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ISOMERIZATIONS OF N-(α-AMINOALKYL)-1,2,4-TRIAZOLES AND N-(α-AMINOALKYL)TETRAZOLES.

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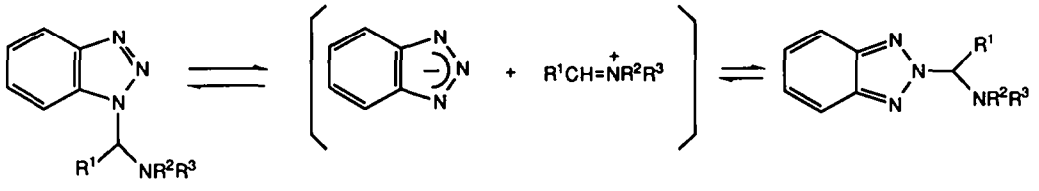
Abstract: *The title compounds exist as equilibrium mixtures of the N-1 and N-2 isomers in solution. However, the crystal structure of 3-(1-hydroxycyclohexyl)-1-(α-pyrrolidinomethyl)-1,2,4-triazole discloses only this isomer in the solid state. Evidence for the nature of the isomerization processes in solution is provided. The kinetic and thermodynamic parameters are measured and qualitatively assessed.*

Previous work has demonstrated that N-(α-aminoalkyl)benzotriazoles exist in solution as equilibrium mixtures of the 1- and 2-substituted isomers.[1,2] Interconversions of these isomers have been studied extensively and the mechanism was established as a dissociation-recombination process[3] (Scheme 1). Implicit in such tautomerism is an activation of the C-N bond toward cleavage in compounds (**1**), and this tendency has been utilized advantageously in many synthetic transformations involving reactions of compounds of type **1** with nucleophiles: the alkylation of primary and secondary amines,[4,5,6] amides[7] and thioamides,[8] the preparation of α-aminoesters,[9] β-aminoesters,[10] and β-aminoketones.[11]



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Scheme 1

Such facile "substituent" isomerizations have been reported for a few other azoles with N-linked substituents, including SiR_3 (silylotropy) in benzimidazoles[12] or SnR_3 (stannotropy) in pyrazoles;[13] however these processes have not been widely explored.[14] We now report that N-(α-aminoalkyl)-1,2,4-triazoles **2**, and the corresponding tetrazoles **3**, also undergo fast N-1 to N-2 substituent isomerizations, similar to those observed for benzotriazoles **1**, although no substituent migration to N-4 is observed in **2**.

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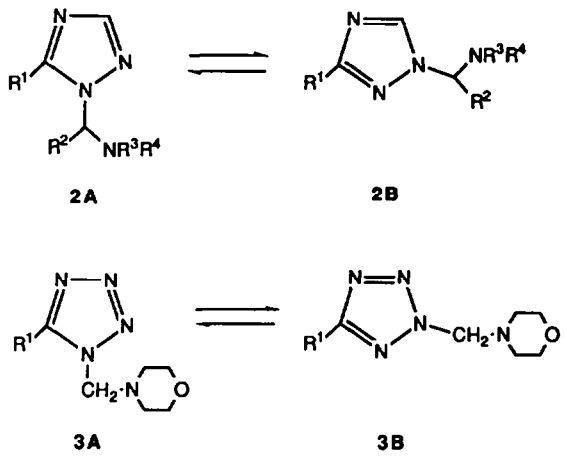

2	R^1	R^2	NR^3R^4
a	H	H	$N(CH_2)_4$
b	H	H	$N(CH_2)_4O$
c	H	H	NHCOPh
d	H	Ph	$N(CH_2)_4O$
e	Me	H	$N(CH_2)_4$
f	PhCH(OH)	H	$N(CH_2)_4$
g	$(CH_2)_5CHOH$	H	$N(CH_2)_4$

3	R^1	
a	H	**Scheme 2**
b	Me	

Preparation of the compounds: Ring-unsubstituted N-(α-aminomethyl)-1,2,4-triazoles **2a, 2b, 2d** and corresponding tetrazoles **3** (Scheme 2) were prepared from equimolar amounts of 1,2,4-triazole (or tetrazole), formaldehyde (benzaldehyde for **2d**), and a secondary amine, according to the previously used general procedure.[1,2] Compound **2c** was formed satisfactorily by mixing 1,2,4-triazole, benzamide, and paraformaldehyde and briefly heating at 200°C (azeotropic distillation with benzene or toluene afforded only low yields of the expected product **2c**). Ring lithiation of N-(1-pyrrolidinomethyl)-1,2,4-triazole **2a** and subsequent reactions with methyl iodide, benzaldehyde, and cyclohexanone, afforded compounds **2e, 2f,** and **2g,** respectively, in a procedure described in the following paper.[15] Details of the novel compounds are listed in Table 1, or in Ref 15.

