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PMR CHARACTERIZATION OF DIASTEREOMERIC FORMS OF 6- AND 7-MEMBERED CYCLIC COMPOUNDS BEARING TWO EQUIVALENT CHIRAL ATOMS

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Abstract—*meso* and *dl* diastereomeric pairs of cyclic compounds with geminal *probe* groups in suitable position were analysed by PMR: anisochronism of diastereotopic *probe* protons was used for assignment of configuration; moreover, analysis of ring proton signals gave information on conformational features.

Recently we reported on the use of geminal *probe* groups (e.g. Me groups) for PMR characterization of *meso* and *dl* forms of some acyclic compounds bearing two equivalent chiral centers in 1,5-position.[1]

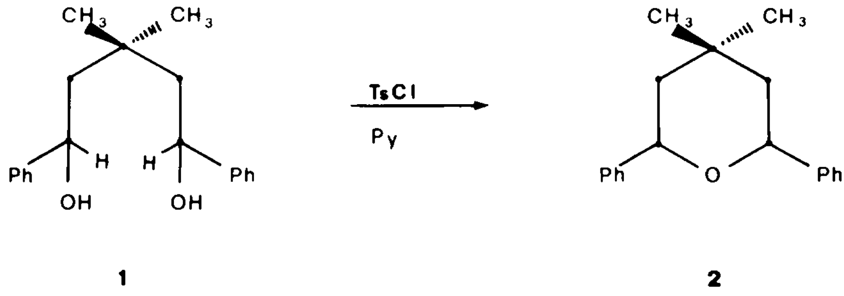
During the investigation we reacted both *meso* and *dl* 1,5-diphenyl-3,3-dimethyl-1,5 pentanediols (**1**) with tosyl chloride in pyridine, obtaining respectively *dl*-(*trans*) and *meso*-(*cis*) forms of 2,6-diphenyl-4,4-dimethyl-tetrahydropyran (**2**) (Scheme A); this result showed that cyclization reaction had occurred with configurational inversion at the substitution site.

This kind of stereoselective cyclization, leading to tetrahydrofuran[2-4] or tetrahydropyran[5] derivatives was already known; in our case, it made both diastereomeric forms of **2** accessible, of which only one (*meso-cis* **2**, obtained by catalytic hydrogenation of 6,6-dimethyl-6H-pyrano [3,2-b; 5,6-b′]bis-[1] benzothiophene[6]) was known.

The assignment of configurations to *meso* and *dl* **2** was easily achieved by applying symmetry principles[7] to the geminal Me groups' signals; in addition, the interesting conformational features obtained by careful analysis of PMR spectra prompted us to extend the use of geminal Me *probe* groups to other cyclic diastereomeric *meso*-(*cis*) and *dl*-(*trans*) pairs.[a]

Some 5 and 6-membered cyclic compounds fullfilling this requirement have been characterized by PMR in a single diastereomeric form[8-10]; *meso* and *dl* forms of 1,3-dioxolans,[11] 1,3 dioxa-2-thians[12] and 1,3-dioxans[13] bearing geminal Me groups in suitable position have formerly been submitted to PMR analysis. Early examples of similar diastereomeric pairs, for which PMR data are missing, are 2,2,5,5-tetramethyl-1,3-cyclohexanediol (**3a**) and its diacetyl-(**3b**) and dibenzoyl-(**3c**) esters, whose configurational assignment was based on optical resolution of *dl* form of **3a**;[14] we decided then to resynthesize these three diastereomeric pairs and to submit them to PMR analysis.

In order to extend the series also to 7-membered ring compounds, we reduced 1,2-benzo-5,5-dimethyl-cyclohept-1-en-3,7-dione (**4**), thus affording *meso* and *dl* 1,2-benzo-5,5-dimethyl-cyclohept-1-en-3,7-diols (**5a**); a partial reduction product, 1,2-benzo-5,5-dimethyl-7-hydroxy-cyclohept-1-en-3-one (**6**) was also obtained. The separation of diastereomeric forms of **5a** was achieved by fractional crystallization or by column chromatography, and both forms were then acetylated to the diastereomeric diesters **5b** (Scheme B).



Scheme A.

