Sterically controlled population of the 1,2-*cis*-form of 1,2-dimethyl-3-*tert*-butyldiaziridine

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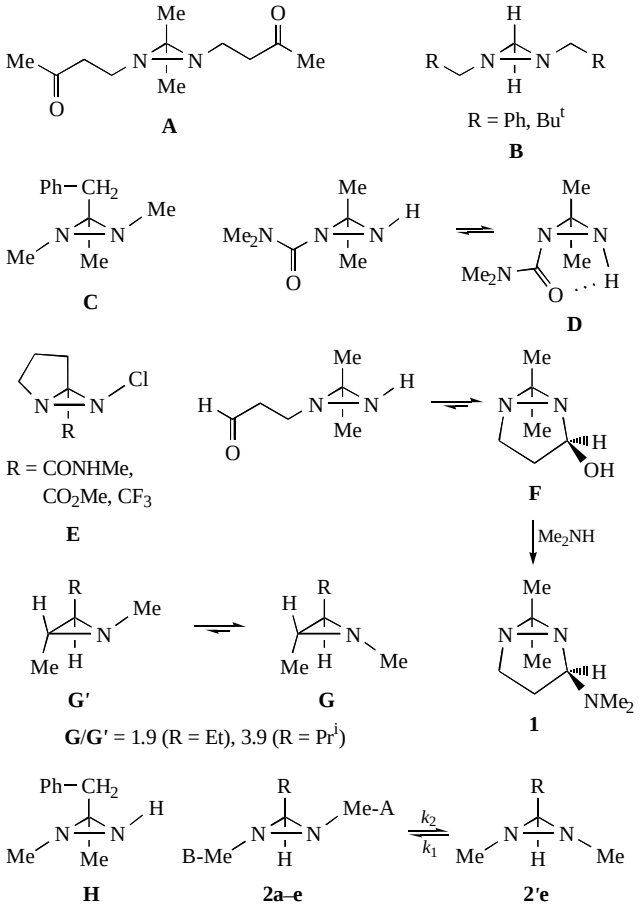
1,2-Dimethyl-3-R-diaziridine (R = Bu^t) has been synthesized for the first time; as revealed by NMR the population of its 1,2-*cis*-form was shown to increase in polar solvents [1,2-*cis*/1,2-*trans* = 2 (D_2O), 0.5 ($CDCl_3$), 0.03 (C_6D_6); for 1,2-*trans* → 1,2-*cis* in C_6D_6 at 32 °C $\Delta G^{\#}$ = 25 kcal mol^{-1}] whereas solely the 1,2-*trans*-form was detected in diaziridines when R = Me, Et, Pr^i, Ph.

As a rule monocyclic diaziridines in solution[1–3] and in the solid[4] and gaseous[5–7] states exist as 1,2-*trans*-isomers because the 1,2-*cis*-form is destabilized by n–n interaction of the nitrogen lone pairs and non-bonded interaction of N-substituents. According to *ab initio* calculations (3–21G with full geometry optimization) the energy difference between the 1,2-*cis*- and *trans*-forms is 8.6 kcal mol^{-1}, and the equilibrium concentration of the 1,2-*cis*-form is vanishingly small. Therefore the symmetrically-substituted diaziridines have C_2 symmetry and are chiral.[1] This was undoubtedly confirmed by isolation of diaziridines **A**,[2] then **B** and **C**[9] in the optically active form, probably due to their rather high nitrogen inversion barrier [*cf.*, for 1,2,3-trimethyldiaziridine in toluene $\Delta G^{\#}_{inv}$ = 27.7 kcal mol^{-1} (60 °C), $\Delta H^{\#}$ = 26.6 kcal mol^{-1}, $\Delta S^{\#}$ = –4.2 e.u., lg A = 12.6, E_a = =27.3 kcal mol^{-1}].[8]

Nevertheless, population of the 1,2-*cis*-form was observed earlier in monocyclic diaziridine **D** where it is stabilized by an intramolecular H-bond.[10] In addition, using kinetically controlled chlorination of 1,6-diazabicyclo[3.1.0]hexanes the bicyclic 1,2-*cis*-diaziridines **E** were obtained, which are isomerized into the thermodynamically more stable 1,2-*trans*-forms.[11] In both cases destabilizing n–n interaction is weakened by n–π conjugation with a substituent at N or C, respectively.

