Circular Dichroism and Electronic Absorption Studies on Some *N*-Monosubstituted and *N*,*N*-Disubstituted Benzamides

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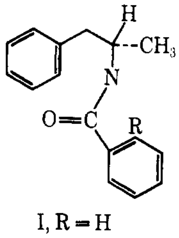
Abstract: The absorption and circular dichroism spectra of some *N*-monosubstituted and *N*,*N*-disubstituted benzamides are reported. The principle features and solvent effects in the circular dichroism spectra can be best explained by assuming that the n → π* transition of the benzamido chromophore is responsible for a Cotton effect between the two aromatic transitions. The signs of the Cotton effects are correlated with absolute configuration.

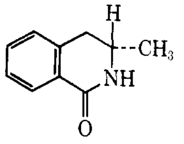
The carbonyl group is an extremely useful chromophore in circular dichroism (CD) and optical rotatory dispersion (ORD) studies, and considerable effort has been expended in understanding its optical properties.[1] Increasing attention is being given to the CD and ORD properties of other chromophoric groups in order to uncover useful regional rules of rotation, analogous to the octant rule of the carbonyl group,[2] or to use these optical phenomena as a sensitive probe for investigating molecular and electronic structure. In particular, some progress has been made in understanding the rotatory properties of aromatic chromophores,[3] although the authors of ref 3 noted that the Cotton effects of aromatic substances have not been adequately studied. An adequate study of aromatic chromophores, especially those subject to conformational mobility, can be fraught with experimental and interpretive complications. Reliable CD data are sometimes impossible to obtain in regions of weak optical activity and strong absorption, and the assignment of the transitions responsible for the Cotton effects may be complicated by the presence of rotamers or solvated species which have different absorption and CD properties. Nevertheless, the origin and characteristics of the observed Cotton effects of the aromatic chromophore must be known before the CD data can be applied with certainty to structure analysis.

We have undertaken a CD study of the benzamido chromophore in order to determine or verify the absolute configurations of some *N*-monosubstituted and *N*,*N*-disubstituted benzamides produced in our laboratories by microbiological oxygenation.[4,5] In this article we present the experimental results and our interpretation of the absorption and CD data of the benzamides given in Table I (see Results and Discussion). The observed rotations of some molecules, especially the *N*-monosubstituted benzamides, are small, and accurate CD measurements in regions of high absorption were not possible. Because of this experimental difficulty, special precautions given in the Experimental Section were taken to minimize errors due to false rotations and base line drift.

The literature is practically void of ORD studies of the benzamido chromophore and, to our knowledge, no systematic CD studies through the benzamido transitions in the accessible ultraviolet region of the spectrum have been carried out. Potapov, *et al.*,[6] in a series of communications reported the ORD of some *N*-benzoyl derivatives of secondary amines above 300 nm and attributed the reversal of sign of the plain curve with solvent change to amide mesomerism effects. Recently, Potapov, *et al.*,[7] in a communication describing the effects of cyclic structure on the ORD of aromatic compounds reported the ORD of *N*-benzoyl-(+)-α-benzylethylamine (I), (+)-*N*-(α- benzylethyl)amide of *o*-toluic acid (II), and (+)-3-methyl-3,4- dihydro-1- isoquinoline (III). These authors attributed the strong positive Cotton effect of III at 270 nm to the absorption band at 278 nm and associated the Cotton effect of I near 230 nm with the absorption band of the amide group conjugated with the benzene ring. The absorption curves of I–III were not given in this communication and, except as noted above, the relationship between the ORD and absorption data was not discussed. The CD results for the benzamides of Table I presented in this communication indicate that the rotatory properties of the benzamide chromophore are more complex than is evident from past ORD studies.



I, R = H
II, R = CH$_3$



III

Experimental Section

Circular dichroism measurements were made at 27° on a Cary 60 ORD–CD instrument calibrated with 10-camphorsulfonic acid. The concentration of the benzamide solution was normally about 0.5 mg/ml, and the cell path lengths ranged from 0.1 to 5.0 cm. Changes in cell path length or concentration near 265 nm were

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(1) (a) C. Djerassi, "Optical Rotatory Dispersion: Applications to Organic Chemistry," McGraw-Hill, New York, N. Y., 1960; (b) L. Velluz, M. Legrand, and M. Grosjean, "Optical Circular Dichroism. Principles, Measurements and Applications," Verlag Chemie, Weinheim, 1965; P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, San Francisco, Calif., 1965.

(2) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, **83**, 4013 (1961).

(3) P. Crabbé and W. Klyne, *Tetrahedron*, **23**, 3449 (1966).

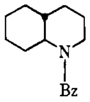
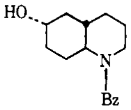
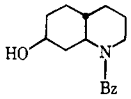
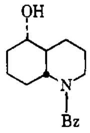
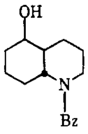
(4) See R. A. Johnson, H. C. Murray, and L. M. Reineke, *J. Amer. Chem. Soc.*, **93**, 4872 (1971).

(5) R. A. Johnson, H. C. Murray, L. M. Reineke, and G. S. Fonken, *J. Org. Chem.*, **33**, 3207 (1968).

(6) (a) V. M. Potapov and A. P. Terent'ev, *Zh. Obshch. Khim.*, **31**, 1720 (1961); (b) V. M. Potapov, V. M. Dem'yanovich, L. I. Lazutina, and A. P. Terent'ev, *ibid.*, **32**, 1187 (1962); (c) V. M. Potapov, V. M. Dem'yanovich, and A. P. Terent'ev, *ibid.*, **35**, 1340 (1965).

(7) V. M. Potapov, V. M. Dem'yanovich, L. D. Solov'eva, and A. P. Terent'ev, *Dokl. Akad. Nauk SSSR*, **185**, 614 (1969).

