "NMR Spectroscopy. An Introduction", J. Wiley and Sons, New York, 1980, p. 178.

9 M. Kamel, S. Sherif, and M. M. Kamel, *Tetrahedron*, 1964, **20**, 211.

10 M. Marky, H. Schmid, and H.-J. Hansen, *Helv. Chim. Acta*, 1979, **62**, 2129.

11 (a) J. H. Boyer, "Heterocyclic Compounds", vol.7, ed. by R. C. Elderfield, J. Wiley and Sons, New York, 1961, p. 463. (b) F. Benson and W. L. Savell, *Chem. Rev.*, 1950, **46**, 1.

12 (a) *CRC Handbook of Chemistry and Physics*, 69th Ed., p. D-163. (b) *ibid.*, p. E-58.

13 For discussions on DNMR see (a) R. J. Abraham and P. Loftus, "Proton and Carbon-13 NMR Spectroscopy. An Integrated Approach", Heyden, London, 1980; (b) J. Sandstrom, "Dynamic NMR Spectroscopy", Academic Press, New York, 1982, p. 96; (c) L. M. Jackman and F. A. Cotton, "Dynamic NMR Spectroscopy", Academic Press, New York, 1974.

14 D. P. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution. Supplement 1972.", ed. by IUPAC, Analytical Division, Butterworths, London, 1972.

15 A. R. Katritzky and K. Yannakopoulou, unpublished results.

16 J. H. Burckhalter, V. C. Stephens, and L. A. R. Hall, *J. Am. Chem. Soc.*, 1952, **74**, 3868.

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