Our ^{1}H- and ^{13}C-NMR measurements are recorded in Table 2 and 3, respectively. While the ^{13}C spectral assignments agree well with previous work,[12,14] literature work[16,17] on ^{1}H-NMR of N-substituted and N-unsubstituted 1,2,4-triazoles seems to disagree.

Table 1. Preparation and characterization of azoles **2b-d** and **3**

Com.	Yield (%)	mp (°C)	%C	Calc. % H	% N	Molecular Formula	% C	Found % H	% N	Recryst. Solv.	Crystal Form
2b	83	80-85	49.98	7.19	33.31	$C_7H_{12}N_4O$	49.67	7.23	33.79	EtOAc[a]	Prisms
2c	80	163-165	59.39	4.99	27.71	$C_{10}H_{10}N_4O$	59.38	4.96	28.31	EtOAc	Flakes
2d	29	107-111	63.91	6.60	22.94	$C_{13}H_{16}N_4O$	63.48	6.64	23.22	EtOAc	Prisms
3a	80	80-82	*m/e* =	169.09636		$C_6H_{11}N_5O$	*m/e* =	169.09445		[b]	Needles
3b	81	74-79	45.89	7.15		$C_7H_{13}N_5O$	45.72	7.15		PhH/Hexane[c]	Prisms

[a] bp = 118-120/2 mm Hg. [b] Washed with ether/hexane. [c] 1:1, v/v.

For conclusive confirmation of our assignments, we obtained a 2D proton-carbon correlation spectrum (HETCOR) for compound **2e** in $CDCl_3$. This verified that the downfield signal (151.4 ppm), due to C-3 in the ^{13}C-NMR spectrum, correlates with the upfield proton signal at 7.78 ppm (H-3) and the upfield signal at 143.0 ppm, due to C-5, correlates with the downfield proton at 8.07 ppm (H-5).

Table 2. ^{1}H-NMR spectra of 1*H*- (**A**) and 2*H*-isomers (**B**) of azoles **2a-f** and **3a,b** ($CDCl_3$/TMS)

	R^1	Ring H-5[a]	Ring H-3[a]	R^2	CH[a]	NR^3R^4
2aA	-	8.21	7.95	-	5.15	2.71(m, 4 H), 1.75(m, 4 H)
2bA	-	8.15	7.97	-	5.00	3.70(t, J = 4 Hz, 4 H), 2.59(t, J = 4 Hz, 4 H)
2cA[b]	-	8.51	7.94	-	5.77[c]	8.02(t, J = 6 Hz, NH), 7.82(dd, J = 7,1 Hz, 2 H) 7.58(t, J = 7 Hz, 1 H), 7.47(dd, J = 7,1 Hz, 2 H)
2dA	-	8.26	8.02	7.38[d]	6.05(s)	3.74(m, 4 H), 2.54(m, 4 H)
2eA	2.52[a]	-	7.78	-	5.01	2.71(m, 4 H), 1.76(m, 4 H)
2fA	7.48-7.26[g]	-	7.78	-	4.55[f]	2.57(m, 4 H), 1.81(m, 4 H)
2gA	2.08-1.35[e]		7.74	-	5.03	2.70(m, 4 H), 1.76(m, 4 H)
3aA	-	8.72	-	-	5.31	3.70(t, J = 4 Hz, 4 H), 2.61(t, J = 4 Hz, 4 H)
3bA	2.6[a]	-	-	-	5.08	3.70(t, J = 4 Hz, 4 H), 2.65(t, J = 4 Hz, 4 H)
2aB	-	8.21	7.95	-	5.15	2.71(m, 4 H), 1.75(m, 4 H)
2bB	-	8.15	7.97	-	5.00(s)	3.70(t, J = 4 Hz, 4 H), 2.59(t, J = 4 Hz, 4 H)
2dB	-	8.26	8.02	7.38[d]	6.08(s)	3.74(m, 4 H), 2.54(m, 4 H)
2eB	2.39[a]	8.07	-	-	5.03	2.71(m, 4 H), 1.76(m, 4 H)
2fB	7.48-7.26[h]	7.99	-	-	5.01	2.64(m, 4 H), 1.72(m, 4 H)
2gB	2.08-1.35[e]	8.55	-	-	5.07	2.70(m, 4 H), 1.76(m, 4 H)
3aB	-	-	-	-	5.52	3.70(t, J = 4 Hz, 4 H), 2.65(t, J = 4 Hz, 4 H)
3bB	2.56[a]	-	-	-	5.40	3.70(t, J = 4 Hz, 4 H), 2.65(t, J = 4 Hz, 4 H)

