Self-Induced Nonequivalence in the ^{1}H-NMR Spectra of the (+)- and (−)-Isomers of a Cannabinoid Ketone Intermediate

RAYMOND A. H. F. HUI,* SALVATORE SALAMONE* AND THOMAS H. WILLIAMS†

*Roche Diagnostic Systems, Incorporated and †Hoffmann-La Roche, Incorporated
340 Kingsland Street, Nutley, NJ 07110-1199*

HUI, R. A. H. F., S. SALAMONE AND T. H. WILLIAMS. *Self-induced nonequivalence in the ^{1}H-NMR spectra of the (+)- and (−)-isomers of a cannabinoid ketone intermediate.* PHARMACOL BIOCHEM BEHAV **40**(3) 491–496, 1991.—The ^{1}H-NMR spectra in deuteriochloroform of racemic and optically pure (trans)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-3-pentyl-6H-dibenzo[b,d]pyran-9(8H)-one (1) are nonsuperimposable, while nonracemic mixtures of the (+)- and (−)-isomers show two sets of signals for the phenolic and aromatic protons in ratios directly proportional to the enantiomeric composition of the mixture. This is a new example of "self-induced nonequivalence" or "diastereomeric solute-solute interaction," a known but seldom reported phenomenon. The magnitude of the chemical shift differences are dependent on the ratios of the two enantiomers while the chemical shift δ values are concentration dependent. The overall effect was clearly observable even at a concentration of 0.01 M. In a practical sense, optical purities of samples of the cannabinoid ketone (1) are readily determined by ^{1}H-NMR without the use of additional chiral shift reagents.

Self-induced nonequivalence   Proton NMR   Cannabinoid   Diastereomeric solute-solute interaction
Tetrahydrocannabinoid   Optical purity   Enantiomeric purity

DETERMINATIONS of enantiomeric purities of compounds by ^{1}H-NMR are often made by the use of chiral shift reagents or chiral NMR solvents, termed "chiral solvating agents" (CSAs) by Pirkle (9). In some cases, optically enriched samples of compounds in an *achiral* solvent *by themselves* show two sets of signals in their NMR spectra, in ratios directly proportional to the amount of each enantiomer present. In these cases, the solute functions as its own CSA. This phenomenon of "self-induced nonequivalence" or "diastereomeric solute-solute interaction" first reported by one of us (10) has since been observed and studied by others (1–10) and analysed statistically (7). However, the examples in the literature remain few in number. We report here an example of this phenomenon in the cannabinoid field.

METHOD

The appropriate amounts of the racemic, enantiomerically pure, and artificially mixed ketones were separately dissolved in deuteriochloroform (CDCl$_3$) (99.8% atom D) to give concentrations of 0.02 M or of from 0.01 M to 0.08 M (concentration dependence study) and the ^{1}H-NMR spectrum for each solution recorded at RT on a Varian XL-400 instrument.

RESULTS AND DISCUSSION

The 400-MHz ^{1}H-NMR spectra (Figs. 1 and 2) of 0.02 M solutions in CDCl$_3$ at RT of the (+)-6aS,10aS- and (−)-6aR, 10aR-enantiomers of the cannabinoid ketone (trans)-6a,7,10, 10a-tetrahydro-1-hydroxy-6,6-dimethyl-3-pentyl-6H-dibenzo[b,d]-

TABLE 1

VARIATION OF ^{1}H-NMR δ SHIFT VALUES OF THE OH AND AROMATIC SIGNALS WITH RATIOS OF (+)-1 and (−)-1

(+)-(1):(−)-(1) Ratio	OH Minor	OH Major	Aromatics
1.0:0.0	—	6.76	6.25(d), 6.205(d)
7.5:1.0	6.85	6.75	6.25(s),* 6.21(d)
4.0:1.0	6.85	6.77	6.25(s),* 6.213(d)
2.0:1.0	6.82	6.78	6.25(d), 6.23(d), 6.22(d)
1.0:1.0	—	6.80	6.25(d), 6.23(d)
1.0:4.0	6.85	6.75	6.25(s),* 6.213(d)
0.0:1.0	—	6.76	6.25(d), 6.205(d)

(s) Singlet; (d) doublet; *slightly broadened singlet.

