An NMR Study of the Equilibria Involved with Benzotriazole, Carbonyl Compounds, and their Adducts

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A ^1H and ^{13}C NMR study of the equilibrium mixtures of benzotriazole and several carbonyl compounds with their adducts, in [$^2H_6$]benzene and other solvents, affords the equilibrium constants for the reversible formation of N-1 (K_1) and N-2 (K_2) isomeric adducts. Thermodynamic parameters have been computed. Adduct formation is generally less predominant in sterically crowded cases. In general the N-1 isomer predominates over the N-2 isomer, however, with the sterically hindered 4,7-dimethylbenzotriazole this order is reversed.

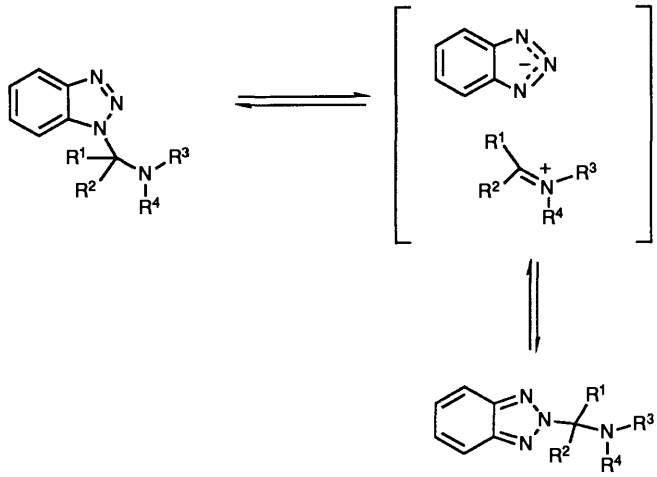
The carbonyl groups of aldehydes and ketones in the presence of water are in equilibrium with the corresponding geminal dihydroxy adducts.[1] The tendency for such addition of water at a carbonyl group varies enormously with structure, depending greatly on both steric and electronic factors. The equilibrium constant for the hydration of methanal in aqueous solution is very large [$CH_2(OH)_2/CH_2O$ = *ca.* 2 000 at 20 °C].[2] For aliphatic aldehydes it is moderate (*e.g.* for ethanal *ca.* 1.2 at 25 °C)[3] and for most ketones it is small (*e.g.* for propanone *ca.* 0.002 at 25 °C).[1] However, this pattern is changed by the presence of electron-withdrawing substituents. Aldehydes and ketones containing groups such as α-trihalomethyl or α-carbonyl can exist in the hydrated form in the solid state, for example, chloral hydrate,[4] phenylglyoxal hydrate, and hexafluoropropanone hydrate.[5]

The addition products of carbonyl compounds with secondary amines are known as hemiaminals. Unlike the unstable addition products of carbonyl compounds with primary amines, which readily lose water to form imines, *N,N*-disubstituted hemiaminals are relatively stable and in some cases may be isolated (*e.g.* the adduct between 2-chlorobutanal and morpholine.[6] More often, however, these compounds are converted into the more stable aminals[7] or, if an α-hydrogen is present, the hemiaminal may dehydrate across the adjacent carbon–carbon bond, in the presence of drying agents, to give synthetically useful enamines.[8]

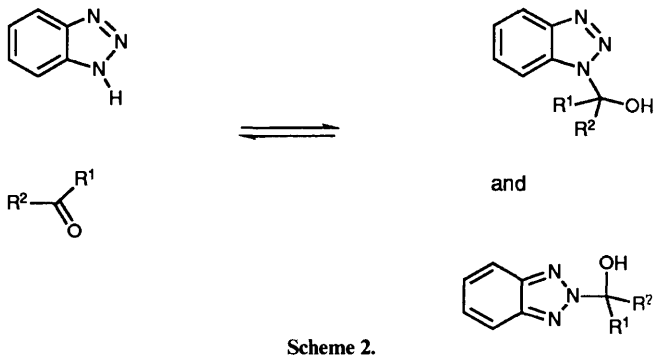
The reaction of benzotriazole with methanal to give hydroxymethylbenzotriazole is well known.[9] In 1987 our group showed that aliphatic aldehydes quite generally, and some aromatic aldehydes, form stable crystalline adducts with benzotriazole.[10a] A preliminary investigation at that time indicated an equilibrium between the starting materials and the 1-benzotriazolyl adduct in solution.

