Conformational Control in the 3,7-Diazabicyclo[3.3.1]nonane System

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The twin-chair or boat-chair conformation of 3,7-diazabicyclo[3.3.1]nonanes can be selected by forming *N,N'*-derivatives in which the N atoms have planar or pyramidal bonding patterns, respectively, *e.g.*, acyl substituents for the former and arylsulphonyl or alkyl for the latter.

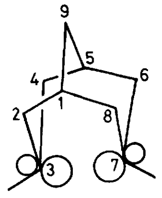
Recent *X*-ray studies of several *N,N'*-dialkyl derivatives of 3,7-diazabicyclo[3.3.1]nonane have shown that these compounds adopt the boat–chair conformation,[1—3] a result that can be attributed to repulsion between the lone pairs of electrons of the N atoms at the 3 and 7 positions in the alternative twin-chair conformation.

We have investigated the relationship between the conformation adopted by 3,7-diazabicyclo[3.3.1]nonane derivatives and the degree of pyramidal character of the N atoms. When the geometry at N is markedly pyramidal, *i.e.*, the hybridization is close to sp^3, the lone-pair electron density is concentrated in the *endo* position [see (**1**)], giving maximum repulsion and favouring the boat–chair conformation. When the geometry at N is planar and the hybridization is sp^2, the lone-pair density is distributed equally between lobes in both the *endo* and *exo* positions [see (**2**)] and the *endo–endo* repulsion would be expected to be less; moreover, substituents that favour sp^2 hybridization at N also result in delocalization of the lone-pair electron density away from N.

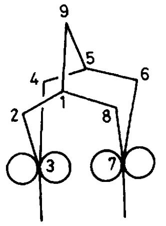
In accord with this hypothesis, we find that crystal structures† of (**3**), (**4**), and (**5**) show molecules with essentially planar bonding patterns at N and the conformation adopted is the twin-chair (see Figure 1).

The crystal structure of (**6**)† contains molecules with the boat–chair conformation and a distinctly pyramidal arrangement of bonds at N (see Figure 2). We have determined the crystal structures of several *N*-arylsulphonyl compounds and all have pyramidal, rather than planar, bonding patterns at N (see following paper). The ^{15}N–^{1}H spin coupling constant of 80.8 Hz in benzenesulphonamide itself[4] is consistent with pyramidal N.[5]

Compounds (**3**)‡ and (**4**)‡ were formed by ring opening[6] ($NaNO_2$–HCl; $ClCO_2Et$) of (**10**) prepared by Mannich condensation[6] of $(PhCH_2)_2CO$, H_2CO, and NH_4OAc. Compounds (**5**) and (**6**) were prepared by acylation [$(CF_3CO)_2O$/pyridine; *p*-$MeC_6H_4SO_2Cl$–pyridine/CH_2Cl_2] of (**9**). Synthesis



(1)



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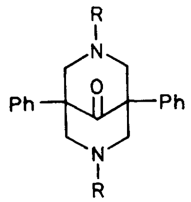
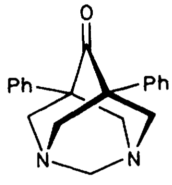


(3) R = NO
(4) R = CO_2Et
(5) R = $COCF_3$
(6) R = $SO_2C_6H_4Me$-*p*
(7) R = CH_2Ph
(8) R = Me
(9) R = H



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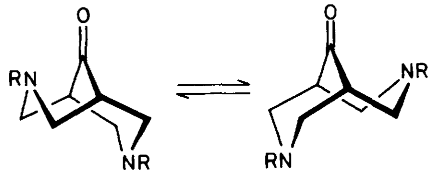

(11) (12)

Table 1. Out-of-plane angle (θ) of the N–R bond from the C(2)–N(3)–C(4) or C(6)–N(7)–C(8) plane in various 3,7-diazabicyclo[3.3.1]nonanes.

