Z/*E* isomerisation of ferrocenyl- and arylmethylidene-substituted derivatives of quinuclidine and camphor

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2-Ferrocenylmethylidene-3-methyl-1-azoniabicyclo[2,2,2]octane-3-cation and 2-ferrocenylmethylidene-1,2,7,7-tetramethylbicyclo-[2,2,1]heptane-2-cation tetrafluoroborates and tetraphenylborates having bulky substituents in their molecules have been found to isomerise in solutions with inversion of configuration at the double bond. Tetrafluoroborates and tetraphenylborates of the 3-methyl-2,3-(1-piperidinium-1,4-diyl)-1-ferrocenylallyl cation and the 3-methyl-2,3-(1,2,2-trimethylcyclopentane-1,3-diyl)-1-ferrocenylallyl cation with bulky substituents at the C_1 atom isomerise in solutions with inversion of configuration at the C_1–C_2 bond.

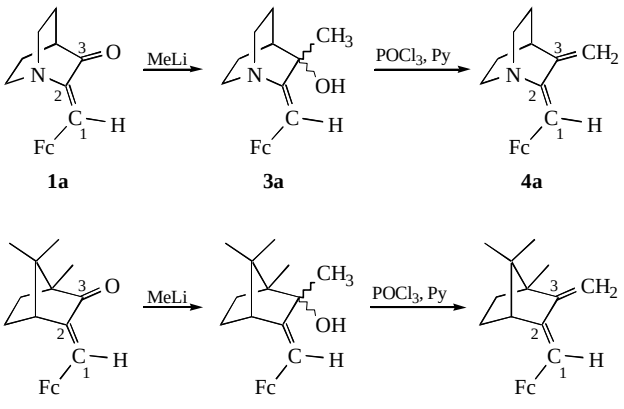
2-Ferrocenylmethylidenequinuclidone **1a**[1,2] and 3-ferrocenylmethylidenecamphor **2a**,[3,4] prepared by condensation of 3-quinuclidone and camphor hydrochlorides with ferrocenecarbaldehyde in the presence of bases, are formed as the *Z*-isomer in the case of **1a** and as mostly *E*-isomer for compound **2a**. These *Z*- and *E*-configurations at the C_1=C_2 double bonds are retained in s-*cis*-ferrocenyl-1,3-dienes **4a** and **6a** synthesised from **1a** and **2a**[1–3] (Scheme 1).

According to tentative data, compounds **1a**–**6a** exhibit fairly high antiviral activities.[2,3]

It is well known that various isomers of the same compound can exhibit different biological activities. Therefore, it is of interest to compare the dependences of biological activities of compounds on their structures for compounds based on *Z*- and *E*-isomers with s-cisoid conformations of the molecules.

In this work, we have studied *Z*/*E* isomerisation of ferrocenyl- and arylmethylidene-substituted derivatives of quinuclidine and camphor.†

We found that treatment of compounds **3a**, **4a**, **5a** and **6a** with HBF_4 or $HBPh_4$ yields salts of the *Z*-2-ferrocenylmethylidene-3-methyl-1-azoniabicyclo[2,2,2]octane-3-cation **7a**,**b** and *E*-2-ferrocenylmethylidene-1,2,7,7-tetramethylbicyclo[2,2,1]heptane-2-cation **8a**,**b**, respectively.

