SYNTHESIS AND RESOLUTION OF BIS- AND TRIS-(BENZIMIDAZOL-1-YL)METHANES

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(Dedicated to Professor Edward C. Taylor on the occassion of his 70th birthday)

Abstract —Bis- and tris-(benzimidazol-1-yl)methane deriva-tives are reported with different substituents at position 2 of the benzimidazole ring. When the substituents are large enough, these compounds, even the bis-derivatives, can be resolved using hplc on CHIRALPAK OT(+) columns. For some compounds, the racemization barriers have been measured and their steric origin ascertained ($\Delta G^{\ddagger} = a + b$ MR, MR being the molar refractivity).

In preceding papers,[1,2] we have described the propeller-like conformation of poly-benzimidazolylmethanes and their spectral properties. In the first one,[1] the chromatographic resolution on microcrystalline cellulose triacetate (MCTA), the X-ray structures of the racemic and that of one enantiomer and the dynamic nmr study of tris(2-methylbenzimidazol-1-yl)methane (**2a**) were described. The second publication,[2] dealt with bis(2-substituted benzimidazol-1-yl)methanes (**1**), with **a**, R = CH_3, **b**, R = C_2H_5, **d**, R = *t*-C_4H_9 and **e**, R = 1-adamantyl. The use of ^{13}C nmr spectroscopy as well as dipole moments and molar Kerr constants, allowed us to determine the major conformations of these last compounds in solution.

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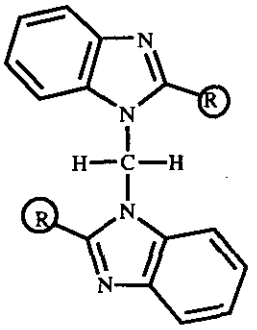

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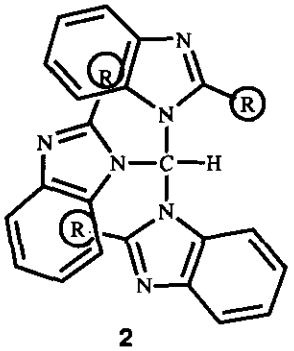

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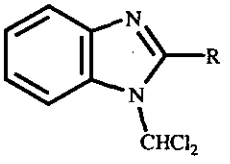
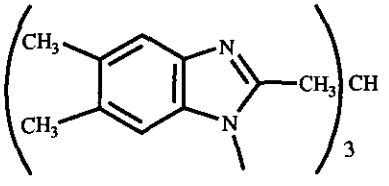
R = CH_3 (**a**), C_2H_5 (**b**), i-C_3H_7 (**c**), *t*-C_4H_9 (**d**), 1-adamantyl (**e**), Cl (**f**), 1-piperidyl (**g**)

In this paper, we report the synthesis, enantiomeric resolution and spectral characteristics of derivatives (**1**) and (**2**) for **a**, R = CH_3, **b**, R = C_2H_5, **c**, R = i-C_3H_7, **d**, R = *t*-C_4H_9, **e**, R = 1-adamantyl, **f**, R = Cl, and **g**, R = 1-piperidyl.

Synthesis. Derivatives (**1**) and (**2**) were prepared from 2-R-1*H*-benzimidazoles (R being the substituent at position 2) by reaction with dichloromethane and trichloromethane (chloroform) under solid-liquid (KOH) phase transfer catalysis but with experimental conditions a little different from those described for compounds (**1a**),[3-5] and (**2a**).[1,6] In the case of R = *t*-C_4H_9 and R = 1-adamantyl, the tris-derivatives (**2d**) and (**2e**) cannot be obtained for obvious steric reasons. Only very small amount of compounds (**3d**) and (**3e**), were isolated. Starting from 1*H*-2,5,6-trimethylbenzimidazole, the tris-derivative (**2h**) was also prepared.





3d, R = *t*-C_4H_9, **3e**, R = 1-adamantyl **2h**

Enantiomeric resolution on a chiralpak OT(+) hplc column. The results obtained at 10°C with this column,[7] are reported in Table 1; nearly baseline separations are obtained in most cases

except for **1e**. The remaining compounds (**1a-1c**, **1f**, **1g**, **2g**) were not resolvable under these conditions.