[a] All singlets, unless when indicated. [b] Most likely one species in solution in view of the very high energy barrier (see Table 5). [c] d, J = 7 Hz. [d] m, 5 H. [e] m, 10 H. [f] dd, J = 12 Hz, 2 H. [g] m, 5 H and δ 6.10 ppm (s, 1 H, CH). [h] m, 6 H and δ 5.92 ppm (s, 1 H, CH)

Spectral evidence for isomerization: We have now shown that ring unsubstituted N-(α-aminoalkyl)-1,2,4-triazoles interconvert between forms **A** and **B** in solution at 20°C at rates which are slow in the NMR time-scale. However, this was not immediately evident, as isomers **2A** and **2B** are identical when R^1 = H and each gives rise to the same spectrum. The presence of two isomers was at first observed for the ring deuterated compound[15] (R^1 = D): the preparative method utilized was expected to afford selectively **2aA** (R^1 = D), but the product isolated displayed two signals around 8.2 and 8.0 ppm in the ^{1}H-NMR spectrum, each integrating for half a proton, instead of the expected single resonance, indicating an equilibrium mixture of **2aA** and **2aB** (R^1 = D). Again, the ^{13}C-NMR spectrum of the compound, expected from its method of preparation to be 1-(1-pyrrolidinomethyl)-5-methyl-1,2,4-triazole **2eA**, displayed four ring signals (two quaternary and two tertiary) demonstrating that it was a mixture of **2eA** and **2eB**. However, both of these results could have been due to the formation of non interconverting isomers, rather than to the formation of an equilibrium mixture.

Table 3. ^{13}C-NMR spectra of 1*H*-(A) and 2*H*-isomers (B) of azoles **2a-g**, and **3a,b** ($CDCl_3$)

	R^1	Ring C-3	Ring C-5	R^2 CH	NR^3R^4	
2aA	-	151.0	143.1	-	66.0	49.2, 23.3
2bA	-	151.6	143.4	-	70.5	66.4, 49.8
2cA[a]	-	152.0	144.6	-	52.7	167.9, 132.5, 132.4,128.7, 127.2
2dA	-	151.6	143.0	135.1, 129.0 128.8, 127.5	82.9	66.8, 49.6
2eA	12.0	152.6	149.9	-	65.4	50.2, 22.7
2fA	139.8, 127.8, 127.6 125.4, 68.0	157.5	149.4	-	66.6	51.0, 23.4
2gA	25.3, 21.4[c]	.[c]	149.0	-	.[c]	51.1, 23.4
3aA	-	-	142.7	-	69.7	66.4, 49.5
3bA	9.0		.[c]	-	68.3	66.4, 50.1
2aB	-	151.0	143.1	-	66.0	49.2, 23.3
2bB	-	151.6	143.4	-	70.5	66.4, 49.8
2dB	-	151.6	143.0	135.1, 129.0 128.8, 127.5	82.9	66.8, 49.6
2eB	13.8	160.8	143.9	-	64.4	49.9, 23.8
2fB	141.7, 128.5, 128.3 126.5, 68.0	165.6	144.2	-	70.4	49.9, 23.8
2gB	66.7, 37.4, 25.4, 22.0	169.8	143.7		70.5	50.0, 23.9
3aB	-		152.6	-	73.9	66.5, 49.7
3bB	10.8		162.6	-	73.5	66.5, 49.7

[a] Most likely only one species present, due to the very high barrier to isomerization. [b] Quaternary carbon atoms. [c] Signal not detected.

