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SYNTHESIS AND CONFORMATION OF R-(+)-2-(α-PHENYLETHYL)BENZOPHENONE

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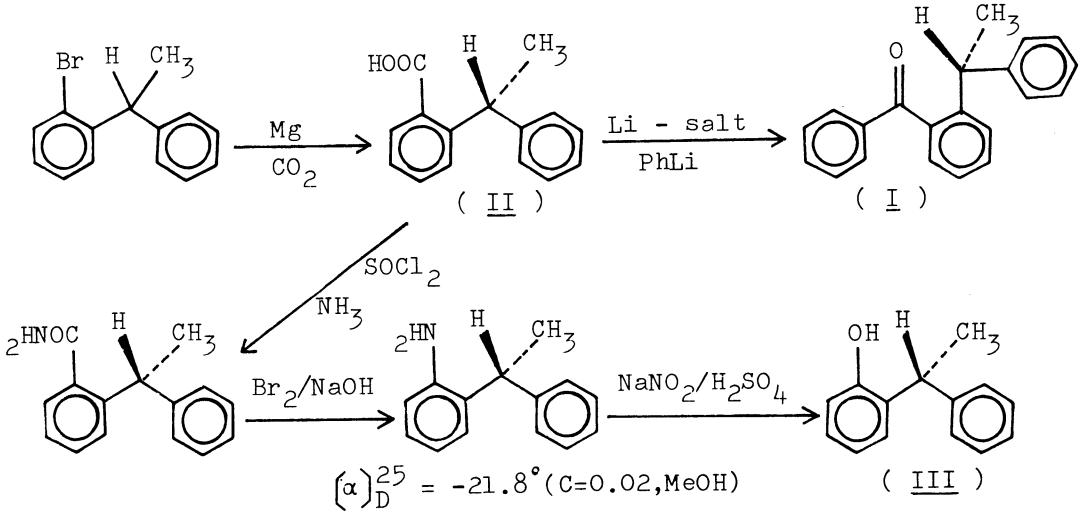
As a model of chiral benzophenone, R-(+)-2-(α-phenylethyl)-benzophenone was prepared. The NMR and optical data indicate that rotations of the benzoyl and α-phenylethyl moieties are unrestricted in the range of -100 to 150°C, and therefore benzophenone skeleton is not chiral. A preferable conformation is discussed.

Ion-pairs of benzophenone carboxylic acid and chiral amine have been known to display an induced circular dichroism arising from the n - π* electric transition of the carbonyl group.[1,2] We assumed that the induced optical activity is affected not only by electric perturbation of the chiral molecule for the chromophore molecule but also by molecular asymmetry of the chromophore molecule induced by chiral interaction in the ion-pairs.[3] This paper describes the synthesis and conformational analysis of R-(+)-2-(α-phenylethyl)benzophenone (I) as a model of chiral benzophenone. The ketone I was prepared by the following scheme.



$[\alpha]_D^{25}$ = -21.8°(C=0.02,MeOH)

Optical resolution of the acid (II) was carried out by recrystallization with R-(+)-α-phenylethylamine ($[\alpha]_D^{25}$ = +41°(neat), ca. 100 % optically pure) in a mixed solvent of benzene and methanol. After recrystallizing 5 times the less soluble 1 : 1 salt (mp. 159°C) was decomposed by hydrochloric acid to give pale yellow prisms, mp. 58 - 60°C, $[\alpha]_D^{25}$ = +110°(C = 0.02, MeOH), Anal., Found: C,