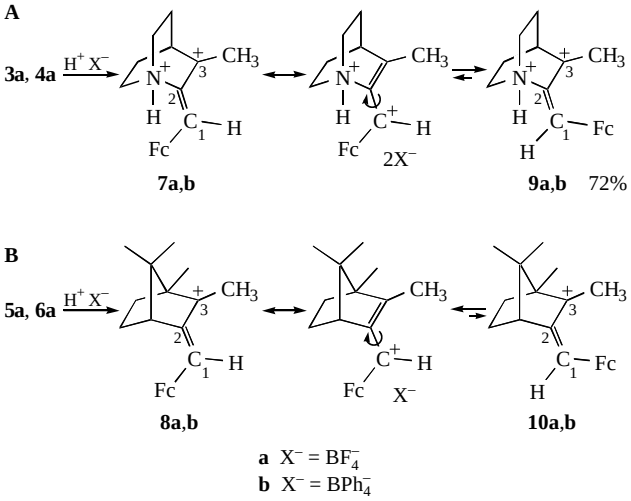


1a **3a** **4a**

2a **5a** **6a**

Scheme 1

† *Typical procedure*. An initial compound (**1**–**6**, 2 mmol) was added to a solution of a 50% excess of $NaBPh_4$ in 20 ml of glacial acetic acid.[13] The mixture was stirred at 70–80 °C for 6 h, cooled to 20 °C and poured into 100 ml of a 5% solution of Na_2CO_3. The products were extracted with benzene. After evaporation of the solvent, the residue was subjected to chromatography on Al_2O_3 (activity grade III) using hexane as the eluent. This yielded two products. The yields of the products are presented in the Schemes.



Scheme 2

According to the accepted classification,[5,6] the salts **7a**,**b** and **8a**,**b** contain 'exterior' bulky substituents at the C_1 and C_3 atoms and a 'vertex' substituent at the C_2 atom in the allylic system. The substituents at C_2 and C_3 are rigidly linked to each other in the cyclic structures. All this makes the molecules sterically strained[7] and enables their *Z*/*E* isomerisation.

In fact, our study of the ^{1}H NMR spectra (TMS, Bruker CXP-200 spectrometer) of the tetrafluoroborates **7a** and **8a**[3] at room temperature has shown that *Z*-**7a** gradually isomerises into *E*-**9a**, and *E*-**8a**[3] gradually isomerises into *Z*-**10a**,‡ which is manifested as a doubling of all the ^{1}H NMR signals (Scheme 2).

The integrated intensities of the corresponding signals in the equilibrium state indicate that in mixtures **A** and **B**,

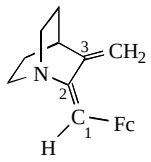
‡ *Z*-**7a**: ^{1}H NMR (CD_2Cl_2) δ: 2.08 (m, 2H), 2.32 (m, 2H), 2.42 (s, 3H, CH_3), 3.30 (m, 1H), 3.46 (m, 2H), 3.98 (m, 2H), 5.29 (s, 5H, C_5H_5), 4.98 (m, 1H, C_5H_4), 5.34 (m, 1H, C_5H_4), 6.52 (m, 2H, C_5H_4), 7.84 (s, 1H, CH–Fc), 9.01 (s, 1H, NH). Found (%): C 45.84, H 4.77, B 4.63, F 30.83, Fe 11.42, N 3.04. Calc. for $C_{19}H_{23}B_2F_8FeN$ (%): C 46.08, H 4.68, B 4.44, Fe 11.28, N 2.82. Decomp. 210–215 °C.

E-**9a**: ^{1}H NMR (CD_2Cl_2) δ: 2.06 (m, 2H), 2.25 (m, 2H), 2.37 (s, 3H, CH_3), 3.25 (m, 1H), 3.44 (m, 2H), 3.96 (m, 2H), 5.26 (s, 5H, C_5H_5), 4.97 (m, 1H, C_5H_4), 5.30 (m, 1H, C_5H_4), 6.47 (m, 1H, C_5H_4), 6.50 (m, 1H, C_5H_4), 7.80 (s, 1H, CH–Fc), 8.80 (s, 1H, NH). Found (%): C 46.23, H 4.52, B 4.32, Fe 11.41, N 3.07. Calc. for $C_{19}H_{23}B_2F_8FeN$ (%): C 46.08, H 4.68, B 4.44, Fe 11.28, N 2.82. Decomp. 203–209 °C.