Table I. Circular Dichroism and Absorption Data of *N*-Substituted Benzamides

Compd no.	Compound	Abs config at amido C[a]	Solvent[b]	λ_{max} ($[\theta]_{max}$), deg cm^2 dmol^{-1}			λ_{max} (ϵ_{max}), l. cm^{-1} mol^{-1}	
				Band 1[c]	Band 2	Band 3	B_{2u}[d]	B_{1u}
R = -NHC(=O)C_6H_5								
1	$CH_3C(R)HCH_2C(CH_3)HCH_3$	*R*	M	273 (−70), 279 (−130)	242 (1,840)	218 (−1100)	260–280	225 (10,500)
			D	272 (−), 280 (−)	258 (2,400)	222 (−2700)	270, 278	223 (10,200)
			C	272 (−), 279 (−)	258 (1,860)	225 (−830)	269, 277	224 (10,000)
2	$CH_3C(R)HCH_2CH_2C(CH_3)HCH_3$	*R*	M	272 (−230), 278 (−240)	255 (230)	230 (−1300)	270, 279	226 (10,600)
			D	270 (−), 278 (−)	256 (1,130)	225 (−3000)	269, 277	224 (9,900)
			H	270 (−), 277 (−)	258 (1,000)	225 (−1500)		
3	$CH_3C(R)HCH_2CH_2CH_2CH_3$	*R*	M	273 (−140), 279 (−180)	250 (450)	227 (−810)	269, 277	224 (10,600)
			D	270 (−), 278 (−)	253 (1,200)	225 (−1600)	269, 277	223 (9,800)
4	$CH_3C(R)HCH_2CH_2CH_3$	*R*	M	273 (−80), 278 (−110)	245 (790)	220 (−500)	260–280	224 (10,600)
			D	272 (−), 278 (−)	256 (1,200)	225 (−750)	268, 277	224 (9,770)
5	$CH_3C(R)HCH_2CH_3$	*S*	M	272 (250), 278 (200)		225 (1800)	260–280	225 (10,500)
			D	278 (+)	255 (−960)	222 (3600)	267, 277	223 (9,850)
6	$CH_3C(R)HCH_2C(OH)(CH_3)CH_3$	*R*	M	272 (−), 280 (−67)	240 (3,300)	218 (−1900)	269, 277	226 (10,900)
			D		252 (3,300)		268, 277	224 (10,300)
7	$CH_3C(R)HCH_2CH_2CH_2OH$	*S*	M	272 (200), 278 (200)	255 (−260)	228 (2000)	260–280	225 (10,900)
			D	272 (+), 278 (+)	258 (−1,000)	225 (3000)	268, 277	224 (9,900)
8	$CH_3C(R)HCH_2C(CH_3)HCH_2OH$	*S*	M	273 (+), 280 (96)	246 (−2,100)	220 (2100)	269, 277	226 (10,600)
			D		255 (−2,800)	221 (1400)	269, 277	225 (10,300)
9	$CH_3C(R)HCH_2OH$	*S*	M	272 (280), 277 (200)	235 (1,400)	210 (−2600)[e]	268, 277	225 (10,800)
			D	272 (420), 278 (340)	248 (880)	215 (−3600)[e]	268, 278	223 (9,950)
10	$CH_3CH_2C(R)HC(OH)HCH_3$	*S*	M	270 (280), 278 (210)		210 (−4400)[e]	268, 278	225 (10,700)
			D	272 (+), 278 (+)	233 (−3,500)		268, 277	224 (9,850)
R = -NHC(=O)$C_6H_4OCH_3$								
11	$CH_3C(R)HCH_2C(CH_3)HCH_3$	*R*	M		260 (−1,600)	238 (2,300)	272, 282	252 (15,800)
			D	276 (600), 283 (600)			272, 282	246 (14,800)
12	$CH_3C(R)HCH_2CH_2CH_3$	*R*	M		256 (−1,600)	230 (600)[e]	272, 283	251 (15,900)
			D	277 (400), 283 (600)			273, 283	247 (15,500)
13	$CH_3C(R)HCH_2CH_3$	*S*	M		250 (5,400)		272, 282	252 (15,500)
			D	276 (−400), 283 (−400)	244 (5,800)		272, 283	247 (15,150)
R = -NHCO-2,4,6,-$(CH_3)_3C_6H_2$								
14	$CH_3C(R)HCH_2C(CH_3)HCH_3$	*R*	M	270 (10), 279 (50)			260–280	
			D	269 (90), 277 (90)			260–280	
			H	270 (100), 278 (180)			260–280	
15	$CH_3C(R)HCH_2CH_2CH_3$	*R*	M	270 (400), 278 (400)			260–280	
			D	268 (500), 278 (500)			260–280	
16	$(CH_3)_2CHCH_2CH(CH_3)NH$-$COC_6H_4CH_3$-*o*	*R*	M		234 (2,500)		260–280	
			D		242 (2,100)		260–280	
17[f]			M	265 (−1,000), 271 (−900)	228 (9,200)			
			D	269 (−600), 275 (−900)	235 (7,000)			
			H	277 (−1,600), 283 (−1,550)	233 (7,500)			
			C	277 (−1,500), 283 (−1,400)	233 (7,300)			
18			M	266 (−1,200), 270 (−990)	227 (8,500)			
			D	270 (−1,000), 275 (−1,200)	231 (7,000)			
19			M	267 (−980), 272 (−920)	228 (10,600)			
			D	275 (−1,100)	233 (8,500)			
20			M	266 (1,100)	226 (−6,500)			
			D	269 (800), 275 (1,000)	233 (−6,200)			
21			M	266 (970), 272 (750)	227 (−7,300)			
			D	268 (500), 275 (670)	233 (−5,700)			