TABLE 2

VARIATION OF ^{1}H-NMR δ SHIFT VALUES OF THE OH AND AROMATIC SIGNALS WITH CONCENTRATION FOR 4:1 MIXTURES OF (+)-1 AND (−)-1

Total Concentration	OH Minor	OH Major	Aromatics
0.01 M	6.39	6.32	6.26(s),* 6.21(d), 6.187(d)
0.02 M	6.85	6.77	6.25(s),* 6.213(d)
0.04 M	7.27	7.20	6.28(d), 6.24(s)*
0.06 M	7.51	7.44	6.295(d), 6.255(m), 6.24(s)*
0.08 M	7.65	7.59	6.305(d), 6.265(m), 6.24(s)*

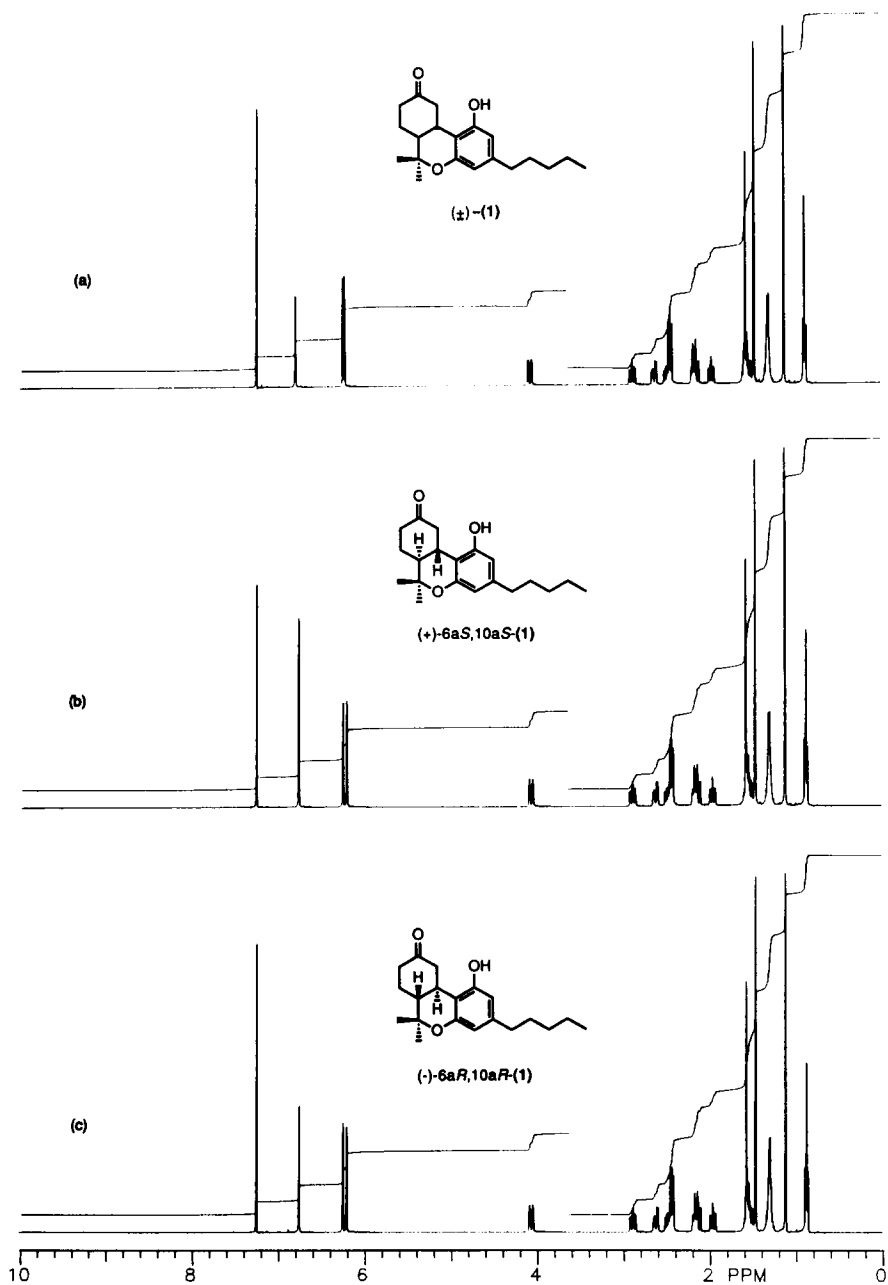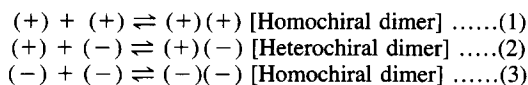(s) Singlet; (d) doublet; (m) multiplet; *slightly broadened singlet.