Compound	R	θ(chair)°	θ(boat)°
(3)	NO	1.2, 1.6	
(4)	CO_2Et	3.7, 6.3	
(5)	$COCF_3$	4.2, 8.5	
(6)	$SO_2C_6H_4Me$-*p*	24.9	32.5
(7)[a]	CH_2Ph	49.1	47.7
(8)†	Me	50.6	54.5

[a] See ref. 2.

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† *Crystal data.* (**3**): $C_{19}H_{18}N_4O_3$, M = 350.3, orthorhombic, space group $Pca2_1$, a = 17.830(3), b =10.280(3), c = 9.270(3) Å, U = 1699 Å^3, $F(000)$ = 736, Z = 4, Mo-K_α radiation, λ = 0.71069 Å, μ(Mo-K_α) = 1.03 cm^{-1}, direct phasing procedure (MITHRIL)[9] for structure solution followed by least-squares refinement with 1225 reflections for which $I \geqslant 2.5\sigma(I)$, R = 0.051, R_w = 0.054, with $w = 1/\sigma^2(|F|)$. (**4**): $C_{25}H_{28}N_2O_5$, M = 436.5, monoclinic, space group $P2_1/n$, a = 11.274(4), b = 19.920(4), c = 11.572(2) Å, β = 119.95(5)°, U = 2251 Å^3, $F(000)$ = 928, Z = 4, μ(Mo-K_α) = 0.97 cm^{-1}, 3231 reflections for which $I \geqslant 2.5\sigma(I)$, R = 0.059, R_w = 0.073, with $w = 1/\sigma^2(|F|)$. (**5**): $C_{23}H_{18}N_2O_3F_6$, M = 484.4, orthorhombic, space group $Pna2_1$, a = 12.977(2), b = 17.429(3), c = 9.131(2) Å, U = 2065 Å^3, $F(000)$ = 992, Z = 4, μ(Mo-K_α) = 1.52 cm^{-1}, 1499 reflections for which $I \geqslant 2.5\sigma(I)$, R = 0.058, R_w = 0.078, with $w = 1/\sigma^2(|F|)$. (**6**): $C_{33}H_{32}N_2O_5S$, M = 600.7, monoclinic, space group $I2/c$, a = 20.139(3), b = 15.988(3), c = 18.951(2) Å, β = 93.39(2)°, U = 6091 Å^3, $F(000)$ = 2368, Z = 8, μ(Mo-K_α) = 2.18 cm^{-1}, 3636 reflections for which $I \geqslant 2.5\sigma(I)$, R = 0.047, R_w = 0.056, with $w = 1/\sigma^2(|F|)$. (**8**): $C_{21}H_{24}N_2O$, M = 320.2, monoclinic, space group $P2_1/c$, a = 7.901(1), b = 10.809(2), c = 20.883(3) Å, β = 97.23(3)°, U = 1769 Å^3, $F(000)$ = 688, Z = 4, μ(Mo-K_α) = 0.80 cm^{-1}, 3169 reflections for which $I \geqslant 2.5\sigma(I)$, R = 0.047, R_w = 0.065, with $w = 1/\sigma^2(|F|)$. Results are in good agreement with a previous *X*-ray analysis[1] but are of higher precision. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

‡ All crystalline compounds gave satisfactory n.m.r., mass spectral, and microanalytical data: m.p.s.; (**3**) 262—264 °C; (**4**) 140—141; (**5**) 224—226; (**6**) 260—261.