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[a] Absolute configuration of compounds **1**, **5**, **6**, **8**, **9**, **11**, **13**, **14**, and **16** are known from previous work reported in literature. Absolute configuration of compounds **2**, **3**, **4**, **7**, **10**, **12**, and **15** are assigned in the present work. [b] M = methanol, D = dioxane, C = cyclohexane, H = *n*-hexane. [c] Only the sign is given for cases where band 1 occurs as dips on the wing of the oppositely signed band 2. [d] Discernible shoulders or regions of broad absorption are indicated. [e] Band maxima were not reached. [f] Bz = -C(=O)C_6H_5.

necessary to record CD curves under optimum conditions and sometimes resulted in discontinuities in the CD curves (Figures 1 and 3). Special precautions were taken to assure that the CD bands in regions of strong absorption and weak optical activity (below 230 nm for some *N*-monosubstituted benzamides) were real. To detect errors due to irreproducible placement of cell, cell contaminations, and base line drift, all sample and solvent scans were started in regions where the sample had zero activity and checked against air. The difference between sample and solvent lines in these regions was always 0.001 deg ellipticity or less. The false rotation of the Cary 60-CD was checked with dichromate and optically inactive benzamide solutions and found to be about +0.0015 deg ellipticity at a dynode voltage of 5 (about 2.5 absorbance units). The maximum correction for false rotation in the region of the 225-nm band of some *N*-monosubstituted benzamides was not greater than 50% of the observed rotations, and the position of the observed band was not changed by correcting for false rotation throughout the band. In cases of very weak optical activity, three separate CD curves were obtained and averaged. Because of the weak optical activity and high noise levels, we believe that the signs and positions of the CD bands of the *N*-monosubstituted benzamides at short wavelength are relatively certain as compared to their intensity. Peak-to-peak noise levels of the CD sample lines are indicated in the figures by vertical bars.

Absorption spectra were obtained on a Cary 15 spectrophotometer using a cell path length of 1.0 cm and benzamide concentrations of about 0.02 mg/ml. All solvents were of analytical or spectrograde quality.

A description of the benzamides not described below can be found in a previous paper (**17–21**)[5] or in the accompanying paper (**1–4**, **6–8**, **10**).[4] The CD data given for **5** and **13** have been corrected to 100% optical purity. The optical purities of the remaining benzamides are unknown.

(1*S*)-1-Methylpropylamine was prepared by resolution of racemic amine with *d*-tartaric acid. The amine tartrate was converted directly to the amides **5** and **13** by Schotten–Baumann reactions with the appropriate acid chlorides. The specific rotation of the amine must be (+) since benzamide **5** has (+)-rotation and has been related to the (+)-amine.[8] Consequently, the absolute configuration of the amine must be 1*S*.[9]

(1*S*)-*N*-(1-Methylpropyl)benzamide (5) was obtained as colorless needles from methanol–water: mp 91–93°; $[\alpha]_D$ +15° (*c*, 0.956, $CHCl_3$); $[\alpha]_D$ +14° (*c* 4.112, EtOH) (lit.[8] mp 92–92.5°; $[\alpha]_D$ +30.74° (*c* 4.0, EtOH). The optical purity is about 50%.

(1*S*)-*N*(1-Methylpropyl)-4-methoxybenzamide (13) was obtained as colorless crystals from methanol–water: mp 121–123°; $[\alpha]_D$ +22° (*c* 0.3764, $CHCl_3$).

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.14; H, 8.49; N, 6.70. The optical purity should be similar to that of **5**, about 50%.

(1*R*)-1-Methylbutylamine. Racemic amine (218 g) was resolved by recrystallization of the *d*-tartrate. The free amine was distilled through a 10-cm Vigreux column, 23.6 g of forerun, bp 75–86°, and 3.90 g of product, bp 86–89°, $[\alpha]_D$ −7.95° (neat).

Benzamides **12** and **15** were prepared by the Schotten–Baumann procedure using amine of $[\alpha]_D$ −7.95°.

(1*R*)-*N*-(1-Methylbutyl)-4-methoxybenzamide (12) was obtained as colorless crystals from methanol–water: mp 131–133°; $[\alpha]_D$ −31° (*c* 0.424, $CHCl_3$).

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.73; H, 8.81; N, 6.30.

(1*R*)-*N*-(1-Methylbutyl)-2,4,6-trimethylbenzamide (15) was obtained as colorless crystals by recrystallization from methanol–water: mp 116–118°; $[\alpha]_D$ −24° (*c* 0.402, $CHCl_3$).

Anal. Calcd for $C_{15}H_{33}NO$: C, 77.20; H, 9.94; N, 6.00. Found: C, 76.85; H, 10.00; N, 6.88.

Benzamides **11**, **14**, and **16** were prepared by Schotten–Baumann reactions of the appropriate acid chlorides with (1*R*)-1,3-dimethylbutylamine of $[\alpha]_D$ −11.50° (lit.[4] $[\alpha]_D$ −11.70°).

(1*R*)-*N*-(1,3-Dimethylbutyl)-4-methoxybenzamide (11) was obtained as colorless crystals (methanol–water): mp 116–118°; $[\alpha]_D$ −26° (*c* 0.995, $CHCl_3$).

Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00; N, 5.95 Found: C, 71.35; H, 8.77; N, 6.00.

(1*R*)-*N*-(1,3-Dimethylbutyl)2,4,6-trimethylbenzamide (14) was obtained as colorless crystals (methanol–water): mp 119–121°; $[\alpha]_D$ −27° (*c* 1.139, $CHCl_3$).

Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.80; H, 10.22; N, 5.95.