79.91; H, 5.99. $C_{15}H_{14}O_2$ requires C, 79.62; H, 6.24. The optically active II was led to the amide of R-(+)-α-phenylethylamine. The optical purity of the acid II was determined as ca. 60 % excess from the intensity ratios of the methine signals at 4.69 (J = 7.6) and 4.71 ppm (J = 7.6 Hz) of the NMR spectrum of the amide (δ_{ppm} from TMS in carbon tetrachloride). The (+)-acid II was led to the phenol III by Hofmann rearrangement followed by diazotization, $[\alpha]_D^{25}$ = +34.6°(C = 0.069, MeOH). The (+)-phenol III has been assigned as R-configuration.[4] The lithium salt of the (+)-acid II was reacted with phenyllithium in diethyl ether to give the ketone I[5] with good yield, pale yellow oil, bp. 170 - 171°C/1mmHg, Anal., Found: C, 87.85; H, 6.38. $C_{21}H_{18}O$ requires C, 88.08; H, 6.33. $[\alpha]_D^{25}$ = +124°(C = 0.02, MeOH). Since these reactions do not involve the asymmetric carbon, the configuration of the asymmetric carbon in III, II, and I is identical. Then, the chiral carbon in I is assigned as the R-configuration. The ordinary absorption and CD spectra of I are indicated in Fig. Ia. The CD spectrum in longer wavelength displays a large positive Cotton effect with broad vibrational structuring

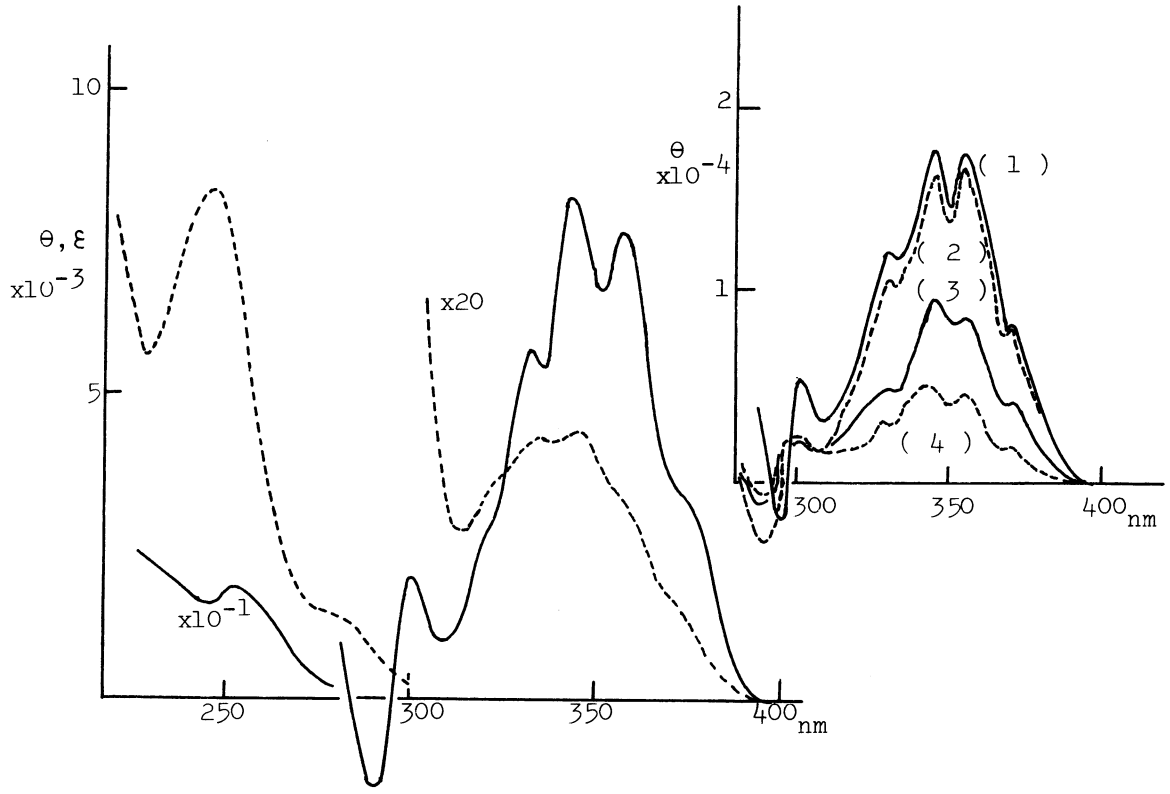
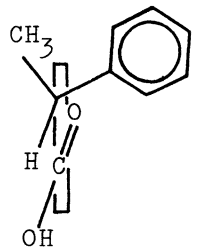