More information was gathered from a cross-over NMR experiment, in which simple mixing of equimolar amounts of **2b** and **2e** afforded spectral signals arising from the cross-over products [**2a** and N-(α-morpholinomethyl)-5-methyl-1,2,4-triazole **2h**], in addition to those from the starting materials. Specifically, the ^{1}H-NMR spectrum of the mixture showed eight singlets in the aromatic region and six in the N-CH_2-N region. If no cross-over products were formed, the expected number of signals would be four and three, respectively (Table 4). Partial overlapping of some the peaks did not allow precise integration and assessment of isomeric distribution. Moreover, it was evident, that equilibrium was not attained instantaneously: the ^{1}H-NMR spectrum examined after a few days, showed somewhat different ratios compared to the spectrum recorded immediately after mixing. Similarly, the ^{13}C-NMR spectrum displayed the anticipated number of peaks arising from **2b**, **2e** and cross-over products **2a**, **2h** (Table 4). This experiment suggests that the isomerization is intermolecular, just as in the case of the corresponding benzotriazoles;[2] although the isomerizations are spontaneous in both reactions, for the 1,2,4-triazoles they are somewhat slower. In addition to the above evidence, variable temperature ^{1}H-NMR experiments showed conclusively that N-1 to N-2 interconversion occurs: increase of the temperature brought about peak broadening and eventual coalescence of the triazole ring signals, as discussed below.

In contrast to these observations, the equilibrium involving compound **2g** is strongly biased in favor of **2gB** in solution. The ^{1}H-NMR spectrum in $CDCl_3$ revealed only a small amount of the second species **2gA** (6%). A comparison of the ^{13}C-NMR chemical shifts (in $CDCl_3$) with solid state NMR data (valid according to a previous investigation[12]), suggested that these ring substituted triazoles exist mainly in the **B** form. The X-ray structure obtained for **2gB** confirmed this assignment (Figure 1) and also proved that in the solid state this compound exists in the **B** form only. The method of preparation, (lithiation of **2a** at C-5 and alkylation)[15] was expected to result in formation of isomer **2gA**, but evidently it isomerized under the conditions of formation in favor of the least hindered form **B**.

Tetrazoles **3a** and **3b** were also mixtures of two isomers in solution. Unlike forms **A** and **B** in triazoles **2a-2d**, for tetrazoles the isomeric structures are not identical. The mole fractions of the isomers **3A** and **3B** in the solution were very different, thus detection and distinction of the two forms was easy. The assignments of the ^{13}C-NMR spectra were made according to literature values[14] and those of the ^{1}H-NMR spectra were deduced from examination of the relative intensities of the peaks and literature data for model tetrazoles.[18] Chemical shifts are listed in Tables 2 and 3.

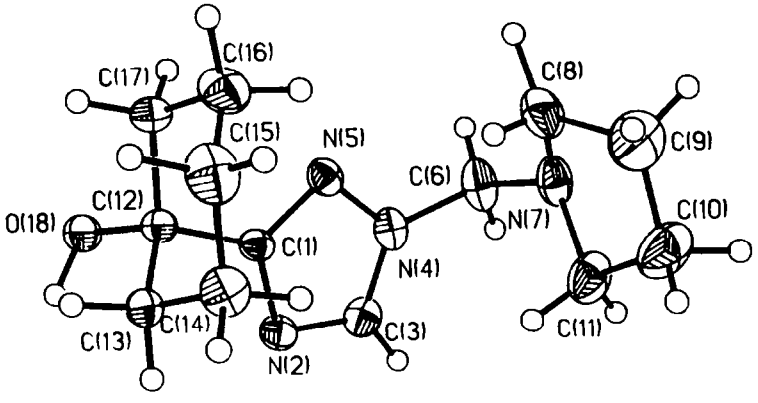

Figure 1. X-Ray structure of 3-(1-hydroxycyclohexyl)-1-(α-pyrrolidinomethyl)-1,2,4-triazole

Table 4. Results from the cross-over experiment in $CDCl_3$.