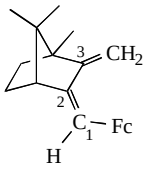
Z-**10a**: ^{1}H NMR (CD_2Cl_2) δ: 0.79 (s, 3H), 0.92 (s, 3H), 1.13 (s, 3H), 1.81 (s, 3H), 1.65 (m, 2H), 1.72–1.83 (m, 2H), 3.46 (m, 1H), 4.85 (s, 5H, C_5H_5), 4.96 (m, 1H, C_5H_4), 5.38 (m, 1H, C_5H_4), 6.07 (m, 1H, C_5H_4), 6.20 (m, 1H, C_5H_4), 8.42 (s, 1H, CH–Fc). Found (%): C 60.59, H 6.32, B 2.29, Fe 13.04. Calc. for $C_{22}H_{27}BF_4Fe$: C 60.84, H 6.27, B 2.53, F 17.50, Fe 12.86. Decomp. 240–244 °C.

respectively, the isomer **9a** predominates by a factor of *ca.* 3 (after 16 h), and the initial **8a** predominates by a factor of 1.5 after about the same period.

Thus, the salts **7a**/**9a** and **8a**/**10a** isomerise in solutions with inversion of configuration at the C_1–C_2 bond. Upon treatment of equilibrium mixtures **A** and **B** with *N*,*N*-dimethylaniline, isomeric s-*cis*-1,3-dienes *E*-**4b** and *Z*-**6b**[§] were isolated.



E-**4b** ~70%



Z-**6b** ~40%

The hindered rotation around allylic bonds,[8–10] the geometries of alkenyl cations and steric interactions in them for bulky substituents[10–12] have been thoroughly studied in relation to hydroxyallyl carbocations including ferrocene cations. The ferrocenylchalcones used previously for protonation and for the preparation of oxyallylic cations are linear and exist as mixtures of s-*cis*- and s-*trans*-conformers.[13] Since α-ferrocenyl carbocations are chiral,[12,13] in some cases this results in the formation of mixtures of two diastereoisomeric hydroxyallyl cations owing to free rotation around the single C_2–C_3 bond in the initial compounds.

We isolated the solid tetrafluoroborates *Z*-**7a** and *E*-**8a** as single isomers. These compounds can isomerise only *via* rotation around the C_1–C_2 allylic bond, despite the fact that this rotation is hindered. In our opinion, in this particular case, the rotation is facilitated by the following factors:

1. The marked ability of ferrocene to stabilise the positive charge in the α-ferrocenyl carbocations.[8,9] When no other strong stabilisers of the cationic centre are present in the position 3 of the allylic system, the positive charge is largely localised on the C_1 carbon atom.

2. The influence of the bulky BF_4 anion, which promotes isomerisation leading to a sterically more strained 'internal' arrangement of the CH_3 and Fc groups. This influence is especially pronounced in the case of quinuclidine derivatives, which also contain an ammonium centre.

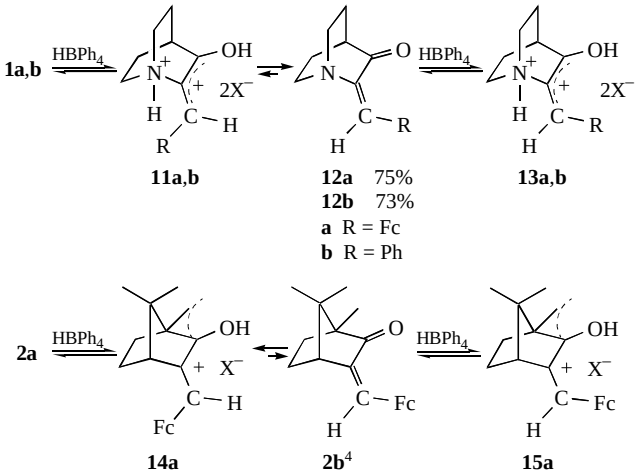
This conclusion is confirmed by the fact that for camphane derivatives, the degree of inversion of the configuration is smaller. An increase in the size of the anion also increases the degree of isomerisation. For tetraphenylborates, the following ratios of the isomeric allyl cations in the mixtures were obtained: *Z*-**7b**:*E*-**9b** = 3:17; *E*-**8b**:*Z*-**10b** = 1:1.