FIG. 1. 400 MHz ^{1}H-NMR spectra of: (a) (trans-rac)-1; (b) (+)-6aS,10aS-(1); (c) (−)-6aR, 10aR-(1).

pyran-9(8H)-one(1) as shown in Figs. 1b, 2b, 1c and 2c are identical to each other, as expected, but are different from that for the racemic modification shown in Figs. 1a and 2a.

The low-field portions of the spectra of artificial nonracemic mixtures (all 0.02 M in CDCl$_3$ at RT) of (+)-(1) and (−)-(1) in ratios of 7.5:1, 4:1 and 2:1 respectively are also shown in Fig. 3a, b, c and the δ chemical shift values are included in Table 1.

It is seen that there are two OH signals in each spectrum, the integration ratios of which are directly proportional to the ratios of each enantiomer present. The aromatic proton region is less clearly resolved, but the existence of two sets of signals in each spectrum is also apparent. In keeping with the theory and previous studies (1–10) the phenomenon may be ascribed to the pres-

ence of different populations of monomer and dimers of the enantiomers as outlined below:

$$(+) + (+) \rightleftharpoons (+)(+) \text{ [Homochiral dimer]} \dots\dots(1)$$
$$(+) + (-) \rightleftharpoons (+)(-) \text{ [Heterochiral dimer]} \dots\dots(2)$$
$$(-) + (-) \rightleftharpoons (-)(-) \text{ [Homochiral dimer]} \dots\dots(3)$$