These benzotriazole aldehyde adducts were at the time all formulated as benzotriazol-1-yl derivatives. The corresponding amino derivatives are prepared in three-component reactions between benzotriazole, an aldehyde, and an amine, and these benzotriazolylalkyl amines are of great synthetic importance.[10] In general, they exist in the crystalline state entirely as the benzotriazol-1-yl isomers. However, extensive investigations have shown that in solution they exist as equilibrium mixtures of the benzotriazol-1- and -2-yl derivatives.[11] Their interconversion mechanism has been shown to be intermolecular (Scheme 1) and the parameters affecting the rates and equilibrium positions in solution have been examined.[12]

It seemed probable, therefore, that the adducts of benzotriazole with carbonyl compounds would also exist in solution as mixtures of benzotriazol-1- and -2-yl isomers



Scheme 1.



Scheme 2.

(Scheme 2). We have now undertaken a study of a variety of these compounds and investigated the equilibria between the isomeric 1- and 2-adducts and the starting materials.

These equilibria are conveniently examined *in situ* using ^1H and ^{13}C NMR spectroscopy. In the present work the equilibria between reactants and adducts, and between 1-isomers and 2-isomers, are examined at different temperatures and in a variety of solvents. Equilibrium constants and free-energy differences ($\Delta G°$) are calculated.

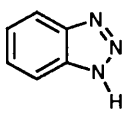
Results and Discussion

The ^1H and ^{13}C NMR spectra of solutions containing

Table 1. Calculated K_1, K_2, $\Delta G°_1$, and $\Delta G°_2$ values for benzotriazole carbonyl adduct equilibria, measured at 23 °C.

Benzotriazole	Carbonyl compound	Solvent	K_1/dm^3 mol^{-1}	K_2/dm^3 mol^{-1}	$\Delta G°_1$/ kcal mol^{-1}	$\Delta G°_2$/ kcal mol^{-1}
(1)	CH_3CHO	C_6D_6	22.3	1.87	−1.83 ± 0.04	−0.37 ± 0.06
	CH_3CH_2CHO	C_6D_6	18.6	1.40	−1.72 ± 0.05	−0.20 ± 0.05
	CH_3CH_2CHO	$(CD_3)_2SO$	16.8	1.22	−1.66 ± 0.04	−0.12 ± 0.03
	CH_3CH_2CHO	$CDCl_3$	13.4	1.40	−1.51 ± 0.05	−0.20 ± 0.04
	CH_3CH_2CHO	C_5D_5N	14.6	1.42	−1.58 ± 0.05	−0.21 ± 0.03
	$(CH_3)_2CHCHO$	C_6D_6	14.7	1.16	−1.58 ± 0.06	−0.09 ± 0.04
	$(CH_3)_3CCHO$	C_6D_6	1.28	0.114	−0.15 ± 0.08	1.28 ± 0.05
	2-PyrCHO	C_6D_6	2.62	0.200	−0.57 ± 0.04	0.95 ± 0.06
	c-Hexanone	C_6D_6	0.100	0.034	1.35 ± 0.05	1.99 ± 0.03
	CH_3COCH_3	C_6D_6	<0.001			
	c-Pentanone	C_6D_6	<0.001			
	p-tolualdehyde	C_6D_6	<0.001			
	CH_3COCO_2Et	C_6D_6	0.110	0.018	1.30 ± 0.07	2.36 ± 0.07
(2)	CH_3CH_2CHO	C_6D_6	12.3	1.02	−1.48 ± 0.05	−0.012 ± 0.02
(3)	CH_3CH_2CHO	$(CD_3)_2SO$	0.250	1.04	0.82 ± 0.04	−0.023 ± 0.03
(4)	CH_3CH_2CHO	$(CD_3)_2SO$	9.44	1.37	−1.32 ± 0.03	−0.185 ± 0.04
			4.62[a]		−0.90 ± 0.05[a]	

