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Tetrahedron: *Asymmetry* 17 (2006) 2191–2194

Tetrahedron: *Asymmetry*

Configurationally stable methylates of methano- and ethano-Tröger bases☆

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Received 10 July 2006; accepted 31 July 2006
Available online 22 August 2006

Abstract—It was discovered that bis-methylation of methano-Tröger base is smooth in pure dimethylsulfate, providing new, configurationally stable, bis-methylate **3a**. Mono- and bis-methylates **2b** and **3b** of ethano-Tröger base were synthesized. The crystal structures of racemic ethano-Tröger base and of its enantiopure methiodide (+)-(5*R*,11*R*)-**2b** benzene clathrate are also reported.
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1. Introduction

The crystal structure of the racemic Tröger's base **1a** (TB) methiodide **2a** dioxane clathrate was reported by Vögtle et al. as a new promising chiral inclusion host.[1] However, easy racemization of this compound through a ring-opened iminium intermediate[2] is an obstacle for its intended use. However, the synthesis of configurationally stable ethano-TB (2,8-dimethyl-6*H*,12*H*-5,11-(1,2-ethano)dibenzo[*b*,*f*][1,5]diazocine) **1b**[3] opened up new possibilities in the chemistry of these bicyclic molecules. Thus, quaternary ammonium salts of the types **2b** and **3b** will have a much higher configurational stability, due to the fact that the aforementioned racemization mechanism will not be possible. Another opportunity to enhance the configurational stability of the chiral TB-derived cationic species is bis-alkylation of the parent compound **1a** to produce structure **3a.** Enantiopure ammonium salts are necessary for different enantioselective applications, such as the preparation of inclusion complexes,[4] ion exchangers,[5] ionic liquids[6] or phase transfer catalysts.[7] Achiral quaternary diammonium cations similar to **3a** and **3b** are efficient DNA compaction reagents.[8]

2. Results and discussion

It has been stated previously that bis-alkylation of TB **1a** is not possible.[1] Therefore, we attempted to methylate **1a** and **1b** in dimethylsulfate—a strongly polar solvent with a high alkylating power.

We have discovered that bis-methylation of parent **1a** is smooth in pure dimethylsulfate, yielding *N*,*N*′-dimethyl bis-methylsulfate **3a**.[9] The structure of the C_2-symmetric cation **3a** in solution was unequivocally proven by NMR spectroscopic data, including NOESY and C–H correlation. Such an ion is stabilized with respect to racemization, and its signals in the ^{1}H NMR spectrum were doubled in the presence of chiral 2,2′-dihydroxy-1,1′-binaphthyl (BINOL).[9]

We have reproduced the synthesis and enantioresolution of **1b**, according to published procedures,[3] and synthesized its enantiopure methiodide (+)-**2b** from (+)-**1b** and methyl iodide.[9] The reaction of (−)-**1b** with dimethylsulfate yielded bis-methylate (−)-**3b**.[9] We herein report the crystal structures of the free base (±)-**1b** and of the methiodide (+)-**2b** (inclusion compound with benzene) (see Table 1 for crystallographic data).[10]

In the crystal structure of the racemic compound **1b** the molecule has a non-crystallographic C_2-symmetry with the twin-twist chair conformation, previously found for similar ring systems.[11] A peculiarity of the molecular

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☆ Asymmetric Nitrogen. Part 98. For part 97, see Ref. 14.

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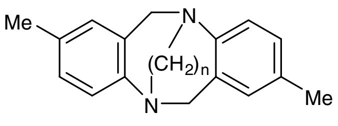
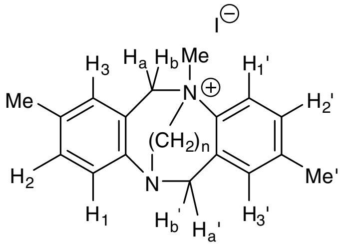
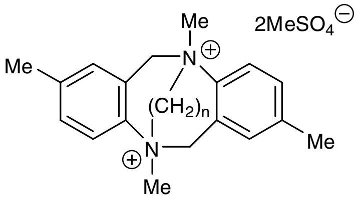
doi:10.1016/j.tetasy.2006.07.041