When the (+)-isomer is in excess the population of dimer species will be biased towards Eqn. (1) under conditions of fast exchange. By external comparision, the average environment experienced by the (+)-isomer will be different (diastereomeric) from that experienced by the (−)-isomer and two signals for the reporter nuclei can be observed, one corresponding to the weighted average of the three inherent signals from the populations of
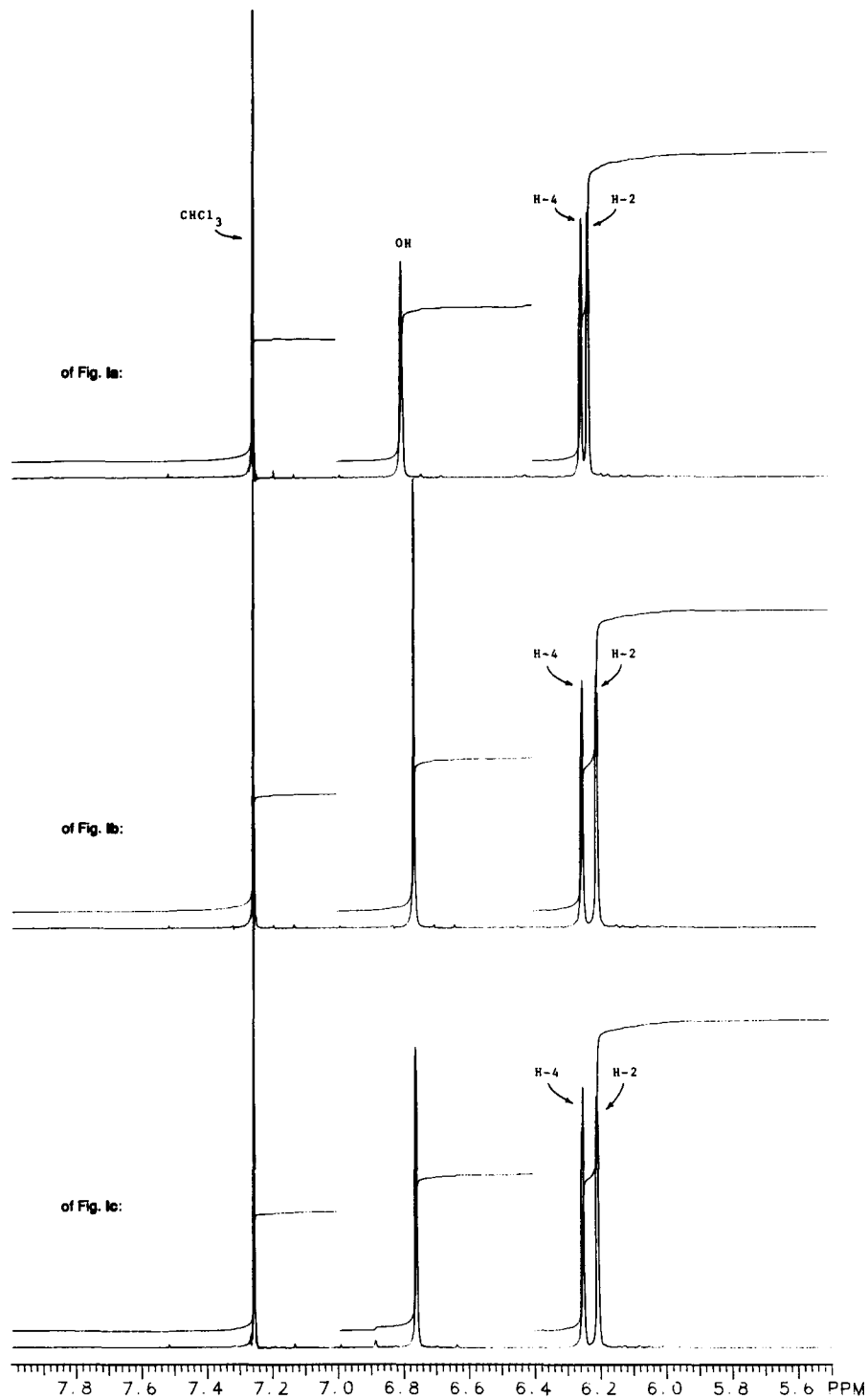
FIG. 2. Low-field expansions of the spectra shown in Fig. 1.

(+), (+)(+) and (+)(−) species and the other from the weighted average of (−), (−)(−) and (+)(−) signals.

Inversion of the enantiomeric populations, in theory, should leave the spectral observation unchanged (i.e., identical) as borne out by inspection of Fig. 4a and 4b. The enantiomer assignments of the major and minor peaks will merely be reversed

as each enantiomeric mixture is the mirror image of the other.

As expected, Fig. 3 also shows that the major and minor OH signals approach each other as the enantiomeric purity decreases and coalesce as the sample becomes racemic. Similarly, the two sets of aromatic signals gradually change and coalesce into a single set.