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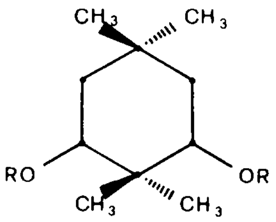
[a] Heretofore only *meso* and *dl* prefixes will be used; it is intended that *meso* forms are also *cis*, and *dl* forms are also *trans*.



3a : R = H

3b : R = CO-CH$_3$

3c : R = CO-Ph

An attempted synthesis of diols, homologues of **5a**, was unsuccesful: treatment of **4** with Me-Li gave only a partial reaction product: 1,2-benzo-5,5,7-trimethyl-7-hydroxy-cyclohept-1-en-3-one (**7**) which, unlike (**6**), was found to be stabilized as hemiketal form (**7′**) (Scheme B).

RESULTS AND DISCUSSION

Table 1 shows the PMR data of the diastereomeric pairs: *meso* forms were recognized by unequivalence of diastereotopic probe groups,[7] which was much more marked than in the acyclic series;[1] this feature could be related to the lesser conformational flexibility of cyclic structures as compared with the acyclic ones.

All compounds contain two equivalent or enantiotopic ABX ring proton systems: a constant feature which was apparent from their chemical shifts values was a general downfield shift when passing from *meso* to *dl* forms: no such regularity could be found in the acyclic analogues.[1]

This deshielding effect was easily explained for the X proton, whose chemical shift in the *dl* form was clearly a mediated value from an axial-equatorial protons pair in place of two axial protons in the *meso* form,[15] furtherly strengthened in the benzocycloheptene derivative by the anisotropy of the aromatic ring.

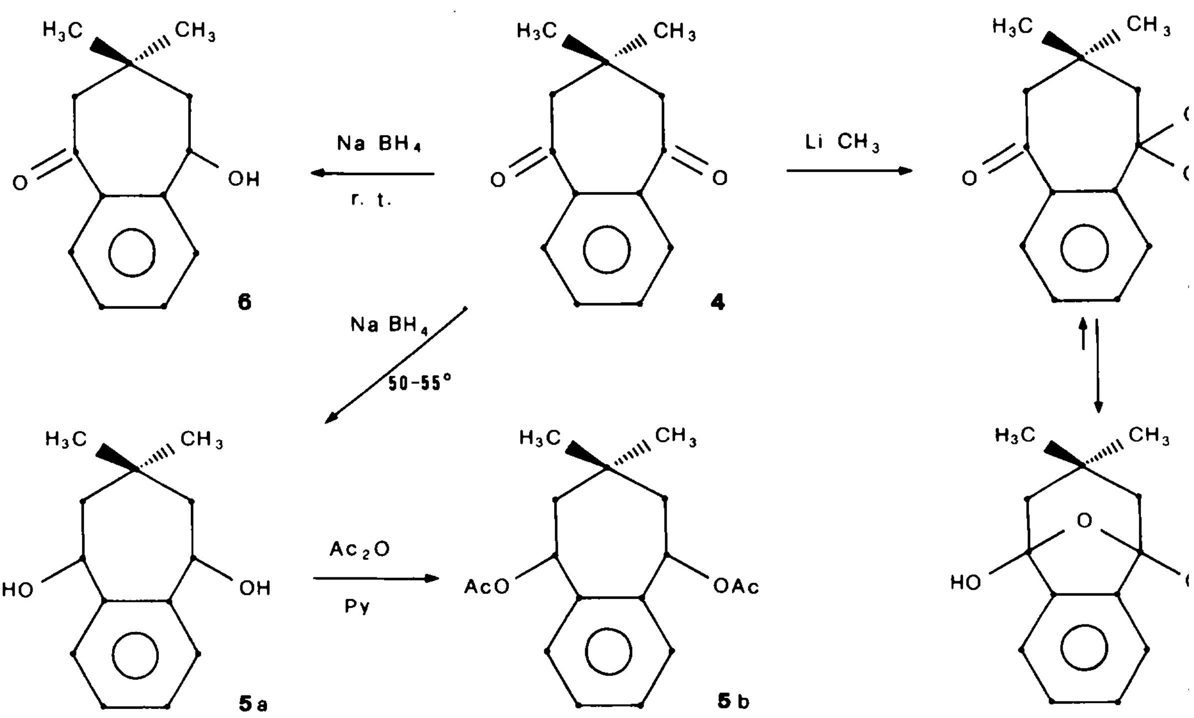
For the AB part of the system, no immediate explanation could be found: it is known, however, that axial substituents, such as phenyl or hydroxyl, which were present in one half-moiety of *dl* forms, exert a deshielding effect on vicinal axial protons[16,17] whereas shielding effects are usually reported on vicinal equatorial protons;[17] the chemical shifts observed by us for H$_A$ and H$_B$ in *dl* forms were mediated values for two interchanging ea-ae proton pairs, and seemed to indicate that the above mentioned deshielding effect on the axial proton was predominant.