[a] For N-3 isomer.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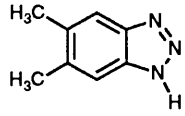
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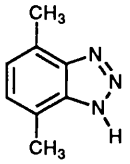
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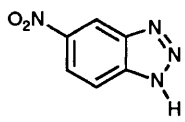
(4)

benzotriazole compounds (**1**)–(**4**) and carbonyl compounds reveal the presence of free reagents and both isomeric N-1 and N-2 adducts in equilibrium. That the equilibria are reached rapidly is evident from the fact that even after a few days the ratios of adduct to free reagents, and of N-1 to N-2 isomers remain unaltered.

Assignments of Signals and Evaluation of Equilibrium Constants.—The assignments of the ^1H signals to specific isomers were based on the intensity, multiplicity or shape of the signal, and characteristic chemical shifts and coupling constants. In general, many of the ^1H signals of the dominant N-1 isomer could be assigned while most of the signals of the N-2 isomer overlapped with other signals. The low intensity of the N-2 isomer signals also made it difficult to make complete assignments. In the case of aldehydes, the ratio of adducts to free reagents can readily be obtained from the ratio of the intensities of the aldehyde proton (-C*H*O) and the corresponding proton in the adduct (C*H*-OH). The alkyl or aryl protons of the carbonyl compounds and those of the adducts also give signals at different positions. The intensities of these signals also provide estimates of the ratios of adduct to free reagents. In each case, the spectra were recorded two or three times and the results were averaged.

The ^{13}C signals of almost all the carbon atoms of benzotriazole, of the carbonyl compounds, and of the isomeric N-1 and N-2 adducts could be readily assigned because of the larger spread of the ^{13}C chemical shifts and infrequent overlap of the signals. The assignments were made on the basis of signal intensities (quaternary carbon resonances being of low intensity due to poor relaxation) and on the basis of characteristic chemical shifts of the N-1 and N-2 isomers found in other benzotriazole derivatives. The ratios of N-1 to N-2 isomer have been obtained from ^1H spectra, except in the equilibria of the benzotriazole with methanal adduct where ^{13}C NMR spectroscopy was used, due to overlapping of the N-2 isomer proton signals with other more intense signals. From the above results, the equilibrium constants for the formation of N-1 isomer (K_1) and N-2 isomer (K_2) were computed and the results are given in Table 1, along with the free energies of the equilibria.

Effect of Structure on the Equilibria.—The adduct formed between benzotriazole and methanal is quite stable in the crystalline state.[9] In accordance with this observation, the ^1H and ^{13}C NMR spectra of the hydroxymethylbenzotriazole adduct in $(CD_3)_2SO$ do not indicate the presence of significant quantities of free benzotriazole and methanal. The ^{13}C NMR spectra of the adduct contains the signals due to both N-1 and N-2 isomers and the N-1:N-2 ratio has been computed to be approximately 40:1 using the intensities of the methylene carbons. From the equilibrium constants listed in Table 1 it is clear that adduct formation is hampered by an increase in steric crowding at the carbonyl centre; the proportion of adduct formation decreasing in the order: $CH_3CHO > (CH_3)_2CHCHO > (CH_3)_3CCHO$. However, it is found that the ratio of the N-1 to N-2 isomers (*ca.* 10–13 times) remains almost the same in these aldehydes. Increasing bulk at the carbonyl centre is expected to favour the N-2 isomer due to *peri* interactions with the adjacent ring proton. The absence of such a preference towards N-2 isomer formation could be rationalized by postulating a predominance of a conformation with the bulky group(s) pointing away from the 7-*peri* hydrogen of the benzotriazole ring. Pyridine-2-carbaldehyde forms N-1 and N-2 isomer adducts almost in the same ratio as the other aldehydes. *p*-Tolualdehyde, with diminished electrophilicity, fails to afford adducts in significant concentration.