(+)(-) Heterochiral dimer   (-)(-) Homochiral dimer
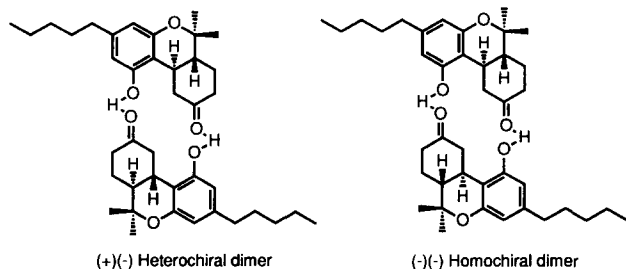
In the present case, the postulated heterochiral (+)(−) and homochiral [illustrated for (−)(−)] dimer species can be represented as shown in Diagram 1. Note that the overall symmetry of the two species is different, and will be a factor in the average environment experienced by each enantiomer in the nonra-

cemic mixtures.

The phenomenon is also concentration dependent (2–7, 9, 10) and the effect of varying the total solute concentration from 0.01 M to 0.08 M in $CDCl_3$ for a 4:1 mixture of (+)-(1) and (−)-(1) is shown in Fig. 5.

Nonequivalency in the present case persists strongly even at a concentration of 0.01 M (Fig. 5a). There is a "crossing of peaks" for the aromatic signals with comparatively small changes in chemical shift. In contrast, the shift difference for the pair of hydroxy resonances remains large throughout while the chemical shifts appropriately demonstrate very large changes.

In principle (9), any chiral compound that is able to self-associate might demonstrate diastereomeric solute-solute interactions or self-induced nonequivalence. The present example constitutes an additional cautionary note in attempted proofs of identity of compounds by comparision of NMR spectra of their racemic and chiral forms.

In a practical sense, the phenomenon allows the estimation of optical purities of substances by NMR, such as in the present case, without the need for any additional chiral additives or the use of chiral solvents.
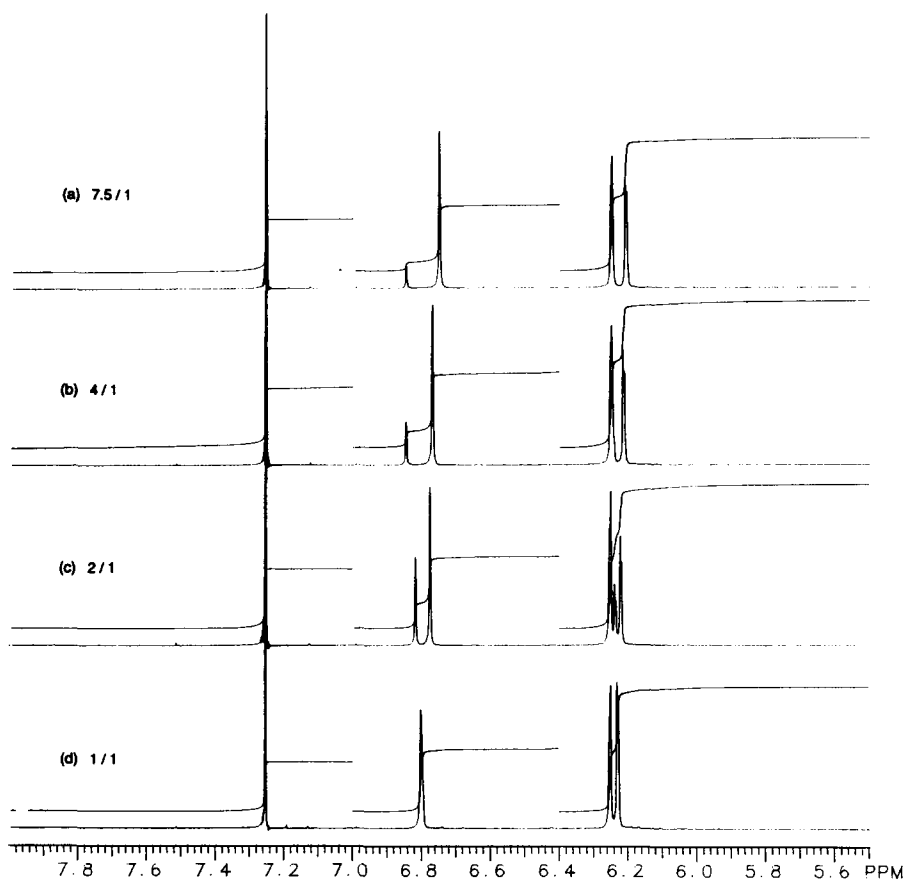