Geminal coupling constants $^2J_{AB}$ showed rather constant values for the three ring systems; in contrast, vicinal coupling constants showed different patterns: with the exception of **3a** (see below), all *meso* forms appeared conformationally unitary, with both substituents equatorial; $^3J_{aa}(={}^3J_{AX})$ and $^3J_{ea}(={}^3J_{BX})$ depended strongly on the nature and size of the ring:

Ring system	$^3J_{aa}$(Hz)	$^3J_{ea}$(Hz)	Ref.
Tetrahydropyran	12	2	18
Cyclohexane	13	3.5	19
Benzocycloheptene	11.5	1.5	20

The low values of both coupling constants in the cycloheptene derivatives could be related to their particular dihedral angles: a Dreiding model showed $\emptyset_{aa} = \sim 150^\circ$ and $\emptyset_{ea} = \sim 90^\circ$.

The ABX system of *meso*-**3a** showed particular features: in CDCl$_3$ solution, vicinal coupling constants ($J_{AX} \cong 11$Hz, $J_{BX} \cong 5$Hz) were intermediate between the above values for the cyclohexane series; this could indicate a conformational equilibrium between the diequatorial and diaxial conformers, the former being



Scheme B.

Table 1*. PMR data of diastereomeric forms **2**, **3**, **5**

Compounds	Diastereomeric form	ν, Probe-CH$_3^{(**)}$ singlet (s)		A B X Systems$^{(***)}$						ν, other protons
				ν_A	ν_B	ν_X	$-J_{AB}$	J_{AX}	J_{BX}	
2	meso	1.03	1.28	1.50	1.62	4.71	13.5	12	2	7.1-7.5 (m,10 H,arom.).
	dl	0.97	0.97	1.75	1.91	5.02	14	4	8.5	7.0-7.6 (m,10 H,arom.).
3a	meso	0.98 0.78	1.10 0.98	1.38 (1.32)	1.38 (1.45)	3.36 (3.41)	? (13)	8 (11)	8 (5)	——
	dl	1.06 0.97	1.06 0.97	1.42	1.52	3.67	13.5	8	3	——
3b	meso	0.96 0.93	1.08 0.99	1.38	1.49	4.74	13	13	3.5	2.04 (s, 6H,OCOCH$_3$).
	dl	1.04 0.96	1.04 0.96	1.46	1.59	4.92	14	7.5	4	2.05 (s, 6H,OCOCH$_3$).
3c	meso	1.10 1.06	1.28 1.22	1.58	1.71	5.08	13	13	3.5	7.3 -7.6(m,3H,3,4,5-arom.), 7.9 -8.1(m,2H,2,6-arom.).
	dl	1.16 1.12	1.16 1.12	1.67	1.82	5.32	13	8.5	3	7.3-7.6(m, 3H,3,4,5-arom.), 7.9-8.1(m, 2H,2,6-arom.).
5a	meso	0.88	1.26	1.34	1.68	4.76	13	11	1.5	7.0-7.2(m,2H, arom.), 7.3-7.5(m,2H, arom.).
	dl	1.15	1.15	1.64	1.77	5.11	13.5	1.5	8.5	7.0-7.2(m,2H, arom.), 7.3-7.6(m,2H, arom.).
5b	meso	0.94	1.41	1.53	1.72	6.00	13	11.5	1.5	2.21(s,6H,OCOCH$_3$), 7.1-7.5(m,4H,arom.).
	dl	1.15	1.15	1.67	1.91	6.20	14	2	8.5	2.12(s,6H,OCOCH$_3$), 7.1-7.4(m,4H,arom.).