Of the ketones studied, cyclohexanone forms N-1 and N-2 adducts, although to a much lesser extent than the aldehydes. Neither cyclopentanone nor acetone lead to significant adduct formation. Presumably, the relief of *I*-strain provides the driving

Table 2. ^{13}C NMR shifts for N-1 and N-2 adducts of benzotriazoles (**1**)–(**4**) with R^1R^2CO in C_6D_6.

Triazole	R^1	R^2	C-3a	C-4	C-5	C-6	C-7	C-7a	C-H	R
(**1**) (N-1)[a]	H	H	145.6	119.1	124.1	127.4	111.0	132.4	70.3	
(N-2)[a]			144.0	118.3	126.7	126.7	118.3	144.0	78.2	
(N-1)	CH_3	H	146.3	119.2	124.4	127.2	111.9	132.0	81.0	22.0
(N-2)			144.5	118.6	126.7	126.7	118.6	144.5	85.9	14.8
(N-1)	CH_3CH_2	H	146.3	119.3	124.5	127.2	112.0	132.1	85.9	29.3, 9.4
(N-2)			144.4	118.6	126.7	126.7	118.6	144.4	90.7	29.9, 10.4
(N-1)	$(CH_3)_2CH$	H	146.2	119.2	124.5	127.2	112.4	132.3	89.9	34.4, 18.7, 17.9
(N-2)			144.3	118.6	126.7	126.7	118.6	144.3	94.4	35.1, 17.8, 18.1
(N-1)	$(CH_3)_3C$	H	145.7	118.9	124.3	127.1	113.9	133.4	92.5	38.1, 25.8
(N-2)			144.0	118.6	126.7	126.7	118.6	144.0	96.0	37.4, 25.4
(N-1)	2-Pyr	H	146.8	119.7	124.4	127.5	111.6	132.1	83.5	155.7, 137.6, 148.5, 124.1, 121.9
(N-2)			145.9	118.7	126.7	126.7	118.7	145.9	88.6	155.7, 148.4, 137.5, *b*
(N-1)	$CO_2CH_2CH_3$	CH_3	146.7	119.8	*b*	127.8	112.8	132.6	88.4	170.0, 63.1, 25.2, 13.7
(N-2)			144.0	118.8	127.1	127.1	118.8	144.0	90.6	63.2, 23.8, 13.6, *b*
(N-1)	$-(CH_2)_5-$		146.7	119.4	124.0	126.7	114.3	132.7	91.6	37.9, 25.5, 22.9
(N-2)			144.4	118.7	126.4	126.4	118.7	144.4	93.8	37.7. 25.3, 22.9
(**2**) (N-1)	CH_3CH_2	H	145.6	118.4	134.0	137.4	111.4	132.1	85.8	29.3, 20.5, 20.0, 9.5
(N-2)			143.8	117.1	136.9	136.9	117.1	143.8	90.4	29.9, 20.2, 9.2
(**3**) (N-1)[a]	CH_3CH_2	H	145.9	126.8	123.5	128.5	118.8	131.9	83.8	27.0, 16.1, 9.8
(N-2)[a]			143.9	125.4	125.3	125.3	125.4	143.9	89.8	29.1, 18.5, 9.1
(**4**) (N-1)[a]	CH_3CH_2	H	147.7	116.3	144.3	121.9	112.8	134.4	85.0	28.7, 9.2
(N-2)[a]			142.0	*b*	*b*	120.5	119.8	150.2	*b*	*b*
(N-3)[a]			144.7	120.4	118.8	146.1	109.0	131.0	91.1	29.0, 9.2

[a] $(CD_3)_2SO$ as the solvent. [b] Signal not observed.