(1*R*)-*N*-(1,3-Dimethylbutyl)2-methylbenzamide (16) was obtained as colorless crystals (acetone–Skellysolve B): mp 75–76°; $[\alpha]_D$ −21° (*c* 0.988, $CHCl_3$).

Anal. Calcd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.39. Found: C, 77.05; H, 9.75; N, 6.43.

(1*S*)-*N*-(1-Methyl-2-hydroxyethyl)benzamide (9) was prepared from commercially available (Aldrich Chemical Co.) L-2-amino-1-propanol (2*S*) by the Schotten–Baumann reaction, followed by heating of the product in aqueous methanolic sodium hydroxide to hydrolyze the benzoate ester. Recrystallization from acetone–Skellysolve B gave shiny, colorless flakes: mp 132–133°; $[\alpha]_D$ −8° (*c* 0.466, $CHCl_3$).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.27; H, 7.56; N, 8.19.

Results and Discussion

Compounds which contain the phenyl group normally exhibit three absorption bands in the accessible ultraviolet region of the spectrum: a weak band near 260 nm, which often shows vibrational fine structure, and two more intense bands near 180 and 200 nm. Various nomenclatures have been proposed for these bands.[10] For convenience, we follow the system of Clark and Tinoco[11] and consider the intense band of benzamides **1–13** at short wavelength (Table I) as being derived from the benzene ${}^1A_{1g} \rightarrow {}^1B_{1u}$ transition (200-nm band)[12] and the weak band near 275 nm as being derived from the benzene ${}^1A_{1g} \rightarrow {}^1B_{2u}$ transition, and will henceforth refer to these bands as the B_{1u} and B_{2u} transitions (${}^1L_a$ and ${}^1L_b$, respectively, in Platt's terminology[13]).[14] No attempt was made to measure the absorption or CD of other aromatic (180-nm benzene band) or amide transitions which might occur below 210 nm.

***N*-Monosubstituted Benzamides 1–10.** The principle features of the CD and absorption curves of the *N*-monosubstituted benzamides **1–8** are very similar and are most evident from the CD and absorption spectra of **1** in methanol and dioxane (Figure 1). The CD of **9** and **10** differ from those of **1–8** and will be discussed separately.

The absorption spectrum of **1** exhibits two weak shoulders near 270 and 280 nm attributable to the B_{2u} transition, more evident in dioxane than in methanol, and the strong B_{1u} band near 225 nm ($\epsilon \sim 10{,}000$).

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(8) N. J. Leonard and E. W. Nommensen, *J. Amer. Chem. Soc.*, **71**, 2808 (1949).

(9) A. Kjaer and S. E. Hanson, *Acta Chem. Scand.*, **11**, 898 (1951).

(10) C. N. R. Rao, "Ultraviolet and Visible Spectroscopy: Chemical Applications," 2nd ed, Plenum Press, New York, N. Y., 1967, p 58.

(11) L. B. Clark and I. Tinoco, Jr., *J. Amer. Chem. Soc.*, **87**, 11 (1965).

(12) The assignments of the benzene bands are not certain: G. Herzberg, "Molecular Spectra and Molecular Structure. III. Electronic Spectra and Electronic Structure of Polyatomic Molecules," D. Van Nostrand Co., Inc., Princeton, N. J., 1967, p 555.

(13) J. R. Platt, *J. Chem. Phys.*, **17**, 484 (1949).

(14) Nagakura and coworkers prefer to consider the intense band at 220–260 nm of carbonyl-substituted benzenes as an intermolecular charge-transfer transition rather than as a band derived from the 203-nm benzene band.[15] According to their theory, the CT band arises from two new energy levels which result from an interaction between the highest occupied orbital of benzene and the lowest vacant orbital of the carbonyl group. We prefer to follow the nomenclature and assignment system of Clark and Tinoco[11] and do not consider the possibility that the benzamido chromophore might exhibit both a CT and B_{1u} band at short wavelength. In using this nomenclature system we do not mean to imply that the electronic interactions which lead to the intense benzamido band are small.

(15) (a) S. Nagakura and J. Tanaka, *J. Chem. Phys.*, **22**, 236 (1954); (b) S. Nagakura, *ibid.*, **23**, 1441 (1955); (c) J. Tanaka, S. Nagakura, and and M. Kobayashi, *ibid.*, **24**, 311 (1956).

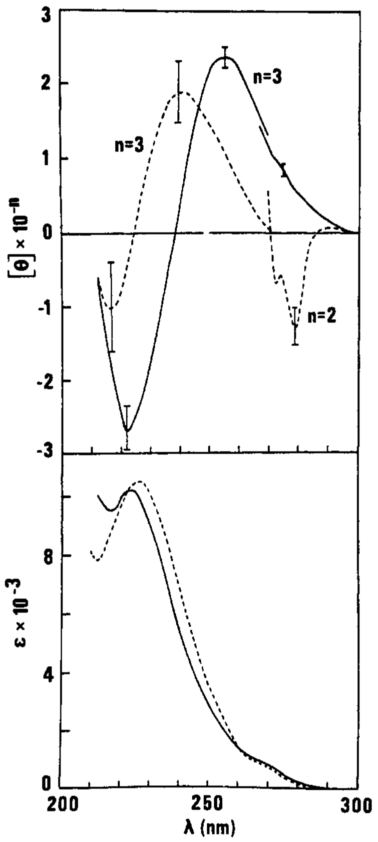

Figure 1. Absorption (lower curves) and CD curves of (2*R*)-*N*-benzoyl-2-amino-4-methylpentane (**1**) in methanol (- - -) and dioxane (——).

Solvent effects are small. The B_{1u} band is shifted a few nanometers toward longer wavelengths when going from dioxane to methanol (Table I), and the B_{2u} maxima near 275 nm are insensitive to solvent change.