Chemical shifts (ν) are expressed in δ (ppm) and coupling costants in Hertz. The spectra were recorded at 100 MHz in CDCl$_3$ (2,3b,3c,5b) and in CD$_3$OD (3a,5a), using TMS as internal standard. For meso 3a the spectrum was recorded also in CDCl$_3$ at 55° and the PMR data for the ABX system are reported in the table in parentheses. **For 3a ,b,c the upper couple of values refers to 5,5-CH$_3$, and the second couple to 2,2-CH$_3$. *** PMR parameters were calculated by a computer program based on classical equations for ABX system(24); values of coupling constants were rounded to 0.5 Hz.

more populated: diaxial *meso*-**3a** could be somewhat stabilized by intramolecular H-bonding.[20]

Rather surprisingly, in CD$_3$OD solution, the ABX system of *meso* **3a** degenerated to an A$_2$X system: no easy explanation of this phenomenon could be found in terms of chair conformers, since intermolecular deuterium bonding with solvent molecules should furtherly shift the above conformational equilibrium towards the diequatorial conformer. A tentative interpretation considers the possible existence of twist-boat conformers in the equilibrium, that could cause minimal difference in chemical shift for the AB couple of protons and hence degeneration; an inspection of Dreiding models shows that such conformers could eventually be stabilized by an H-bonded methanol molecule interposed between the two OH groups.

A similar behaviour was not observed for the analogous 7-membered ring diol (*meso*-**5a**) that exists

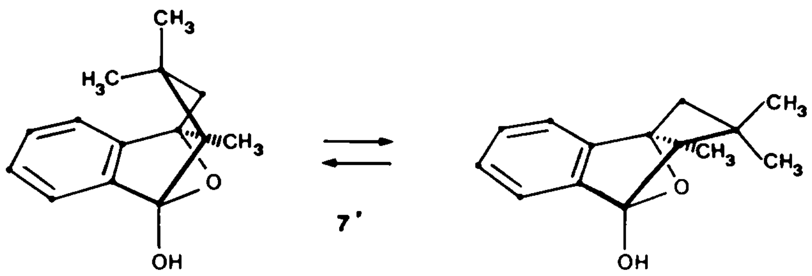


Fig. 1.

entirely as diequatorial chair form in CD_3OD solution, though a diaxial conformer intramolecularly H-bonded has been observed for a similar *meso* benzocycloheptene diol in $CDCl_3$ solution.[20]

In all *dl* forms, conformational equilibrium between the two equivalent chair forms, and possibly also the twist forms, was evidenced by $^3J_{AX}$ and $^3J_{BX}$ values: in the cyclohexane compounds **3** $^3J_{AX} > {}^3J_{BX}$ whereas the reverse was found for tetrahydropyran **2** and benzocycloheptene derivatives **5**; this could be explained by a shift inversion of the axial-equatorial proton pairs, due to the above mentioned deshielding effects of axial substituents on vicinal axial protons.

The conformational equilibrium existing in *dl* forms was also evidenced by the *probe* group chemical shifts, that were very close to the mean of those in the corresponding *meso* form. An exception was *dl*-**2**, whose *probe* groups were more shielded than both *probe* groups of *meso*-**2**; this could be related to the ring current effect of the axial phenyl substituent, that in its most probable conformation (with the phenyl plane almost orthogonal to the Ph–C–H plane[21]) should strongly shield the *cis*-CH_3 group: this effect, mediated on both conformers, could explain the observed shielding.

Finally, an interesting feature was observed in the PMR spectrum of compounds **7**, that was completely in the hemiketal form **7'**, as was also apparent from the IR spectrum; one of the geminal *probe* groups was strongly shielded, more than TMS, showing the existence of a conformational equilibrium shifted toward a cycloheptene boat conformation with one Me group above the aromatic ring (Fig. 1); this was possibly related to the poor steric hindrance of the aromatic nucleus.[21]

It is interesting to note that the analogous hydroxyketone **6** does not give a similar hemiketal form: apparently the presence of the 7-Me group in **7** could shift the conformational equilibrium toward the form with an axial OH group, thus promoting hemiketal formation.