1a, n=1
1b, n=2



2a, n=1
2b, n=2



3a, n=1
3b, n=2

Table 1. Crystal data and structure refinement parameters for (±)-**1b** and (+)-**2b**

	Compound	
	(±)-**1b**	(+)-**2b**
Empirical formula	$C_{18}H_{20}N_2$	$C_{25}H_{29}IN_2$
Formula weight	264.36	484.40
Crystal colour, habit	colourless prism	yellow prism
Temperature (K)	120(1)	120(1)
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1$
a (Å)	11.610(3)	8.853(2)
b (Å)	13.891(4)	25.596(6)
c (Å)	8.6705(18)	10.737(3)
β (°)	91.422(16)	114.322(5)
V (Å^3)	1397.8(6)	2217.0(10)
$Z(Z')$	4(1)	4(2)
$F(000)$	568	984
D_{calc} (g cm^{-1})	1.256	1.451
Linear absorption, μ (cm^{-1})	0.74	14.57
Scan type	ω	ω
θ Range (°)	2.20–28.0	2.22–29.00
Flack parameter	—	0.01(2)
Reflections measured	6477	24240
Independent reflections	3264 [0.0538]	11406 [0.0538]
Observed reflections [$I > 2\sigma(I)$]	2206	9407
Parameters	261	512
Final $R(F_{hkl})$:R_1	0.0552	0.0550
wR_2	0.1261	0.1335
GOF	1.032	1.0590
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.282; −0.319	0.848, −0.666

structure is the larger angle between the axes of the lone electron pairs of the N atoms in comparison to the parent **1a** (106° in **1a** and 151° in **1b**). The dihedral angle between the RMS planes of the aromatic rings was equal to 89°, while the dihedral angle D(N(1)C(19)C(20)N(10)) in the ethylene bridge was equal to 38° (Fig. 1).

The crystal structure of methiodide (+)-**2b** (inclusion compound with C_6H_6) is characterized by two independent molecules of the salt and of the solvent. The conformation of the molecules is similar to that of **1b**, with dihedral angles between the planes of the aromatic rings equal to 75° and 72°, the dihedral angle D(N(1)C(19)C(20)N(9)) in the ethylene bridge equal to −49.7°. Refinement of the Flack parameter yielded (+)-(5*R*,11*R*) absolute configuration (AC) of the molecules (Fig. 2). The scheme of crystal packing of the inclusion compound is shown in Figure 3.

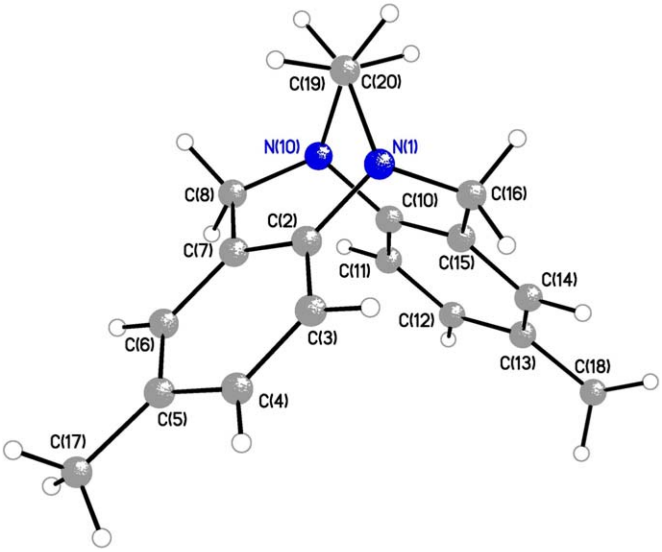


Figure 1. The molecular structure of (±)-**1b** in the crystal.