Table 3. ^1H NMR shifts for adducts of benzotriazoles (**1**)–(**4**) with aldehydes and ketones (R^1R^2CO) in C_6D_6. Chemical shifts are given in ppm (δ). Multiplicities and coupling constants are given in parentheses. Assignable signals for the 2-isomers are given in square brackets.

			Benzotriazole proton signals				CH_2 or CH (α to N)	Other signals
Comp. No.	R^1	R^2	H-4 (*J*/Hz)	H-5 (*J*/Hz)	H-6 (*J*/Hz)	H-7 (*J*/Hz)	(multiplicity, *J*/Hz)	
(**1**)	H[a]	H	7.96 (d, 8.3)	7.43 (m)	7.60 (m)	8.11 (d, 8.1)	6.10 (s)	—
	CH_3	H	7.67 (d, 7.5)	6.91 (t, 7.9)	7.00 (t, 7.1)	7.69 (d, 7.5)	6.43 (q, 6.1)	1.66 (3 H, d, 6.1) [1.83 (3 H, d, 6.0)][b]
	CH_3CH_2	H	7.73 (d)[c]	6.92 (m)	7.04 (m)	7.73 (d)[c]	6.32 (t, 6.8)	2.17 (1 H, m), 2.05 (1 H, m) 0.71 (3 H, t, 8.5), [2.32, 2 H, m][b]
	$(CH_3)_2CH$	H	7.74 (d, 8.3)	6.93 (m)	7.05 (m)	7.76 (d, 7.4)	6.16 (d, 7.4)	2.55 (1 H, m), [2.78, 1 H, m][b] 1.12 (3 H, d, 6.6), 0.51 (3 H, d, 6.8)
	$(CH_3)_3C$	H	7.74 (d, 8.4)	6.97 (m)	7.07 (m)	7.91 (d, 8.4)	6.35 (s) [6.41, s][b]	1.02 (9 H, s), [1.10, 9 H, s][b]
	2-Pyr	H	7.81[d] (m)	6.84–6.96 (m)	6.84–6.96 (m)	7.81[d] (m)	7.02–7.08[d]	8.23 (1 H, m), 7.56 (1 H, m) 7.11 (1 H, m), 6.66 (1 H, m)
	CO_2Et	CH_3	7.98 (d, 8.2)	—	7.12 (m)	8.02 (d, 8.4)	—	2.47 (3 H, s), [2.44, 3 H, s][b] 0.78–0.91 (3 H, m)
	$-(CH_2)_5-$		7.99 (d, 8.2)	—	7.11 (m)	8.21 (d, 8.5)	—	obscured by free cyclohexanone
(**2**)	CH_3CH_2	H	7.44 (s)	—	—	7.61 (s)	6.36 (t, 6.8)	2.26 (m), 2.18 (m), 0.78 (t, 7.6) 2.00 (s), 1.96 (s)
(**3**)[a]	CH_3CH_2	H	—	[7.07][b] (s)	[7.07][b] (s)	—	[6.13, t, 6.6][b] 6.13 (t, 6.6)	[2.63 (3 H, s), 2.60 (3 H, s)][b] [2.28 (2 H, m), 0.89 (3 H, t, 7.4)][b]
(**4**)[a]	CH_3CH_2	H	9.03 (d, 2.0)	—	8.43 (dd, 7.1, 2.0)	8.23 (d, 7.1)	6.41 (t, 6.6) [6.48, t, 6.7][b]	2.20–2.40 (m), 1.02 (3 H, t, 7.3)
(**4**)[a,d]			9.00 (d, 2.0)	—	8.25 (dd, 6.4, 2.0)	8.33 (d, 6.4)	6.25 (t, 6.8)	overlapping with other signals

[a] $(CD_3)_2SO$ as solvent. [b] 2-isomer. [c] Signals almost superimposed, coupling constants unresolved. [d] 3-isomer.

force for the formation of adducts in the case of cyclohexanone. Ethyl pyruvate leads to adduct formation to approximately the same extent as found in cyclohexanone.