EXPERIMENTAL

General. M.ps were determined using a Büchi capillary melting point apparatus and are uncorrected. Elemental analyses were made by Dr. A. Reho, using a Hewlett–Packard 185 C,H,N analyzer. IR spectra were recorded on a Perkin Elmer 257 spectrometer and agreed with the proposed chemical structures. ^1H NMR spectra were recorded on a Varian HA-100 or a Jeol C-60 HL spectrometer, using TMS as internal standard; chemical shifts are reported in ppm (δ) and the following abbreviations are used: s, singlet; dd, double doublet; m, multiplet. ^1H NMR data of diastereomeric forms **2**, **3**, **5** are listed in table 1 and are not reported in this section. Their diastereomeric purity was close to 100%. Column chromatographies were carried out on Merck silica gel (230-400 mesh ASTM).

2,6-*Diphenyl*-4,4-*dimethyl-tetrahydropyran* **2**. Tosyl chloride (0.50 g, 2.62 mmol) and single diastereomeric form[1] of **1** (0.25 g, 0.88 mmol) were dissolved in dry pyridine (10 ml) and stirred at r.t. for 24 hr.

The mixture was poured on ice and the ppt collected, washed with water and crystallized. *Meso* **1** gave (*trans*)-*dl* **2** (0.20 g, 85% yield) m.p. 56–58° from MeOH-H_2O, (Found: C, 85.50; H, 8.23. $C_{19}H_{22}O$ (266.4) requires: C, 85.67; H, 8.33%). *dl* **1** gave (*cis*)-*meso* **2** (0.21 g, 90% yield), m.p. 77–78° from MeOH (^1H NMR spectrum identical with that of a specimen prepared according to lit.[6], m.p. 77–78°).

1,2-*Benzo*-5,5-*dimethyl-cyclohept*-1-*en*-3,7-*dione* (**4**). 1,2-Benzo-5,5-dimethyl-cyclohept-1-en-3-one[22] (5 g, 26.6 mmol) was added to a soln of $KMnO_4$ (6.43 g, 40.7 mmol) and $Mg(NO_3)_2 \cdot 6H_2O$ (12.95 g, 50.5 mmol) in water (50 ml).[23]

The mixture was stirred and heated at 65–70° for 72 hr. After cooling the ppt (MnO_2) was filtered off, washed several times with ether and the aqueous soln extracted with ether. The combined ethereal extracts were dried on Na_2SO_4 and evaporated to dryness under vacuum. The remaining solid product was chromatographed on silica gel, using 90:10 cyclohexane-ethyl acetate as eluent, giving starting material (2.75 g) and dione **4** (1.75 g, 72% yield taking into account the starting material recovered), m.p. 93–95° from EtOH–H_2O, (Found: C, 76.94; H, 7.02. $C_{13}H_{14}O_2$ (202.2) requires: C, 77.20; H, 6.98%). ^1H NMR ($CDCl_3$/60 MHz) δ: 1.25 (s, 6H, CH_3); 2.70 (s, 4H, CH_2); 7.3–7.8 (m, 4H, arom.).

1,2-*Benzo*-5,5-*dimethyl-cyclohept*-1-*en*-3,7-*diol* (**5a**). A mixture of **4** (2.4 g, 11.9 mmol) and $NaBH_4$ (0.32 g, 8.46 mmol) in MeOH (50 ml) was stirred and heated at 55–60° for 24 hr. After solvent removing, water was added to the residue, the aqueous soln was extracted with ether and the ethereal layer dried on Na_2SO_4; after solvent removing **5a** (2.2 g, 90% yield) was obtained as diastereomeric mixture.

Separation of diastereomeric forms was achieved either by fractional crystallization from ethyl ether petrol ether or, more efficiently, by column chromatography on silica gel, using 75:25 cyclohexane–ethyl acetate as eluent; *dl* **5a**, m.p. 157–59°, (Found: C, 75.98; H, 8.78. $C_{13}H_{18}O_2$ (206.3) requires: C, 75.69; H, 8.80%). *meso* **5a**, m.p. 187–190°, (Found: C, 75.94; H, 8.65. Required as above).