Being stabilized by a covalent bond, the 1,2-*cis*-form of bicyclic diaziridine **F** predominates in the tautomeric equilibrium,[12] and it is the only form present in the 2-dimethylamino derivative **1** obtained in this work.†



Scheme 1

† ^{1}H NMR (400.13 MHz), ^{13}C NMR (100.62 MHz) in $CDCl_3$, standard TMS, δ/ppm, J/Hz; MS (EI, 20 eV), m/z (%).

1: yield 37%, bp 53–55 °C (1 Torr); ^{1}H NMR: 1.14 (s, *endo*-6-Me), 1.20 (s, *exo*-6-Me), 2.08 (m, 3-CH$_2$), 2.79 (ddd, 4-H$_e$, ^2J –12.2, $^3J_{4e3a}$ 10.3, $^3J_{3e3e}$ 5.4), 3.20 (ddd, 4-H$_a$, ^2J –12.2, $^3J_{4e3a}$ 11.0, $^3J_{4e3e}$ 7.3), 3.78 (dd, $^3J_{2e3a}$ 8.8, $^3J_{2e3e}$ 4.4) (*cf.* ref. 20).

2a, yield 38%, bp 72–74 °C; ^{1}H NMR: 1.33 (d, MeC, ^3J 5.5), 2.43 (s, B-Me), 2.45 (s, A-Me), 2.56 (q, HC, ^3J 5.5); ^{13}C NMR: 11.23 (qd, *Me*C, ^1J 126.7, ^2J 6.1), 38.22 (qd, A-Me, ^1J 135.2, ^3J 2.4), 47.12 (qd, B-Me, ^1J 134.9, ^3J 5.2), 61.14 (dq, CH, ^1J 171.5, ^2J 6.1); MS: 86 (9) [M]$^+$, 85 (19), 71 (50), 57 (50), 56 (72), 44 (13), 43 (20), 42 (100). Picrate of **2a**, mp 103–104 °C.

2b, yield 26%, bp 95–96 °C; ^{1}H NMR: 1.10 (t, MeC, ^3J 7.3), 1.60 and 1.70 (m, CH$_2$, ^2J –13.9), 2.40 (t, HC, ^3J 6.1), 2.45 (s, B-Me), 2.46 (s, A-Me); ^{13}C NMR: 10.10 (qt, *Me*C, ^1J 126.3, ^2J 4.6), 19.0 (tm, CH$_2$, ^1J 126.3, ^2J 4.9), 38.32 (qd, A-Me, ^1J 135.2, ^3J 2.8), 47.36 (qd, ^1J 135.2, ^3J 5.2), 67.25 (dtm, CH, ^1J 169.1, ^2J 5.2); MS: 100 (20) [M]$^+$, 99 (6), 86 (31), 85 (20), 84 (50), 71 (60), 70 (48), 58 (10), 57 (10), 56 (20), 44 (15), 43 (30), 42 (100). Picrate of **2b**, mp 105–106 °C.

2c, yield 33%, bp 103–104 °C; ^{1}H NMR: 1.00 (d, MeC, ^3J 6.6), 1.12 (d, MeC, ^3J 6.6), 1.67 (m, *H*CMe$_2$), 2.11 (d, HC, ^3J 9.3), 2.46 (s, B-Me), 2.49 (s, A-Me); ^{13}C NMR: 17.46 (qm, *Me*C, ^1J 125.3), 18.55 (qdm, *Me*C, ^1J 125.6, ^2J 5.8), 24.00 (ddm, *C*HMe$_2$, ^1J 129.2, ^2J 5.8), 37.50 (qd, A-Me, ^1J 134.7, ^3J 2.6), 46.50 (qd, B-Me, ^1J 134.7, ^3J 5.5), 71.26 (dm, CH, ^1J 167.5); MS: 114 (7) [M]$^+$, 99 (17), 84 (23), 71 (50), 70 (18), 58 (28), 57 (10), 56 (10), 43 (40), 42 (100). Picrate of **2c**, mp 108–109 °C.