The methanol CD curve of **1** shows maxima at 272 and 278 nm, which correspond closely with the observed absorption maxima of the B_{2u} transition, and two maxima at 241 and 217 nm. The maxima at 272 and 278 nm are insensitive to solvent change and, in dioxane, occur as dips of the same sign and at the same wavelengths as in methanol on the wings of a positive band at 255 nm. The positive band at 241 nm in methanol is shifted to 256 nm in dioxane and masks the CD maxima at 272 and 278 nm to a large extent. The apparent shift to longer wavelength of the 217 nm band in dioxane is not a general feature of benzamides **1**–**8**. The position of this band in dioxane as compared to its position in methanol is the same for **3**, **5**, **7**, and **8**, at longer wavelengths for **1** and **4**, and at shorter wavelengths for **2**. In an attempt to increase solvent effects, the CD spectra of **1** and **2** were obtained in cyclohexane and *n*-hexane, respectively. The band positions in these solvents do not differ significantly from those in dioxane (Table I).

From their absorption spectra, benzamides **1**–**8** would be expected to exhibit at least two optically active bands near 275 and 225 nm assignable to the B_{2u} and B_{1u} transitions, respectively. The weak CD maxima at 272 and 278 nm can be safely assigned to the B_{2u} transition, however, the CD pattern below 260 nm deserves special attention since more than one interpretation is possible. First, the maximum near 220 nm might be assigned to the B_{1u} transition and the maximum near 240 nm (methanol) to a separate electronic transition not observed in absorption because of weak intensity. Second, the double-humped maximum in this region might be due to a single electronic transition of two different conformers or differently solvated species which absorb at slightly different wavelengths and have oppositely signed CD bands.[16] Benzamides **1**–**8** are subject to conformational mobility, and that one electronic transition ($\pi \rightarrow \pi^*$ or $n \rightarrow \pi^*$) and two such species could account for the double-humped curve in the 260–210-nm region is not unlikely. Unfortunately, we lack the low-temperature capabilities which would offer direct information regarding these possibilities. However, the solvent effects observed for benzamides **1**–**8** and also **11**–**13** are not wholly consistent for the case of a single electronic transition and two or more molecular species in equilibrium. For the latter case, a change in solvent might produce a redistribution of intensity and a wavelength shift, but the wavelength distance between the maxima would be expected to remain approximately constant.[16] In fact, benzamides **1**–**4**, **7**, and **8** (which show well-defined maxima) show greater wavelength separation in dioxane than in methanol, approximately 12 nm difference in the case of **1**.

The observed solvent effects are more consistent for the case of two electronic transitions overlapped in the CD, one at short wavelength of B_{1u} origin and one at longer wavelength of $n \rightarrow \pi^*$ origin. The longer wavelength band near 240 nm in methanol does show those spectral properties associated with an $n \rightarrow \pi^*$ transition—low absorption intensity and a shift toward longer wavelength in nonpolar solvents.[17] If this interpretation is valid and if conformation effects or solvation effects other than a shift in position of the CD bands are negligible, two specific solvent effects would be expected on going from methanol to dioxane. First, both bands should be more intense in dioxane since the increase in band separation would decrease the overlap cancellation of intensity. This effect is observed. All benzamides **1**–**8** except **6** and **8** show an increase in peak height intensity of both CD maxima in dioxane. Second, the observed band positions should be closer to the real positions in dioxane, again because of less band overlap and hence less band distortion. This effect is also observed. The short wavelength band assignable to the B_{1u} transition occurs at or very near the absorption maximum in dioxane, while its position in methanol is more variable (Table I).

The B_{2u} CD pattern of benzamides **1**–**8** in methanol is especially constant from molecule to molecule, but the CD pattern below 260 nm is somewhat variable and, according to the interpretation given above, depends on the relative intensities of the B_{1u} and $n \rightarrow \pi^*$ transitions. Thus, the band near 240 nm in methanol is very weak for **2** and **7** and not observable for **5**, and the dioxane curve of **6** does not show a negative band near 220 nm as does the methanol curve. The significance of the CD results, however, lies in the similarities of the CD curves. All benzamides **1**–**8** exhibit three optically active bands in at least one solvent, the signs of which can be correlated with the absolute configuration of the

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(16) K. M. Wellman, P. H. A. Laur, W. S. Briggs, A. Moscowitz, and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 66 (1965).

(17) M. Ito, K. Inuzuka, and S. Imanishi, *ibid.*, **82**, 1317 (1960).

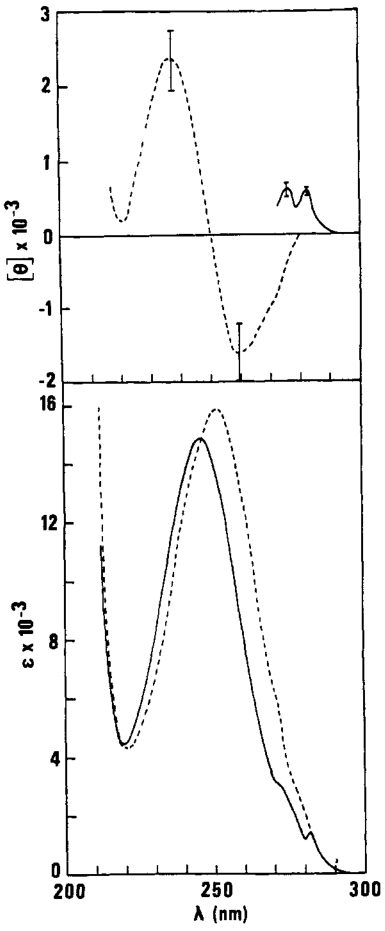


Figure 2. Absorption (lower curves) and CD curves of (1*R*)-*N*-(1,3-dimethylbutyl)-4-methoxybenzamide (**11**) in methanol (- - -) and dioxane (—).