At r.t the same reaction gave 1,2-Benzo-7-hydroxy-5,5-dimethyl-cyclohept-1-en-3-one (**6**) as colorless oil after chromatography purification on silica gel column using 25:25:50 EtOAc-cyclohexane CCl_4 as eluent (60% yield). (Found: C, 76.10; H, 7.99. $C_{13}H_{16}O_2$ (204.3) requires: C, 76.44; H, 7.90%). ^1H NMR ($CDCl_3$/60 MHz) δ: 0.96 (s, 3H, CH_3); 1.09 (s, 3H, CH_3); 1.4–2.2 (m, 2H, AB part of an ABX system, $\delta_A = 1.73$, $\delta_B = 1.97$, $J_{AB} = 14$ Hz) 2.3–2.8 (m, 2H, AB system; $\delta_A = 2.50$, $\delta_B = 2.62$, $J_{AB} = 12.5$ Hz); 3.11 (s, 1H, -OH, exch. D_2O): 4.88 (dd, 1H, X part of ABX system, $J_{AX} = 9$ Hz, $J_{BX} = 3$ Hz); 7.1–7.9 (asym.m., 4H, arom.).

3,7-*Diacetoxy*-1,2-*Benzo*-5,5-*dimethyl-cyclohept*-1-*ene* (**5b**). Acetylation of single diastereomeric form of **5a** was afforded with Ac_2O in dry pyridine by the usual method in 90% yield. *dl* **5b**: m.p. 74–76° from hexane. (Found: C, 70.19; H, 7.84.

$C_{17}H_{22}O_4$ (290.4) requires: C, 70.32; H, 7.64%); *meso* **5b**: m.p. 122–24° from hexane (Found: C, 70.15; H, 7.78. Required as above)

1,2-*Benzo-7-hydroxy-5,5,7-trimethyl-cyclohept-1-en-3-one* (**7**). A soln of dione **4** (0.79 g, 3.9 mmol) in anhydether (10 ml), was added dropwise under dry N_2 to a stirred soln of MeLi (39 mmol) in the same solvent (25 ml). After stirring at r.t. for 1 hr the mixture was carefully washed with ice-cooled water, dried on Na_2SO_4 and evaporated to dryness. Purification by column chromatography on silica gel using 75:25 cyclohexane–EtOAc as eluent, gave **7** (0.61 g, 72% yield) as colorless oil, (Found: C, 76.86; H, 8.53. $C_{14}H_{18}O_2$ (218.3) requires: C, 77.03; H, 8.31%).

The IR spectrum misses the CO stretching band because **7** exists completely in the hemiketal form **7′** (see ¹H NMR). ¹H NMR (CCl_4/60 MHz), 100% hemiketal form: δ: −0.11 (s, 3H, $\mathit{CH}_3-\overset{|}{\underset{|}{C}}-CH_3$); 0.83 (s, 3H, $CH_3-\overset{|}{\underset{|}{C}}-\mathit{CH}_3$); 1.48 (s, 3H, $CH_3-\overset{|}{\underset{|}{C}}-O$); 1.0 1.9 (m, 4H, two AB system: $\delta_A = 1.28$, $\delta_B = 1.74$, $J_{AB} = 13.5$ Hz; $\delta'_A = 1.54$; $\delta_{B'} = 1.60$ $J_{A'B'} = 10.5$ Hz); 4.80 (s, 1H, OH exch. D_2O) 6.60–7.20 (asym.m, 4H, arom.).

2,2,5,5-*Tetramethyl-cyclohexane-1,3-diol* (**3a**) was obtained by $NaBH_4$ reduction of 2,2,5,5-tetramethylcyclohexane-1,3-dione in abs EtOH. Diastereomeric forms *meso* and *dl* were separated by column chromatography on silica gel with EtOAc cyclohexane as eluent (ratios: 15:85 up to 30:70). m.ps of separated diastereomeric forms are in agreement to those previously reported.[14]

1,3-*Diacetoxy-2,2,5,5-tetramethyl-cyclohexane* (**3b**) and 1,3-dibenzoyloxy-2,2,5,5-tetramethyl-cyclohexane (**3c**) were prepared by esterification of the separated diastereomeric forms **3a**, in dry pyridine with Ac_2O or benzoyl chloride by the usual procedure. M.ps of *meso* and *dl* forms were identical to those already reported.[14]

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