2d, yield 28%, bp 50–55 °C (1 Torr); ^{1}H NMR: 2.15 (s, A-Me), 2.62 (s, B-Me), 3.60 (s, HC), 7.37 (m, Ph); ^{13}C NMR: 38.80 (qd, A-Me, ^1J 135.5, ^3J 2.44), 47.30 (qd, B-Me, ^1J 135.1, ^3J 5.3), 66.90 (dm, CH, ^1J 173.3, ^3J 4.7), 127.6, 128.0 and 133.0 (m, Ph); MS: 148 (35) [M]$^+$, 147 (4), 105 (17), 92 (8), 91 (100), 65 (8), 57 (45), 43 (8), 42 (8).

2e, yield 12%, bp 80–85 °C (200 Torr); *trans*-isomer: ^{1}H NMR: 1.08 (s, Bu^t), 2.18 (s, HC), 2.48 (s, B-Me), 2.68 (s, A-Me); ^{13}C NMR: 28.00 (qdh, *Me*$_3$C, ^1J 125.7, ^3J 3.3, ^3J 4.5), 32.00 (dm, Me$_3$*C*, ^2J 4.1), 39.60 (qd, A-Me, ^1J 135.1, ^3J 3.3), 48.60 (qd, B-Me, ^1J 135.1, ^3J 5.7), 73.60 (dm, CH, ^1J 166.4, ^3J 4.9); *cis*-isomer: ^{1}H NMR: 0.88 (s, Bu^t), 2.03 (s, HC), 2.62 (s, MeN); ^{13}C NMR: 24.80 (qdh, *Me*$_3$C, ^1J 125.3, ^3J 2.0, ^3J 4.5), 31.00 (dm, Me$_3$*C*, ^2J 4.1), 37.00 (qd, MeN, ^1J 135.5, ^3J 6.1), 79.80 (dm, ^1J 161.1, ^3J 5.1); MS: 128 (10) [M]$^+$, 113 (4), 86 (40), 84 (62), 72 (14), 71 (100), 57 (11), 43 (16), 42 (38). Picrate of **2e**, mp 140–141 °C.

Benzal methylamine **3**, yield 76%, bp 50–52 °C (5 Torr); ^{1}H NMR: 3.52 (d, Me, ^4J 1.7), 7.4 and 7.7 (m, Ph), 8.30 (q, HC, ^4J 1.7).

Methylimine of pivalic aldehyde **4**, yield 70%, bp 74–76 °C; ^{1}H NMR: 1.10 (s, Bu^t), 3.25 (d, MeN, ^4J 1.6), 7.52 (q, H$_e$, ^4J 1.6).