	^{1}H-NMR	
Soln. of:	Ring signals	N-CH_2-N
2b	8.15, 7.95	5.00
2e	8.07, 7.78	5.03, 5.01
2b + 2e	8.18, 8.04, 8.02, 7.97, 7.95, 7.79, 7.78	5.14, 5.03, 5.01, 5.00, 4.90, 4.84
	^{13}C-NMR	
2b	151.6, 143.4	70.5
2e	160.8, 152.6, 149.9,143.9	65.4, 64.4
2b + 2e	160.7, 160.5, 151.4, 151.2 149.7, 149.6, 143.6 143.5 143.3, 143.2	70.3, 70.0, 69.0, 66.6, 66.1, 66.0

Thermodynamic and kinetic parameters: The equilibrium constants for **2a-d** are necessarily equal to 1 because of symmetry (50 : 50 % mixture). However, for the ring substituted compounds **2e, 2f, 2g,** and for the tetrazoles **3a, 3b,** the 2-substituted form **B** predominates in $CDBr_3$. Integrations of the NMR signals furnished the K values shown in Table 4. The experimental dipole moments[19] of 2-methyl-5-phenyltetrazole (μ = 2.52 D) and of 1-methyl-5-phenyltetrazole (μ = 5.88 D) indicate that 1-substituted tetrazoles are more polar than their 2-substituted isomers and, consequently, 1-substituted tetrazoles should be favored in polar solvents. In toluene-d_8 (ε = 2.38 at 25°C, μ = 0.36 D)[20] and in $CDBr_3$ (ε = 4.39 at 20°C, μ = 0.99 D),[20] the isomeric ratios of **3aA** and **3aB** are similar, with the 2-isomer **B** predominant. However in CD_3NO_2 (ε = 38.6, μ = 3.46 D),[20] the ^{1}H-NMR spectrum of **3a** at 22°C showed that the isomers were in near coalescence and that the situation is reversed: at -23°C there was a clear prominence of the 1-isomer **A** (Table 4). The melting point of DMSO-d_6 (ε = 24.3, μ = 1.69)[20] is too high (18°C) for low temperature spectra with sharp peaks to be obtained.

Similarly, C-substituted 1,2,4-triazoles **2e-g** prefer the least hindered form **B** in solution, and probably exist exclusively in that form in the solid state, as indicated by the crystal structure of a representative of this class, **2g**. The crystal structure also shows that in **2g**, the triazole ring occupies the axial position of the cyclohexyl ring, whereas the hydroxy group occupies the equatorial position. Although unusual, the axial substitution by the bulky pyrrolidinomethyltriazolyl group, is probably a consequence of favorable crystal packing. The ^{1}H-NMR spectrum of **2e** recorded in CD_3NO_2, displayed an isomeric ratio only slightly different than that in bromoform (Table 4). Evidently here the least hindered isomer is the main species in all solvents, regardless of the large differences in polarity of the media. Since experimental dipole moments do not seem to be known for model ring-substituted 1,2,4-triazoles resembling our isomers, we carried out AM1 calculations to obtain dipole moments for model compounds. The calculated values for 1,3-dimethyl-1,2,4-triazole (form **B** type) and 1,5-dimethyl-1,2,4-triazole (form **A** type) were 2.822 D and 3.419 D, respectively. This indicates that increased solvent polarity will only slightly favor form **A**, and it is in line with our observations.

Table 5. Thermodynamic and kinetic parameters for N-(α-aminoalkyl)-1,2,4-triazoles and tetrazoles.[a]

Cpd.	R^1	R^2	NR^3R^4	K^b	T_c [d] (°C)	$\Delta G^{\ddagger}$ [e] (kcal/mole)	Cpd.	R^1	R^2	NR^2R^3	K^b	$\Delta G°$ [c] (kcal/mole)	T_c [d] (°C)	$\Delta G^{\ddagger}$ [e] (kcal/mole)
2a	H	H	$N(CH_2)_4$	1	110	18.8	**2e**	Me	H	$N(CH_2)_4$	0.75 0.89[f]	0.15	130	19.8
2b	H	H	$N(CH_2)_4O$	1	109	18.5	**2f**	PhCH(OH)	H	$N(CH_2)_4$	0.45		115	19.0
2c	H	H	NHCOPh	1	>140	>30	**3a**	H	H	$N(CH_2)_4O$	0.17 0.20[g] 2.40[f]	-1.03	82	17.6
2d	H	Ph	$N(CH_2)_4O$	1	124	19.5	**3b**	H	Me	$N(CH_2)_4O$	0.2	0.95	148	20.0

[a] Measured in $CDBr_3$ unless otherwise specified. [b] K = [A]/[B], measured at 22°C. [c] ± 0.05 kcal/mole. [d] ±3°C. [e] ±0.3 kcal/mole. [f] In CD_3NO_2. [g] In toluene-d_8.