(a) 7.5/1

(b) 4/1

(c) 2/1

(d) 1/1

7.8   7.6   7.4   7.2   7.0   6.8   6.6   6.4   6.2   6.0   5.8   5.6 PPM

FIG. 3. Variation of (+)-(1)/(−)-(1) ratios. Low-field portions of the ^{1}H-NMR spectra. (a), (b), (c), (d): Molar ratio of (+)-(1)/(−)-(1) respectively.
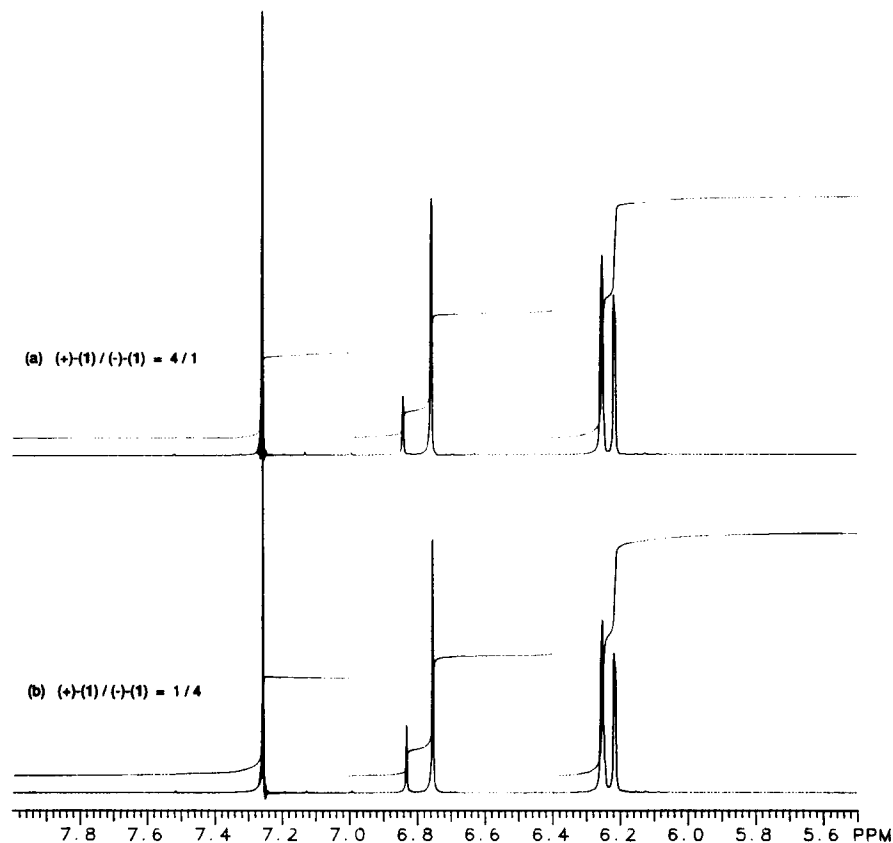
FIG. 4. Inversion of enantiomer ratios. Low-field portions of the ^{1}H-NMR spectra. (a), (b): Molar ratio of the indicated enantiomers.