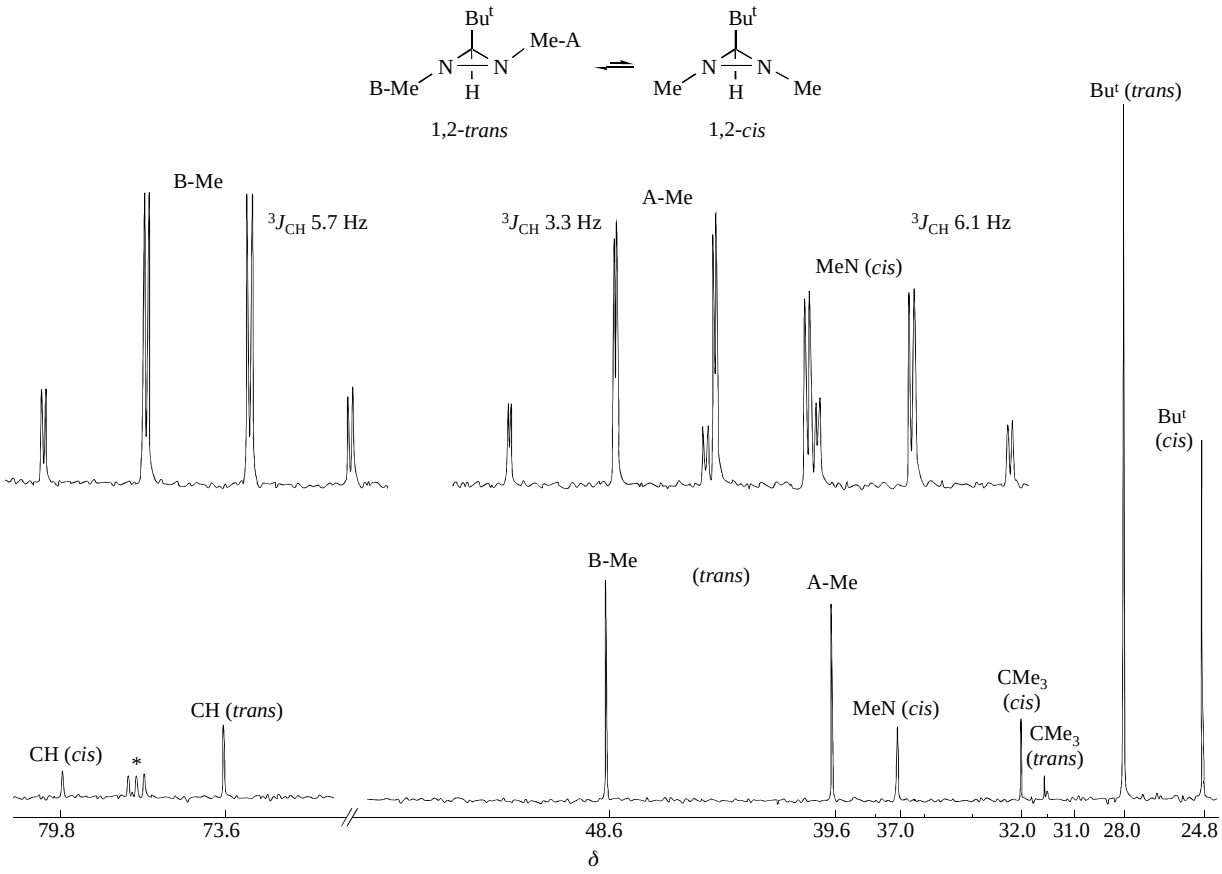


Figure 1 ^{13}C NMR spectrum of **2e** in $CDCl_3$.

The probability of populating the 1,2-*cis*-form in monocyclic 1,2-dimethyl-3-alkyldiaziridine **2** is assumed to be governed by conditions of pure steric control, *i.e.* by destabilization of the 1,2-*trans*-form due to non-bonded interaction of MeN- and RC-substituents, as in unsymmetrically-substituted aziridines **G**[13] and diaziridine **H** where the forms with *cis*-oriented Me groups predominate.[9]

Diaziridines **2a**–**e** were synthesized by a modified method.[14] Previously described compounds **2a**[15] and **2d**[16,17] were not completely studied spectroscopically. Attempts to obtain **2e** by gaseous thermolysis of the corresponding tetrazoline failed, and the latter was cleaved thermally by cycloreversion to imine and azide.‡

The resulting products were characterized by ^{1}H, ^{13}C NMR and mass spectroscopy, as well as by satisfactory elemental analysis of the picrates.† Signals of the 1,2-*trans*-form are assigned on the basis of the high-field shift of the ^{13}C signal of the A-Me group (which differs from those of B-Me by *ca.* 9 ppm due to the shielding γ-effect of the R substituent) and, also, the relationship $^3J_{CH}^{cis} > {}^3J_{CH}^{trans}$ for the carbons of these groups and the ring proton (*cf.* ref. 19) (Figure 1).