Chromatographic chiral separations were carried out on a CHIRALPAK OT(+) column (250 x 4.6 mm). Reference: acetone (V_0); eluent: methanol [filtered over Millipore HV type (0.45 μm) and ultrasound degassed] ; temperatures and pressures: -10°C (21 bars), 0°C (19 bars), 10°C (17 bars) and 14.5°C (16 bars); flow rate: 0.5 ml/min.; concentration: about 0.1 mg of racemic in 1 ml methanol (all solutions were filtered over Millipore HV type filters). UV Merck-Hitachi Lichtograph model L4000 (λ = 254 nm) and 241 MC PERKIN ELMER polarimeters (λ = 436 nm) were used for the detection. The separation coefficient α is defined as $(V_2-V_0/V_0)/(V_1-V_0/V_0)$.

Table 1

Compound	-10°C		0°C		10°C		14.5°C	
	k'_1	α	k'_1	α	k'_1	α	k'_1	α
Bis **1d**	0.35	1.22	0.34	1.35	0.33	1.43	0.32	1.45
Bis **1e**	1.91	1.09	1.87	1.16	1.74	1.17	1.72	1.18
Tris **2a**	0.78	1.33	0.71	1.32	0.64	1.31	0.61	1.30
Tris **2b**	1.13	1.21	1.02	1.26	0.94	1.34	0.88	1.33
Tris **2c**	0.92	1.48	0.93	1.50	0.92	1.45	0.91	1.44
Tris **2f**	1.88	1.63	1.83	1.62	1.62	1.56	1.59	1.53
Tris **2h**	1.19	1.26	1.08	1.27	0.98	1.26	0.94	1.26

Few examples of resolution of residual enantiomers[8,9] of Ar_3CH systems are known, **2a** being one of the rare cases reported in the literature. We have extended the resolution to a whole family of such derivatives, and, more significantly, we report two examples of resolution of Ar_2CH_2 systems.

Racemization experiments. Preparative separations of enantiomers were achieved on MCTA at room temperature (25°C) as previously described,[1] the enantiomeric purity being checked by ^1H nmr spectroscopy in $CDCl_3$ in the presence of Pirkle's alcohol;[1] in all cases, the (+) enantiomer appears first. Surprisingly, the tris-derivative (**2g**) was resolvable on this chiral support.

Racemizations were carried out on enriched samples in diglyme at different temperatures by measuring the decrease of the rotatory power with time. The data were processed using the RACEM program;[10] the results correspond to first-order kinetics. Here are the barriers thus determined: **2a**, $\Delta G^{\ddagger}_{343}$ = 119.12 ± 0.17 kJ mol^{-1}; **2b**, $\Delta G^{\ddagger}_{360}$ = 125.60 ± 0.17 kJ mol^{-1}; **2c**, $\Delta G^{\ddagger}_{393}$ = 129.81 ± 0.17 kJ mol^{-1}; **2h**, $\Delta G^{\ddagger}_{343}$ = 115.73 ± 0.17 kJ mol^{-1}.

Amongst the steric effects,[11-13] we have selected three: E_s^o, v_{eff} and MR. For the three compounds that form an homogeneous set, **2a**-**2c**, these parameters have the following values: E_s^o (-1.24, -1.51 and -2.09),[11] v_{eff} (0.52, 0.56 and 0.76)[12] and MR (5.7, 10.3 and 15.0).[13] The corresponding barriers are linearly related to these parameters:

$$\Delta G^{\ddagger} = 120.46 - 11.73\ E_s^o,\ n = 3,\ r = 0.95 \qquad [1]$$

$$\Delta G^{\ddagger} = 102.17 + 36.96\ v_{eff},\ n = 3,\ r = 0.88 \qquad [2]$$

$$\Delta G^{\ddagger} = 112.97 + 1.1485\ MR,\ n = 3,\ r = 0.99 \qquad [3]$$

Thus, the barrier to the racemization in these 'propeller-like' compounds is of steric origin.

EXPERIMENTAL

Melting points were determined in a capillary tube and are uncorrected. Analytical thin layer chromatography was performed on silicagel Merck Kieselgel 60 F_{254} with a thickness layer of 0.2 mm and column chromatography on silicagel Merck 60 (70-230 mesh) using dichloromethane/ethanol (95/5) as eluent. ^{1}H Nmr (200.13 MHz) and ^{13}C nmr (50.32 MHz) spectra were obtained using a Bruker AC-200 instrument. Chemical shifts (δ) in ppm and coupling constants (*J*) in Hz were measured using Me_4Si as internal standard. The chemical shifts are accurate to 0.01 and 0.1 ppm for ^{1}H and ^{13}C nmr, respectively. Coupling constants are accurate to 0.2 Hz for ^{1}H nmr and to 0.5 Hz for ^{13}C nmr.