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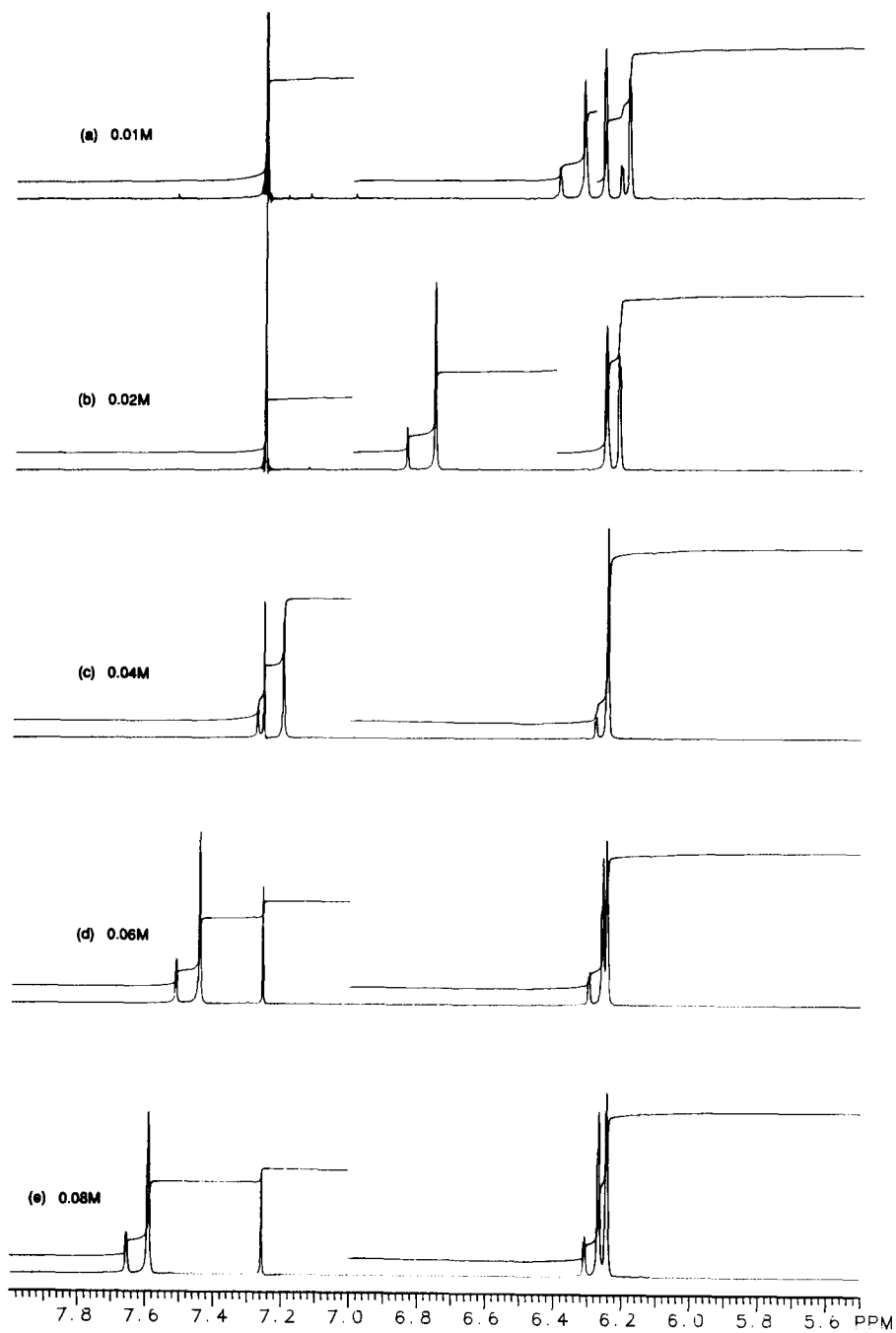
FIG. 5. Effect of concentration for (+)-(1)/(−)-(1)=4/1 mixtures. Low-field portions of the ^{1}H-NMR spectra. (a), (b), (c), (d), (e): Total molar concentration in $CDCl_3$.