Only in the case of **2e** is the expected population of the 1,2-*cis*-form (**2′e**) realized, and equivalency of ^{1}H and ^{13}C for both MeN groups is observed; in addition, the value of $^3J_{CH}$ for the carbons of these groups (6.1 Hz) is close to $^3J_{CH}^{cis}$ of the B-Me group (5.7 Hz) unlike $^3J_{CH}^{trans}$ for the A-Me group (3.3 Hz) (Figure 1). The fact that equivalency of the Me–N groups is also observed in the low-temperature ^{1}H NMR spectrum (at –45 °C, in $CDCl_3$) excludes rigid skewness of the Me–N bonds due to repulsion of the nitrogen lone pairs and Me–N groups. A similar skewness supposed to be present in bicyclic 1,2-*cis*-diaziridines, such as *meso*-2,4-dimethyl-1,5-diazabicyclo[3.1.0]hexane, was also later disproved.[20]

The proportion of 1,2-*cis*-form **2′e** in the equilibrium increases sharply with a rise in the solvent polarity (Scheme 1) in accordance with its own greater polarity compared with that of the 1,2-*trans*-form **2e** (μ = 2.6 and 1.0 D, respectively, by MNDO calculations; for the corresponding forms of unsubstituted diaziridine μ = 3.9 and 1.7 D by 3–21G calculations with full geometry optimization;[8] also known[21] are similar experimental values μ = 2.91 and 1.98 D for the 1,2-*cis*- and *trans*- forms, respectively, of 2-methyl-1,6-diazabicyclo[4.1.0]heptane and 1,2-diethyldiaziridine).

Upon distillation a sample enriched with the 1,2-*trans*-form **2e** was prepared, which made it possible to study the kinetics of isomerization (Scheme 1) by a ^{1}H NMR method (in C_6D_6 at 32 °C) and to obtain the following results: $k_1 = 2.6\times10^{-5}$ ($\pm1.6\times10^{-6}$) s^{-1}, $\Delta G_1^{\#} = 24.3\pm0.04$ kcal mol^{-1}; $k_2 = 7.9\times10^{-6}$ ($\pm4.9\times10^{-7}$) s^{-1}, $\Delta G_2^{\#} = 25.0\pm0.04$ kcal mol^{-1}. Thus, for the first time, nitrogen inversion barriers were measured directly for 1,2-*cis* ↔ *trans* isomerization. This is important for understanding the inversional interconversion mechanism of 1,2-*trans*-diaziridines, which may be visualized as a successive inversion of N atoms *via* a monoplanar

‡ Diaziridine **1** was obtained by reaction of compound **F** with excess of Me_2NH (48 h, 20 °C). After evaporation of solvent the product was extracted with diethyl ether and distilled.

General method for the preparation of diaziridines **2a**–**c**. To a solution of $MeNH_2$ (6.2 g, 200 mmol) in 50 ml of Et_2O, with cooling and stirring, was added dropwise a solution of aldehyde (50 mmol) in 20 ml of Et_2O, after which ground anhydrous K_2CO_3 (3 g) was added. After stirring during 24 h at 20 °C a diethyl ether solution of MeNHCl [obtained by the method[14] from aqueous $MeNH_2$ (50 ml, 80 mmol) and 17% solution of NaOCl (30 ml, 60 mmol)] was added. The mixture was kept for 3 days, then filtered and evaporated and the residue was distilled.

Benzal methylamine **3** was obtained by reaction of benzaldehyde with methylamine in benzene (10 h, 20 °C).

Methylimine of pivalic aldehyde **4** was synthesized using reaction of the aldehyde with an excess of $MeNH_2$ in Et_2O over ground KOH (3 days, 20 °C).

General method for the preparation of diaziridines **2d**,**e**. A mixture of Schiff's base (20 mmol), $MeNH_2$ (60 mmol) and MeNHCl (30 mmol) was kept for 7 days at 20 °C, then filtered and evaporated. The residue was chromatographed on silica gel 40/100 μ (**2d**) or Al_2O_3 [**2e**, the fraction after preliminary distillation, bp 50–85 °C (200 Torr)], with Et_2O as eluent, and then distilled *in vacuo*.

transition state and 1,2-*cis*-intermediate.[3,6,8,9,21] The decrease of $\Delta G_2^{\#}$ for **2e** in comparison with that for diaziridine **C** [$\Delta G_{rac}^{\#}$ = 27.8 kcal mol^{-1} (90 °C) in toluene] can be explained by the greater steric destabilization of the ground state of **2′e**, as in the case of 1-isopropyl-3,3-dimethyldiaziridine ($\Delta G^{\#}$ = 25.2 kcal mol^{-1}).[22]

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