We also found that 2-ferrocenyl- and 2-arylmethylidene-ketones with fixed s-*cis*-conformations of the double bonds undergo *Z*/*E*-isomerisation. It is most convenient to carry out this reaction by treatment of the substrates with $HBPh_4$.

Evidently, the inversion of configuration occurs by a similar scheme including the intermediate formation of cations **11a**,**b** and **13a**.[¶]

We were not able to isolate the tetraphenylborates **11a**,**b** and **14a** in a stable crystalline form.

However, we recorded satisfactory ^{1}H NMR spectra of solutions of the compounds **1a** and **12a**[¶] in CF_3COOH. The spectra indicate that the carbonyl group is protonated and that hydroxyallyl carbonium and ammonium ions **11a** and **13a** are formed. The observed signals are broadened, probably due to exchange processes. The samples decompose with time; therefore, it is impossible to follow the dynamics of *Z*/*E*-isomerisation.



Scheme 3

The method proposed can be used to carry out preparative *Z*/*E*-isomerisation of s-*cis*-aryl- and ferrocenylmethylidene-ketones and of s-*cis*-1,3-dienes having bulky substituents at the C_1 atom of the diene system (ferrocenyl, biphenyl, naphthyl, *etc*.). Isomerisation of 1,3-dienes with less bulky substituents (phenyl) is accompanied by dimerisation and polymerisation.

According to a preliminary biological assay, ferrocene-containing compounds **1a**,**b**–**6a**,**b** possess high antiviral (relative to smallpox, tick caused encephalitis, type I and II herpes viruses) and also antistaphylococcus activity.

References

1 E. I. Klimova, L. R. Ruis, M. G. Martinez, N. N. Meleshonkova and A. Marin-Bessera, *Dokl. Ross. Akad. Nauk*, 1996, **351**, 776 [*Dokl. Chem.* (*Engl. Transl.*), 1996, **351**, 320].

2 E. I. Klimova, L. R. Ruis, M. G. Martines and N. N. Meleshonkova, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 2743 (*Russ. Chem. Bull.*, 1996, **45**, 2602).

3 V. N. Postnov, E. J. Klimova, M. Martinez Garcia, N. N. Meleshonkova, V. V. Rybakov and L. A. Aslanov, *J. Organomet. Chem.*, 1994, **476**, 189.

4 M. Salisova, M. Puciova, V. N. Postnov and S. Toma, *Chem. Pap., Chem. Zvesti.*, 1990, **44**, 201.

5 W. F. Sliwinski, T. M. Su and P. von R. Schleyer, *J. Am. Chem. Soc.*, 1972, **94**, 133.

6 P. von R. Schleyer, T. M. Su, M. Saunders and J. C. Rosenfeld, *J. Am. Chem. Soc.*, 1969, **91**, 5174.

7 D. M. Dytnerski, K. Ranganayakulu, B. P. Singh and T. S. Sozensen, *Canad. J. Chem.*, 1982, **60**, 2993.

8 G. A. Olah and R. J. Spear, *J. Am. Chem. Soc.*, 1975, **97**, 1539.

§ *E*-**4b**: ^{1}H NMR ($CDCl_3$) δ: 1.72 (m, 4H), 2.50 (m, 1H), 3.01 (m, 4H), 4.11 (s, 5H, C_5H_5), 4.20 (m, 2H, C_5H_4), 4.44 (m, 2H, C_5H_4), 4.99 (d, 1H, *J* 1.38 Hz, CH_2=), 5.47 (d, 1H, *J* 1.38 Hz, CH_2=), 6.22 (s, 1H, CH=). Found (%): C 71.28, H 6.78, Fe 17.31, N 4.25. Calc. for $C_{19}H_{21}Fe$ (%): C 71.49, H 6.63, Fe 17.50, N 4.38. Mp 63–64 °C.