Free energies of activation were obtained from VT-NMR, and the values are also listed in Table 5. In general the 1,2,4-triazoles **2** possess higher energy barriers than the corresponding benzotriazoles, whereas for tetrazoles **3** the $\Delta G^{\ddagger}$ are lower. The 2-isomers are predominant whereas, in the benzotriazole analogs, the 1-isomers are favored. The value shown for the amide derivative **2c** is only an extrapolation: temperature increase did cause peak broadening and the signals moved toward coalescence, however the barrier is apparently considerably higher higher than those of the other triazoles, and T_c would exceed the boiling point of the solvent d(150°C). The mechanism of the 1- to 2- interconversion was shown above to be intermolecular, however the $\Delta G^{\ddagger}$ values and the very small solvent effects on $\Delta G°$ do not support a pathway of complete dissociation to methyleneiminium 1,2,4-triazolate ions; it is more likely that tight ion pairs are formed in this case. On the other hand, tetrazoles may isomerize through solvent separated ion pairs, like the analogous benzotriazoles, in view of the marked difference in the energies of activation in **3a** and **3b** and the enormous solvent effect on $\Delta G^{\ddagger}$.

Experimental: Compounds **2a-b, 2d, 3a-b** were prepared by stirring equimolar amounts (0.01 mole) of azole, aldehyde and amine in methanol overnight, according to the standard literature procedure.[1] Removal of the solvent under reduced pressure afforded the crude product, which was purified by recrystallization or distillation, as indicated in Table 1 for each case. Compound **2c** was prepared from 1,2,4-triazole, paraformaldehyde and benzamide by gently melting together the solids and then heating the resulting liquid at 200°C for 30 min. Cooling and recrystallization (Table 1) afforded the pure product. The preparation of compounds **2e-g** is described elsewhere.[15]

All spectroscopic work was conducted on a Varian VXR-300 spectrometer. VT-NMR measurements were performed using 0.1 M solution in 5 mm tubes (sealed if required). Deuterated bromoform was distilled and allowed to stand with potassium carbonate and molecular sieves for at least 15 h before use. Solvents were stored over 3 Å molecular sieves. The solutions were cooled after heating and the spectra checked to insure that no decomposition had occured. Temperature was raised in 10°C increments and allowed to stabilize for 5-10 min at each setting. The free energies of activation were calculated from the previously utilized approximate equation.[3] Measurements were rejected if the values were more than 0.3 kcal/mole different; the results in Table 4 are average of at least two runs.

X-Ray Crystal structure analysis:- The crystal structure of **2g** was determined by X-ray diffraction. Colorless crystals of **2g** suitable for diffraction studies were grown by slow evaporation of a benzene solution. The crystals are monoclinic, space group $P2_1/c$, with four molecules per unit cell. The dimensions are a = 12.754(2), b = 12.593(4), c = 8.898(3) Å and β = 103.50(2)°. The cell volume is 1395.6(6) $Å^3$ and for a molecular weight of 250.364 amu, the calculated density is 1.196 g/cm^3. A crystal 0.21 x 0.22 x 0.22 mm was used to measure 2834 reflections of which 1525 with Fobs > 3σ(Fobs) were used in the analysis. The final R was 0.044 and R_w was 0.043 with a GOF of 1.29. The weighting scheme was $w = 1/\sigma(Fobs)^2$ and an empirical extinction correction parameter of 0.00056 was determined. All calculations were carried out using the SHELXTL system on a Model-30 Eclipse. All measurements were made using a Nicolet R3m

diffractometer with graphite monochromatized MoK_α radiation. Final positional parameters, bond distances and angles have been deposited in the Cambridge X-ray data center.

Semiempirical calculations were carried out using the MOPAC program, version 3.0 on a MicroVAX II.[21]

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