The starting 2-substituted 1*H*-benzimidazoles were obtained as follows: 2-methyl-, 2-ethyl-, 2-i-propyl-, 2-*t*-butyl-, 2-chloro- and 2,5,6-trimethylbenzimidazoles were commercial products. 2-Adamantyl-1*H*-benzimidazole was prepared according to Sasaki's procedure[14] and 2-(1-piperidyl)-1*H*-benzimidazole according to Ricci and Vivarelli's procedure.[15]

Synthesis of bis(benzimidazol-1-yl)methanes. Derivatives (**1a**, **1b**, **1d** and **1e**) have already been described.[2] The remaining compounds (**1c**, **1f**, **1g**) were prepared by the same experimental procedure (Table 2).

Table 2

Compd	t (h)	cat (mmol)	KOH (mmol)	Yield (%)	mp (°C)	R_f	Analysis (%) Found C	H	N	Calcd C	H	N
1c	7	10	35.7	88	245	0.31	76.03	7.50	17.04	75.86	7.28	16.86
1f	7	10	48	13	>330	0.44	56.87	3.02	17.40	56.80	3.18	17.67
1g	5	10	36.6	76	255-256	0.44	72.44	7.17	20.37	72.43	7.29	20.28

Synthesis of tris(benzimidazol-1-yl)methanes. In a round-bottom flask provided with a refrigerant and mechanical stirring were introduced 10 mmol of 2-substituted 1*H*-benzimidazole, 50 ml of trichloromethane, tetrabutylammonium bromide (see Table 3) and carefully powdered potassium hydroxide (see Table 3). The mixture is vigorously stirred at room temperature during the time indicated in Table 3. The solids are filtered off, the solvent was evaporated under vacuum and the residue was purified by column chromatography over silica gel using dichloromethane/ethanol (95/5) as eluent.

Table 3

Compd	t (h)	cat (mmol)	KOH (mmol)	Yield (%)	mp (°C)	Rf	Analysis(%) Found C	H	N	Calcd C	H	N
2b	1	10	20	34	216-217	0.28	75.07	6.51	19.03	74.97	6.29	18.74
2c	3	3.3	21.3	48	320-321	0.38	75.87	7.29	16.96	75.88	6.99	17.13
2f	1	10	40	38	202-204	0.59	56.34	2.97	18.07	56.49	2.80	17.97
2g	1	6	45	7	247	0.45	72.20	7.26	20.31	72.40	7.06	20.54
2h	0.5	5	24.1	31	198-200	0.12	76.10	7.19	17.09	75.88	6.99	17.13

The ^{1}H and ^{13}C nmr characteristics of these compounds are reported in Tables 1-4

Table 4
^{1}H Nmr data for bis(2-substituted benzimidazol-1-yl)methanes, chemical shifts (δ) and coupling constants (Hz) in $CDCl_3$

R	H_4	H_5	H_6	H_7	CH_2	R
i-C_3H_7 **1c**	7. 78(d) $J_{4,5}$= 7.4	← 7.08 to 7.30 →			6.41(s)	3.19 (m);1.33(d)
Cl **1f**	7.67(d) $J_{4,5}$=7.3	← 7.17 to 7.35 →			6.48(s)	—
piperidyl **1g**	7.50(d) $J_{4,5}$=7.6	← 6.94 to 7.12 →		7.25(d) $J_{6,7}$=6.3	6.18(s)	3.29(s);1.85(br s); 1.71(br s)

s: singlet; d: doublet; br: broad signal.

Table 5
^{13}C Nmr data for bis(2-substituted benzimidazol-1-yl)methanes, chemical shifts (δ) and coupling constants (Hz) in $CDCl_3$

R	C_2	C_{3a}	C_4	C_5	C_6	C_7	C_{7a}	CH_2	R
i-C_3H_7 **1c**	159.4 (c.m.)	142.2 ^{3}J= 5.4 ^{3}J= 8.8	119.7 ^{1}J=161.1 ^{3}J= 7.5	122.5 ^{1}J= 159.8 ^{3}J=7.3	122.9 ^{1}J=161.1 ^{3}J= 8.0	108.8 ^{1}J=161.0 ^{3}J= 8.2	134.0 ^{3}J= 7.8 ^{3}J= 7.8	51.5 ^{1}J=151.7	26.9;21.4
Cl **1f**	139.8	141.6 ^{3}J=5.3 ^{3}J=8.6	120.0 ^{1}J=162.7 ^{3}J=7.8	123.7 ^{1}J=161.4 ^{3}J=7.4	124.3 ^{1}J=161.9 ^{3}J=8.1	109.5 ^{1}J=163.7 ^{3}J=8.3	134.0 ^{3}J= 8.8 ^{3}J= 8.8	52.9 ^{1}J=152.7	—
piperidyl **1g**	158.3	141.3 ^{3}J=6.0 ^{3}J=8.3	118.3 ^{1}J=161.0 ^{3}J=7.3	121.7 ^{1}J=160.1 ^{3}J=7.7	122.4 ^{1}J=159.0 ^{3}J=7.2	109.4 ^{1}J=162.0 ^{3}J=8.0	132.9 ^{3}J= 8.1 ^{3}J= 8.1	51.7 ^{1}J=153.3	52.8; 25.6 23.9

(c.m.) : complex multiplet.