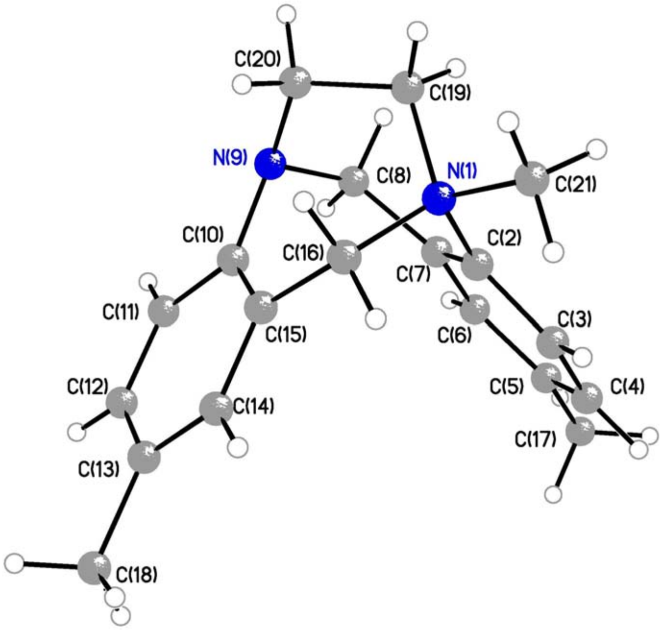


Figure 2. The molecular structure of (+)-(5*R*,11*R*)-**2b** in the crystal.

The CD spectrum of (−)-**1b** (Fig. 4) was used previously to assign the AC based on its 'similarity' with the CD spec-

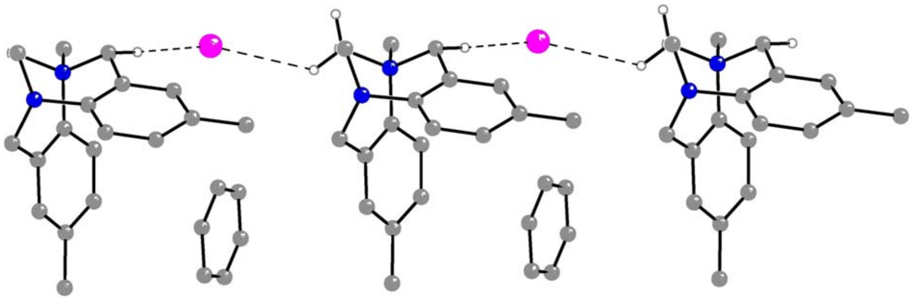


Figure 3. Crystal packing in the inclusion compound of (+)-(5*R*,11*R*)-**2b** with C_6H_6.

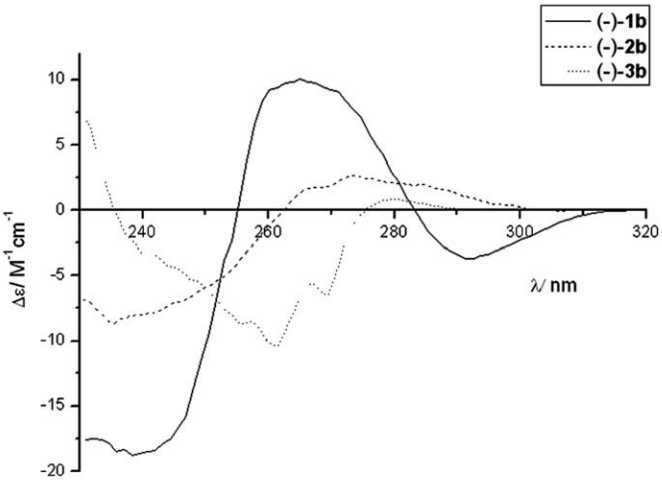
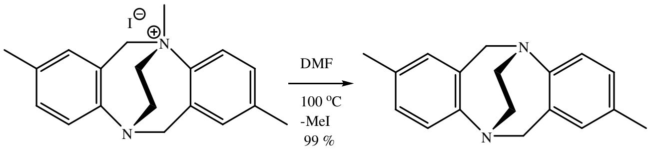


Figure 4. The CD-spectra of (−)-**1b** (MeCN), (−)-**2b** (MeOH), (−)-**3b** (H_2O).



Scheme 1. Desmethylation of (−)-**2b**.