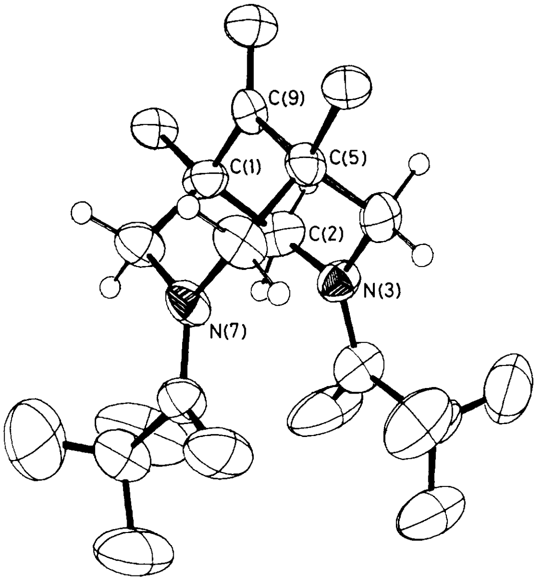

Figure 1. The molecular structure of 1,5-diphenyl-3,7-bis(trifluoroacetyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (**5**). For clarity, the phenyl groups at positions 1 and 5 have been omitted, apart from the C atoms directly bonded to C(1) and C(5). The thermal ellipsoids are drawn at the 50% probability level. The H atoms are represented by spheres of radius 0.1 Å.

of (**9**) by hydrogenolysis (Pd black–MeOH–50 °C) of (**7**), formed by Mannich condensation[7] of $(PhCH_2)_2CO$, H_2CO, and $PhCH_2NH_3OAc$–EtOH, is more efficient than the reported procedure from (**10**).[6]

In the ^{13}C n.m.r. spectrum of (**6**) at low temperatures, the CH_2 signal (δ 55) showed marked broadening but had not separated into two distinct signals by −110 °C when precipitation took place. For (**7**) (boat–chair),[2] broadening of the $^{13}CH_2$ signal on cooling was followed by separation into two distinct peaks ($\delta\nu$ 151 Hz) and the coalescence temperature of −91 °C corresponds to $\Delta G^{\ddagger}$ 35.0 kJ mol^{-1} for the degenerate interconversion (**11**) $\rightleftharpoons$ (**12**). $\Delta G^{\ddagger}$ for the process in (**6**) is <30 kJ mol^{-1}, distinctly less than the value of 40.6 kJ mol^{-1} reported for (**8**) where the coalescence temperature is −63 °C.[8] These results suggest a correlation between $\Delta G^{\ddagger}$ and the degree of pyramidal character at N (see Table 1).

In the ^1H n.m.r. spectra of compounds (**3**)—(**8**), the *N*-substituent is the major influence on the chemical shifts of the skeletal CH_2 groups and these shifts are not diagnostic of the ring conformation.

We conclude that the boat-chair or twin-chair conformation of 3,7-diazabicyclo[3.3.1]nonane derivatives can readily be selected by choice of substituent at N.

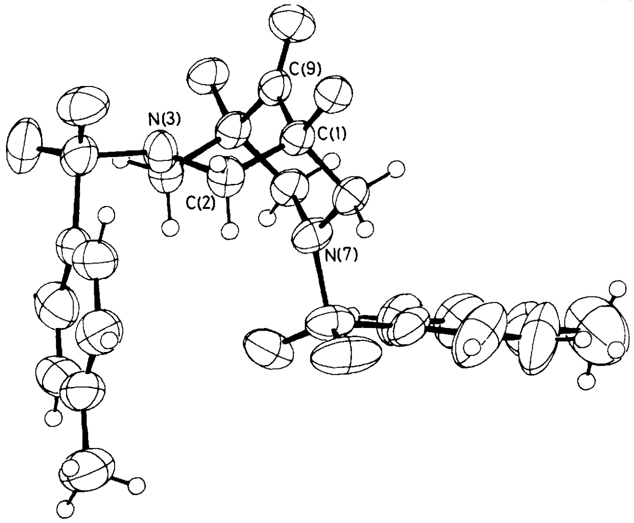

Figure 2. The molecular structure of 1,5-diphenyl-3,7-bis(*p*-tolylsulphonyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (**6**). For clarity, the phenyl groups at positions 1 and 5 have been omitted, apart from the C atoms directly bonded to C(1) and C(5). The thermal ellipsoids are drawn at the 50% probability level. The H atoms are represented by spheres of radius 0.1 Å.

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