Table 6
^1H Nmr data for *tris*(2-substituted benzimidazol-1-yl)methanes
chemical shifts (δ) and coupling constants (Hz) in $CDCl_3$

R	H_4	H_5	H_6	H_7	CH	R
C_2H_5 **2b**	7.84(d) J_{45}= 7.9	7.27(ddd) J_{56}= 7.7 J_{57}=0.9	6.96(ddd) J_{46}= 0.9	5.95(d) J_{67}= 8.3	8.56(s)	2.51(m);2.47(m); 1.34(t)
i-C_3H_7 **2c**	7. 84(d) J_{45}= 8.1	7.26(ddd) J_{56}=7.7 J_{57}= 0.7	6.9.1(ddd) J_{46}= 1.0	5.81(d) J_{67}=8.0	8.73(s)	2.66 (sept); 1.46(bd);1.03(d)
Cl **2f**	7.83(d) J_{45}=7.8	7.36(ddd) J_{56}=7.5 J_{57}=0.9	7.07(ddd) J_{46}=1.1	6.16(d) J_{67}=8.2	8.84(s)	—
piperidyl **2g**	7.69(d) J_{45}=7.8	7.23(ddd) J_{56}=7.3 J_{57}=1.0	6.92(ddd) J_{46}=1.2	6.57(d) J_{67}=8.2	8.27(s)	3.03(v.b.);3.03(v.b.) 1.56(b)
2,5,6-trimethyl **2h**	7.50(s)	—	—	5.88(s.a)	8.42(s)	2.28(s);2.23(s) 2.03(s)

s: singlet; d: doublet; m: multiplet; b: broad

Table 7
^{13}C Nmr data for *tris*(2-substituted benzimidazol-1-yl)methanes, chemical shifts (δ)
and coupling constants (Hz) in $CDCl_3$

R	C_2	C_{3a}	C_4	C_5	C_6	C_7	C_{7a}	CH_2	R
C_2H_5 **2b**	154.7 (c.m.)	142.2 ^3J= 6.1 ^3J= 9.4	120.5 ^1J=162.5 ^3J= 8.0	123.5 ^1J=161.5 ^3J= 7.6	124.7 ^1J=162.3 ^3J=7.8	110.0 ^1J=163.4 ^3J= 8.2	133.3 ^3J=8.5 ^3J=8.5	73.6 ^1J=161.2	21.2;10.7
i-C_3H_7 **2c**	158.9 (c.m.)	142.2 ^3J= 6.2 ^3J= 9.3	120.5 ^1J=162.2 ^3J= 8.2	123.5 ^1J= 161.6 ^3J=7.7	124.6 ^1J=162.4 ^3J= 7.8	110.5 ^1J=163.5 ^3J= 8.1	132.8 ^3J= 8.6 ^3J= 8.6	73.3 ^1J=162.3	27.2;21.9; 21.2
Cl **2f**	139.2 ^3J= 2.1	141.5 ^3J=5.7 ^3J=9.6	120.9 ^1J=163.7 ^3J=8.1	124.5 ^1J=161.4 ^3J=7.6	125.7 ^1J=162.9 ^3J=8.2	110.1 ^1J=164.7 ^3J=8.4	133.3 ^3J= 9.0 ^3J= 9.0	74.8 ^1J=161.3	—
piperidyl **2g**	159.0	141.3 ^3J=5.6 ^3J=9.4	119.1 ^1J=162.2 ^3J=7.9	123.1 ^1J=161.6 ^3J=7.7	123.2 ^1J=160.4 ^3J=8.0	111.7 ^1J=164.8 ^3J=8.6	133.2 (c.m.)	75.3 ^1J=(n.m.)	52.3;25.5; 23.8
2,5,6-trimethyl **2h**	149.3 ^2J= 6.2	140.4 ^3J=6.2	119.9 ^1J=159.3	132.2	133.2 ^1J=160.4	109.7 ^1J=160.6	131.8	74.1 ^1J=162.9	20.4;19.8; 14.4

(c.m.) : complex multiplet; (n.m.): not measurable.

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