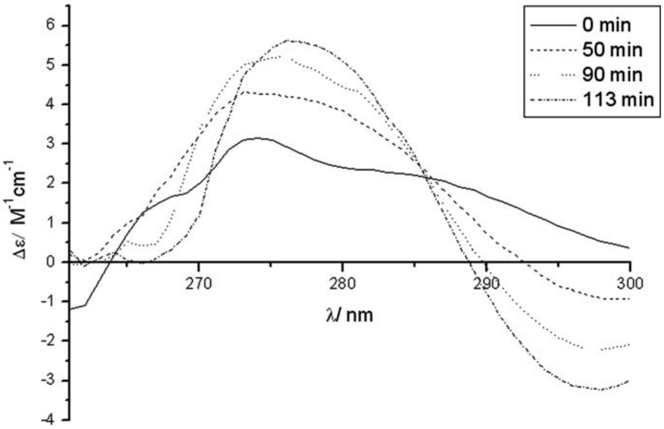


Figure 5. CD spectra changes during the reaction of desmethylation of (−)-**2b** in DMF at 100 °C.

trum of (−)-(5*R*,11*R*)-**1a**.[3] However, according to the X-ray structure determination, the AC of methiodide **2b** is (+)-(5*R*,11*R*), and therefore, by chemical correlation, (−)-**1b** is (5*S*,11*S*). Moreover, the long-wavelength band in the CD spectrum of (−)-**1b** is negative, whereas for (−)-**1a** it is positive,[12] meaning that there is no real similarity in their CD spectra. The CD spectra of **2b** and **3b** (Fig. 4) at room temperature are shown to illustrate their configurational stability.

There are examples in the literature of epimerizations of benzylic ammonium salts on heating.[13] We heated compound (−)-**2b** in DMF at 100 °C to study its possible racemization. To our surprise, we obtained desmethylated free base (−)-**1b** (quantitative isolated yield, identity proven by NMR and CD) with retention of (5*S*,11*S*) configuration (Scheme 1). In Figure 5 the change in the CD spectrum of the reaction mixture with time is depicted. The appearance of the isosbestic point at 285 nm shows that racemization does not occur. A similar desmethylation was observed in MeCN and Bu^{i}OH, and probably occurs due to equilibration to methyl iodide and free base. Similarly, we observed smooth desmethylation of **3a** to **2a** [3 h in DMSO at 120 °C, quantitative yield (NMR)], and of **3b** to **2b** (90% yield under the same conditions). We observed MeOH signals in the reaction mixtures and a significant downfield shift of a residual water signal, probably due to the liberation of the acid. Thus, our compounds might serve as mild chiral methylating reagents.

3. Conclusion

In conclusion, we have obtained several synthetic chiral configurationally stable ammonium salts, which might be used for different enantioselective applications.

Acknowledgements

This work was supported by the Russian Foundation for Basic Research (Grant Nos. 06-03-32840 and 03-03-04010), the Russian Academy of Sciences (Nefedov-Tartakovsky programmes) and INTAS (Grant No. YS 04-83-3442). We are grateful to Dr. M. Zähres (University of Duisburg-Essen) for NMR studies.

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9. Racemic (±)-**1b** (mp 162–164 °C, large prisms from EtOAc) and enantiomeric (+)- and (−)-**1b** (mp 132–134 °C, CH_2Cl_2) were prepared as described previously.[3] Compound (±)-**3a** was obtained from (±)-**1a** after 3 h in 5 mol equiv of $(CH_3)_2SO_4$ at 100 °C as white crystalline mass. Yield 90%, mp 160 °C dec. ^{1}H NMR (400 MHz, CD_3OD), δ, ppm, J, Hz: 2.34 (s, 6H, MeAr, Me′Ar), 3.64 ($MeOSO_3^-$, s, 6H), 4.19 (s, MeN, 6H), 5.41 (d, $^2J = -15$, 2H, H_a, H_a'), 5.57 (d, $^2J = -15$, 2H, H_b, H_b'), 6.12 (s, 2H, NCH_2N), 7.22 (s, H_3, H_3'), 7.56 (d, $^3J = 8.8$, H_2, H_2'), 8.12 (d, $^3J = 8.8$, H_1, H_1'). In the presence of 100 mol % of (*S*)-(−)-binaphthol signals at 2.34 and 4.19 showed splitting into doublets (0.01 ppm at 400 MHz). For $C_{21}H_{30}N_2O_8S_2{*}H_2O$ calc C, 48.45; H, 6.20; N, 5.38. Found: C, 49.06; H, 5.78; N, 5.41.