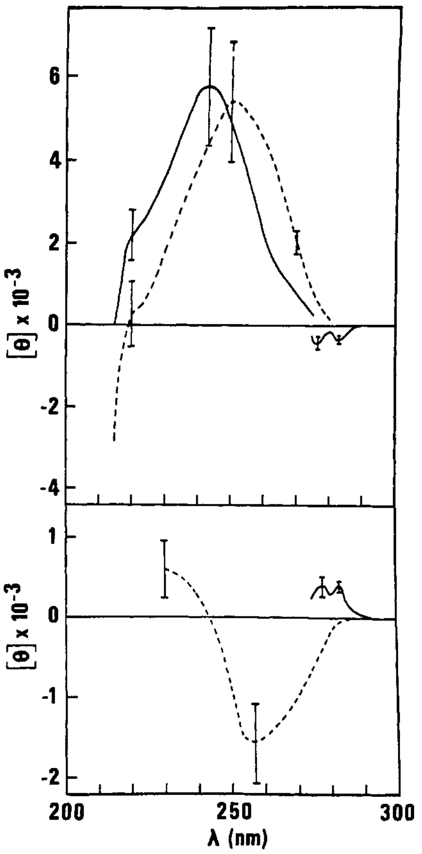


Figure 3. CD curves of (1*R*)-*N*-(1-methylbutyl)-4-methoxybenzamide (**12**, lower curves) and (1*S*)-*N*-(1-methylpropyl)-4-methoxybenzamide (**13**) in methanol (- - -) and dioxane (—).

asymmetric carbon atom bonded to the nitrogen atom. The signs are (−, +, −) in wavelength order for compounds of known *R* configuration, **1** and **6**, and reversed signs for compounds of known *S* configuration, **5** and **8**. On this basis, compounds **2**, **3**, and **4** have the *R* configuration and **7** the *S* configuration. Assuming that the gross features of the CD spectra are determined by the perturbers on or nearest the asymmetric carbon atom, the existence of such a correlation must mean that the conformation at the asymmetric carbon atom of greatest contribution to the CD is similar for **1**–**8**, even though the geometry in other parts of the molecule may differ.

The absorption spectra of **9** and **10** are almost identical with those given for **1**, but their CD spectra differ considerably from those of benzamides **1**–**8** (Table I). Neither compound shows three CD bands of alternating sign when taken in wavelength order, and the CD of **10** below 260 nm is plain in methanol. These CD differences are not especially surprising since, unlike benzamides **1**–**8**, **9**, and **10** contain a hydroxyl group α to the asymmetric carbon atom, and **10** has an ethyl rather than a methyl group on the asymmetric carbon atom. It is interesting to note that the positive B_{2u} Cotton effect of **9** with maxima at 272 and 278 nm is consistent with its absolute configuration (*S*) in terms of the correlation observed for compounds **1**, **5**, **6**, and **8** while the signs of the Cotton effects below 250 nm are not. For benzamides **1**–**10**, the sign of the B_{2u} Cotton effect appears to be the best indication of absolute configuration, and, on this basis, the *S* configuration would be predicted for **10** at position **2**.

***p*-Methoxy Derivatives 11–13.** The absorption curves of the *p*-methoxy derivatives of **1**, **4**, and **5** (**11**–**13**) are very similar to each other and are illustrated in Figure 2 for **11** along with the CD of **11**. The dioxane absorption curve of **11** exhibits two weak absorptions between 270 and 285 nm and a strong band at 246 nm ($\epsilon \sim 15{,}000$) which is shifted to longer wavelengths in methanol (252 nm). The methanol CD curve of **11** shows almost no activity near the absorption maximum at 252 nm, but exhibits positive and negative maxima at 238 and 260 nm, respectively. In dioxane, the ellipticities for **11** below 270 nm are too small to be observed at the concentration required to keep the absorbance below 2. Only the CD maxima attributable to the B_{2u} transition at 276 and 283 can be observed. The CD behavior of **12** is similar to that of **11** (Figure 3) except that the positive band below 250 nm appears weaker than in the case of **11**. The CD of **13** (Figure 3) exhibits only one band in the 220–270-nm region of the spectrum, and the CD maxima of this band in methanol and dioxane correspond closely with those observed in the absorption spectra.

A comparison of the CD curves of **1** and **11** (Figures 1 and 2) might at first suggest that the effect of the methoxy group is to reverse the signs of the three CD bands. This need not be the case, however, since the negative maximum at 260 nm and the positive maximum at 238 nm of **11** in methanol can be assigned to the B_{1u} and $n \rightarrow \pi^*$ transitions, respectively. That the

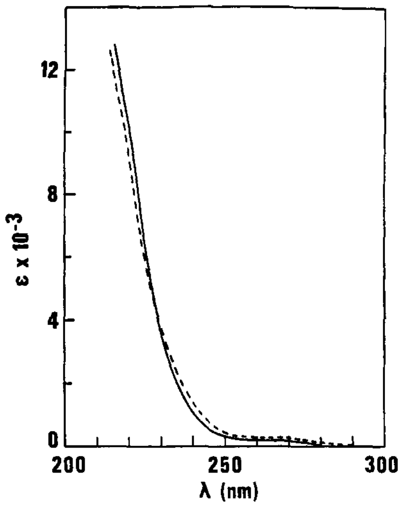


Figure 4. Absorption curves of (1*R*)-*N*-(1,3-dimethylbutyl)-2,4,6-trimethylbenzamide (**14**) in methanol (- - -) and dioxane (—).