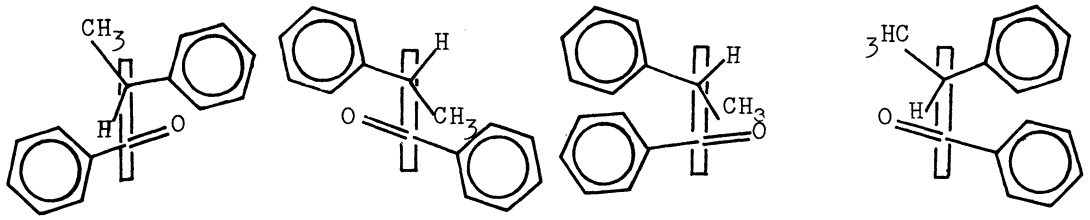
Fig Ia (left) CD (—) and ordinary absorption (----) spectra of I in isooctane at 20°C. Ib (right) temperature-dependent CD spectra in isopentane - methylcyclohexane (5 : 1), (1) -192, (2) -115, (3) -75, and (4) 20°C.

where the vibrational spacings are ca. 1200 cm^{-1}. The log θ_{346nm} and reciprocal of temperature fit on Arrhenius type plot with slope indicating ΔH of -1.0 Kcal/mole in isooctane. The CD intensity increases by lowering temperature and becomes nearly constant at ca. -100°C (Fig. Ib), in mixed solvents of isopentane -methylcyclohexane (5 : 1) or isopentane - ether - ethanol (5 : 5 : 1). The positive and negative Cotton effects observed in 285 - 310 nm are comparatively weak and insensible to the temperatures in appearance.

The NMR spectrum of II shows signals at 1.55 (J = 7.5, 3H), 5.22 (J = 7.5, 1H), 7 - 7.4 (8H), and 7.76 ppm (J = 8.0 and 2.0 Hz, 1H) in D_4 - methanol at 23°C (δ_{ppm} from TMS). Marked line broadening for the methyl and methine signals is observed in the range of -55 to -70°C, indicating that rotation of the phenylethyl moiety is restricted and frozen below the temperatures. The chemical shift values of the methyl and methine protons indicate that the latter proton alone strongly experiences the deshielding effect of the carboxyl group.[6] The preferable conformation of II is illustrated as above, which is analogous to that of 1-phenyl-1-(2,4,6-trimethylphenyl)ethane.[6]



The NMR spectrum of I shows signals at 1.52 (J = 8.0, 1H), 4.34 (J = 8.0, 1H), 7 - 7.5 (12H), and 7.56 ppm (J = 9.0 and 2.0 Hz, 2H) in CS_2 at 23°C (δ_{ppm} from TMS). Unlike the case of II, however, the spectrum in CS_2 or D_6 - DMSO unchanged in the range of -102 to 150°C. Rotations of the benzoyl and phenylethyl moieties are conclusively assumed to be unrestricted in the range of the temperatures. Four possible conformations for I are represented as follows.



(A) (B) (C) (D)

The non-bonded repulsive interactions between phenyl or carbonyl and methyl groups will certainly tend to exclude conformer B and C. This is confirmed from the fact that the methine proton alone experiences the deshielding effect of the

carbonyl group.[6] On the other hand, the conformer A and B are favored by entropy. This may be because in conformer C and D there is considerable interference to rotations of the phenyl groups, whereas in conformer A and B, where they are much further apart, they are able to rotate more freely. In fact, we obtained no evidence for restricted rotations of the terminal phenyl groups from the NMR data. The theoretical consideration predicts that in cases of non- and mono-substituted benzophenones the barrier to rotation is so small that enantiomerization occurs easily by one and/or two ring flip mechanisms, and the helical conformations are energetically predominant.[7,8] In fact, the enantiomerization has been known even in poly-substituted benzophenone,[9] and highly restricted rotations of both phenyl rings are very rare.[9,10] For I the temperature-dependent CD spectra (Fig. Ib) may indicate that rotations of the benzoyl and phenylethyl moieties are frozen below -100°C.

We conclusively assume that conformer A is the most favorable for I, where both benzoyl and phenylethyl moieties rotate on the NMR time scale at the ambient temperatures.

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