   Compound (−)-**2b** × C_6H_6 was obtained as a viscous oil from (−)-**1b** after 24 h in 10 mol excess of the mixture MeI/MeOH 1:1 at 25 °C. It was then crystallized from CH_2Cl_2/benzene in 95% yield to give large yellowish crystals. Mp. 150–153 °C dec. [α] (λ, nm, *c* 2, CH_2Cl_2) = −41 (578); −47 (546); −100 (436); −113 (406). ^{1}H NMR ($CDCl_3$), δ, ppm, J, Hz: 2.01 (s, 3H, MeAr), 2.11 (s, 3H, Me′Ar), 3.73 (dd, $^2J = -16$, ^3J 5, 1H, $(CH_2)_2$), 4.00 (ddd, $^2J = -16$, $^3J = 13.5$, $^3J = 5$, 1H, $(CH_2)_2$), 4.35 (s, 3H, MeN), 4.38 (d, $^2J = -18$, 1H, H_a'), 4.43 (td, $|^2J| = {}^3J = 13.5$, $^3J = 5$, 1H, $(CH_2)_2$), 4.77 (d, $^2J = -18$, 1H, H_b'), 5.08 (dd, $^2J = -13.5$, $^3J = 5$, 1H, $(CH_2)_2$), 5.19 (d, $^2J = -15.4$, 1H, H_a), 6.23 (d, $^2J = -15.4$, 1H, H_b), 6.77 (s, 1H, H_3), 6.80 (s, 1H, H_3'), 6.90 (AB-quartet, $^3J = 8.5$, $\Delta\nu = 11$, 2H, H_1, H_2), 6.98 (d, $^3J = 8.7$, 1H, H_2'), 7.36 (s, C_6H_6, 6H), 7.88 (d, $^3J = 8.7$, 1H, H_1'). For $C_{25}H_{29}IN_2$ calcd (%): H,6.03; C, 61.99; I, 26.20; N, 5.78. Found (%): H, 6.04; C, 61.80; I, 26.19; N, 5.90. Compound (+)-**2b** iodide was obtained in a similar manner and had similar properties.

   Compound (−)-**3b** was obtained from (−)-**1b** after 16 h in 10 mol equiv of MeCN (reflux) with 30% excess Me_2SO_4 as oil, insoluble in MeCN/Et_2O. Yield 90%. [α] (λ, nm, *c* 2, H_2O) = −2 (578); −3 (546); −8 (436); −10 (406). ^{1}H NMR (CD_3OD), δ, ppm, J, Hz: 2.26 (s, 6H, MeAr, Me′Ar), 3.67 (s, 6H, 2MeO), 4.15 (s, 6H, 2MeN), 4.65 (m, 2H, $(CH_2)_2$), 5.08 (m, 2H, $(CH_2)_2$), 5.17 (d, $^2J = -15.7$, 2H, H_a, H_a'), 5.86 (d, $^2J = -15.7$, 2H, H_b, H_b'), 7.12 (s, 2H, H_3, H_3'), 7.40 (d, $^3J = 8.6$, 2H, H_2, H_2'), 7.86 (d, $^3J = 8.6$, 2H, H_1, H_1'). ^{13}C NMR (CD_3OD): 20.56 (q, $^1J = 127$), 58.89 (q, $^1J = 147$), 62.80 (t, $^1J = 149$), 71.63 (t, $^1J = 151$), 123.08 (d, $^1J = 163$), 126.57 (s), 133.59 (d, $^1J = 163$), 134.08 (d, $^1J = 163$), 141.54 (s), 143.36 (s). This salt was not characterized by elemental analysis due to its hydroscopic character.
10. X-ray diffraction experiments were carried out with a Bruker SMART 1000 CCD area detector, using graphite monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å, ω-scans) at 120 K. The low temperature of the crystals was maintained with a Cryostream (Oxford Cryosystems) open-flow N_2 gas cryostat. Reflection intensities were integrated using SAINT software and adsorption correction was applied semi-empirically using SADABS program. The structures were solved by a direct method and refined by the full-matrix least-squares against F^2 in anisotropic approximation for no-hydrogen atoms. The positions of hydrogen atoms were calculated from the geometrical point of view. All calculations were performed using the SHELXTL software. The crystallographic data have been deposited with the Cambridge Crystallographic Data Center, CCDC-608809 for (±)-**1b** and CCDC-608810 for (+)-**2b**. Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).
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