Z-**6b**: ^{1}H NMR ($CDCl_3$) δ: 0.63 (s, 3H), 0.93 (s, 3H), 1.00 (s, 3H), 1.20–1.95 (m, 4H), 2.77 (m, 1H), 4.10 (s, 5H, C_5H_5), 4.17 (m, 2H, C_5H_4), 4.30 (m, 2H, C_5H_4), 4.53 (s, 1H, CH_2=), 5.00 (s, 1H, CH_2), 6.17 (s, 1H, CH=). Found (%): C 76.42, H 7.28, Fe 16.18. Calc. for $C_{22}H_{26}Fe$ (%): C 76.30, H 7.57, Fe 16.13. Orange oil.

¶ *Z*-**1b**: ^{1}H NMR ($CDCl_3$) δ: 2.00 (m, 4H), 2.63 (m, 1H), 3.11 (m, 4H), 6.80 (s, 1H, CH=), 7.38 (m, 3H, Ph), 7.90 (m, 2H, Ph). Found (%): C 78.74, H 7.21, N 6.63. Calc. for $C_{14}H_{15}NO$ (%): C 78.84, H 7.09, N 6.56. Yellow crystals, mp 134–135 °C.

E-**12a**: ^{1}H NMR ($CDCl_3$) δ: 1.94 (m, 4H), 2.61 (m, 1H), 3.06 (m, 4H), 4.13 (s, 5H, C_5H_5), 4.44 (m, 2H, C_5H_4), 5.00 (m, 2H, C_5H_4), 6.61 (s, 1H, CH=). Found (%): C 67.18, H 6.02, Fe 17.53, N 4.39. Calc. for $C_{18}H_{19}FeNO$ (%): C 67.30, H 5.98, Fe 17.39, N 4.36. Violet crystals, mp 113–114 °C.

E-**12b**: ^{1}H NMR ($CDCl_3$) δ: 2.05 (m, 4H), 2.62 (m, 1H), 2.90–3.25 (m, 4H), 7.02 (s, 1H, CH=), 7.35 (m, 3H, Ph), 8.05 (m, 2H, Ph). Found (%) C 79.01, H 6.87, N 6.61. Calc. for $C_{14}H_{15}NO$ (%): C 78.84, H 7.09, N 6.56. Mp 74–75 °C.

11a: ^{1}H NMR (CF_3COOH) δ: 2.12 (m, 2H), 2.28 (m, 2H), 2.98 (m, 1H), 3.35 (m, 2H), 3.71 (m, 2H), 5.78 (s, 5H, C_5H_5), 5.68 (m, 1H, C_5H_4), 5.73 (m, 1H, C_5H_4), 6.25 (m, 2H, C_5H_4), 8.05 (s, 1H, CH–Fc), 8.40 (br. s, 1H, NH).

13a: ^{1}H NMR (CF_3COOH) δ: 2.10 (m, 2H), 2.30 (m, 2H), 2.87 (m, 1H), 3.34 (m, 2H), 3.84 (m, 2H), 5.64 (s, 5H, C_5H_5), 5.28 (m, 1H, C_5H_4), 5.68 (m, 1H, C_5H_4), 6.23 (m, 2H, C_5H_4), 7.96 (s, 1H, CH–Fc), 8.21 (br. s, 1H, NH).

9 W. G. Young, S. U. Sharman and S. Winstein, *J. Am. Chem. Soc.*, 1960, **82**, 1376.
10 M. J. A. Habib, J. Park and W. E. Walts, *J. Chem. Soc., C*, 1970, 2556.
11 G. Olah and M. Mayer, *J. Am. Chem. Soc.*, 1976, **98**, 7333.
12 T. P. Turbitt and W. E. Walts, *J. Am. Chem. Soc., Ser. D.*, 1973, 182.
13 V. N. Postnov, Yu. N. Polivin, D. V. Bazhenov and V. A. Sazonova, *Dokl. Akad. Nauk SSSR*, 1984, **276**, 373 (in Russian).

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