position of the CD and absorption maxima of the B_{1u} transition of **11** are not the same (252 in absorption *vs.* 260 in CD) is no reflection on the validity of this assignment since the real band positions are undoubtedly masked because of overlap effects. If this assignment is correct and if solvent effects other than wavelength shift are negligible, the rotations in the 230- to 270-nm region should decrease (or even yield an antipodal type curve) on going to dioxane since the B_{1u} and $n \rightarrow \pi^*$ bands are shifted toward each other in a nonpolar medium. This is seen to be the case. Only the B_{2u} maxima at 276 and 283 nm are detectable in dioxane. The same reasoning explains the CD curves of **12**. The positive $n \rightarrow \pi^*$ band of **12** is weaker than in the case of **11** but is still significantly overlapped with the B_{1u} band at 257 nm. In the case of **13**, the $n \rightarrow \pi^*$ band is very weak and not detectable, and now the CD maxima at 250 nm (methanol) and 243 nm (dioxane) correspond closely to the absorption maxima at 252 and 246 nm. That the CD curve of **13** is dominated by the B_{1u} band is consistent with the observation that the parent molecule of **13** (**5**) shows very weak $n \rightarrow \pi^*$ activity in dioxane and none in methanol (Table I).

If the assignment given above for the *p*-methoxy derivatives is correct, the Cotton effect signs of the B_{1u} and $n \rightarrow \pi^*$ transition are the same for the parent molecule and *p*-methoxy derivative, while those for the B_{2u} transition are opposite. It is unlikely that this phenomenon is due to a difference in molecular geometry of the parent molecule and *p*-methoxy derivative. The correlation of absolute configuration with the signs of the Cotton effects observed for **1**–**8** indicates that the conformation of greatest contribution to the CO spectrum (in the immediate vicinity of the benzamide chromophore) must be similar for **1**–**8**. This conformation would not be expected to change because of the presence of a *p*-methoxy group. Rather, the sign reversal more likely originates from the electronic effects of the methoxy group on the benzamido transitions. The same phenomenon has been observed in the case of (−)-crinane (IV), (+)-powellane (V), and other alkaloids by DeAngelis and Wildman.[18] The B_{2u} and B_{1u} bands of IV have opposite signs (negative B_{2u}) while both are positive for V. A theoretical understanding of this phenomenon would be interesting as regards the effects of the methoxy group on the orientation of the electric and magnetic vectors associated with the B_{1u} and B_{2u} transitions.

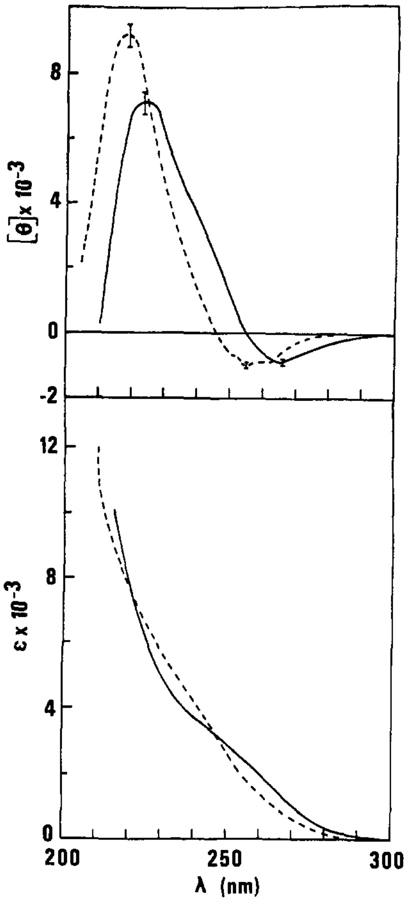
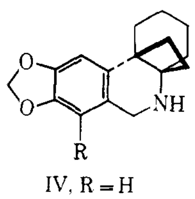


Figure 5. Absorption (lower curves) and CD curves of (4a*R*,8a*S*)-1-benzoyl-*trans*-decahydroquinoline (**17**) in methanol (- - -) and dioxane (—).



IV, R = H
V, R = OCH_3

Aryl-Methyl-Substituted Benzamides 14–16 and *N*,*N*-Disubstituted Benzamides 17–21. The absorption spectra of the *N*,*N*-disubstituted benzamides **17**–**21** are very similar to each other as are those of the aryl-methyl-substituted benzamides **14**–**16**. Representative spectra of **17** and **14** are given in Figures 4 and 5. Unlike the *N*-monosubstituted benzamides, these molecules show strong end absorption but no defined bands. The disappearance of the B_{1u} band for these derivatives has been attributed to nonplanar[19] phenyl and amide

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[18] G. G. DeAngelis and W. C. Wildman, *Tetrahedron*, **25**, 5099 (1969).

[19] By "nonplanar" we mean a greater departure from planarity than is observed in the case of benzamide. M. J. Aroney, R. J. W. LeLevre, and A. N. Singh [*J. Chem. Soc.*, 3179 (1965)] have shown from dipole moment and molecular Kerr constant measurements that the dihedral angle between the phenyl and amide groups of benzamide in dioxane is 37°. The dihedral angle has been shown to be 26° in solid benzamide (X-ray analysis) by Bruce R. Penford and J. C. B. White, *Acta Crystallogr.*, **12**, 130 (1959).

groups and a loss of conjugation as a result of steric interference involving the ortho and nitrogen substituents and the carbonyl oxygen.[20] Interference is relieved by rotation about the phenyl–carbonyl bond rather than the carbonyl carbon–nitrogen bond because of the high resonance energy of the planar amide group.[21] The nmr spectra of the benzamides of Table I also support this interpretation. Thus, molecules which exhibit a strong B_{1u} band (**1–13**) also show the complex fine structure in the aromatic region of the nmr spectrum characteristic of a conjugated carbonyl–phenyl group, while molecules which do not exhibit a strong B_{1u} band (**14–21**) show a single nmr peak (in $CHCl_3$) in the same region. That a single *o*-methyl substituent is sufficient to cause nonplanarity of the phenyl and amide groups is indicated by the end absorption spectrum of **16**.