The nature of substituents in the benzotriazole ring also influence the position of these equilibria and the ratio of N-1 to N-2 isomers. The presence of methyl groups at the 5- and 6-positions of the benzotriazole ring does not change the ratio of the isomers. However, methyl groups at the 4- and 7-positions diminish the N-1 adduct drastically resulting in the predominance of the N-2 isomer. The presence of a nitro group at the 5-position causes the formation of three isomers (N-1, N-2, and N-3), the ratio of these adducts being 61 : 9 : 30. These isomer signals in the NMR spectra have been identified by the chemical shifts, intensity, and SCS considerations. It is pertinent to note

that the N-1 isomer predominates over the N-2 and N-3 isomers in the equilibria of N-[(5-nitrobenzotriazolyl)methyl]-pyrrolidine in chloroform solution.[12]

Effect of Solvent Polarity.—With a view to studying the effect of solvent polarity on the adduct formation, the values of K_1 and K_2 have been determined in different solvents for a representative case *viz.*, benzotriazole and propanal. These data indicate that the adduct is formed to a lesser extent in polar solvents [$CDCl_3$, $(CD_3)_2SO$, C_5D_5N] compared with non-polar solvents (C_6D_6). This same system was investigated at three different concentrations (0.5, 1, and 2 mol dm^{-3}) in $CDCl_3$. No significant variance in either K_1 or K_2 was observed.

Influence of Temperature.—In the case of adducts with propanal, both ^1H and ^{13}C NMR spectra were measured at 23, 30, 37, and 44 °C in C_6D_6. The values of both K_1 and K_2 decrease with increasing temperature. However, the ratio of the N-1 and N-2 isomers suffers little change with temperature, as was observed by Lindsay Smith and Sadd [11b] in their study on the isomerization of 1- and 2-(*N,N*-disubstituted-aminomethyl)benzotriazoles. Linear plots of log K *vs.* $1/T$ were obtained, for both K_1 (r 0.999) and K_2 (r 0.998), from the slopes of which $\Delta H°_1$ (-9.2 ± 1.9 kcal mol^{-1}) and $\Delta H°_2$ (-7.1 ± 2.5 kcal mol^{-1}) values were computed.

Experimental

Materials.—Benzotriazole was recrystallized from benzene. All carbonyl compounds were distilled prior to use and were protected from light. Commercial deuteriated solvents were employed after being dried over 3 Å molecular sieves. Other chemicals used in this study were prepared and purified according to standard literature procedures.

Spectral Measurements.—The solutions for spectral measurements were generally prepared by dissolving the benzotriazole (1 mmol) and the appropriate carbonyl compound (1 mmol) in the deuteriated solvent (1 cm^3) to afford a final concentration of 1 mol dm^{-3} of each of these reagents. In the case of cyclohexanone and ethyl pyruvate, 2 mmol of the carbonyl compounds were used to obtain reasonably intense signals. The equilibria between benzotriazole, methanal, and the N-1 and N-2 adducts (hydroxymethylbenzotriazole isomers) were studied by dissolving 1-hydroxymethylbenzotriazole (1 mmol) in $(CD_3)_2SO$. Equilibrium was attained rapidly and the ratio of N-1 to N-2 isomers was observed to be unchanged even after 2 days. Spectral measurements were made after allowing the solutions to equilibrate with the NMR probe temperature for about 10–15 min.

The benzotriazole–propanal system was investigated at three concentrations (0.5, 1, and 2 mol dm^{-3}) in order to determine whether any significant concentration effects were involved. In each case the K_1 and K_2 values were consistent.

^1H and ^{13}C NMR measurements were performed on a VXR-300 instrument at 300 and 75 MHz respectively in various deuteriated solvents, as indicated. NMR measurements were performed in 5 mm sealed tubes.

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