Following the proposed band assignments given for benzamides **1–13**, benzamides **14–21** would be expected to exhibit only two Cotton effects assignable to the B_{2u} and $n \rightarrow \pi^*$ transitions. Furthermore, the $n \rightarrow \pi^*$ transition should occur at shorter wavelengths than that observed for benzamides **1–13** because of a loss in conjugation of the phenyl and amide groups. This behavior is observed for decahydroquinolines **17–21** (see below), and the 2,4,6-trimethyl derivatives **14** and **15** do show positive B_{2u} maxima near 278 and 287 nm (Table I). Unfortunately, the ellipticities for **14** and **15** below 250 nm are small and immeasurable. As in the case of the *p*-methoxy derivatives **11–13**, the signs of the B_{2u} Cotton effects for **14** and **15** are opposite those of the parent molecules. This sign reversal may not be due to electronic effects alone, however, since the chromophoric geometry of **14** and **15** is different from that of the parent molecules. Unlike **14** and **15**, **16** does not show the weak CD maxima associated with the B_{2u} transition but exhibits a broad band near 235 nm in methanol which is shifted to 242 nm in dioxane (Table I). This band can be assigned to the $n \rightarrow \pi^*$ transition and does occur at shorter wavelengths than that observed for benzamides **1–13**, but the reason why **16** does not show a B_{2u} Cotton effect is unclear.

The CD spectra of the decahydroquinolines **17–21** are very similar, and their characteristic features are illustrated by **17** in Figure 5. Except for minor intensity variations, the hydroxy substituent and the asymmetric carbon atom in the cyclohexane ring do not effect the CD characteristics of the benzamido chromophore in these molecules (Table I). Decahydroquinolines **17–19** show a weak negative Cotton effect near 270 nm and a strong positive Cotton effect near 230 nm. Compounds **20** and **21** have the opposite trans-fused configuration and exhibit mirror image CD curves to those of **17–19** (Table I).

The whole CD curve of **17** undergoes a shift to longer wavelength in dioxane, and small CD maxima or shoulders (barely perceptible on the scale given in Figure 5) occur at 265 and 272 nm in methanol and 268 and 275 nm in dioxane. The positive band at 227 nm in methanol is shifted to 234 nm in dioxane and appears more symmetrical in methanol than in dioxane. In an attempt to produce greater solvent differences, the absorption and CD curves of **17** were obtained in cyclohexane and *n*-hexane. The absorption curves in dioxane, cyclohexane, and *n*-hexane are very similar, and all show a slight shoulder near 250 nm (Figure 5). The CD curves in cyclohexane and *n*-hexane are essentially identical with each other and, except in the 260–310-nm region, are also identical with the dioxane curve. The methanol, dioxane, and *n*-hexane CD curves of **17** between 310 and 260 nm are given in Figure 6 on a scale which more clearly illustrates the solvent effects in this region of the spectrum. The solvent effects are relatively large. The two maxima associated with this band are shifted about 12 nm to longer wavelength when going from methanol to *n*-hexane, and the rotational strength is greater in *n*-hexane than in dioxane or methanol.

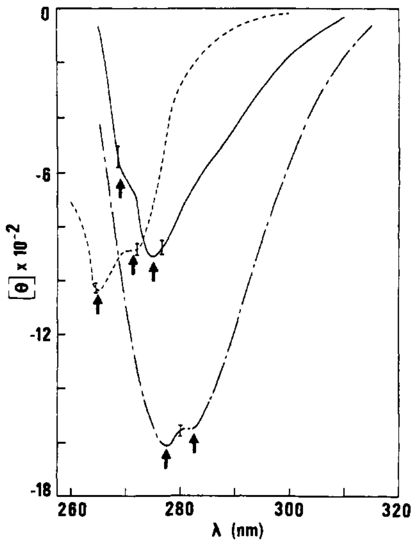

Figure 6. CD curves of (4a*R*,8a*S*)-1-benzoyl-*trans*-decahydroquinoline (**17**) in methanol (- - -), dioxane (—), and *n*-hexane (– - –) The spacing between arrows (band maxima) is approximately 800 cm^{-1}.

The optical activity of **17** in the 260- to 310-nm region might be attributed to a transition involving lone pair electrons because of the direction and magnitude of the solvent effects observed in this region. However, the optical activity in this region is more likely due to the B_{2u} transition for the following reason. The wave number distance between the B_{2u} maxima is the same for benzamides **1–16**, approximately 800 cm^{-1}, and can be attributed to vibrational fine structure involving the symmetric breathing mode of the benzene ring.[12] One would expect the same spacing in the B_{2u} transition of **17** since the excited state vibrational frequency of **17** should also be approximately 800 cm^{-1}. In fact, this is the approximate wave number distance between maxima observed for **17** in the 260- to 310-nm region in all solvents (Figure 6). This interpretation is in agreement with what Horwitz, *et al.*,[22] found for the excited state frequency of this vibration in the case of *p*-cresol and tyrosine, 800 and 808 cm^{-1}, respectively. Evidently, the solvent effects of the B_{2u} transition of **17** and the *N*-monosubstituted benzamides are considerably different. As noted earlier, **1** and **2** show negligible shift of the B_{2u}

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(20) (a) J. T. Edward and S. C. R. Meacock, *Chem. Ind.* (*London*), 536 (1955); (b) K. Yates and B. F. Scott, *Can. J. Chem.*, **41**, 2320 (1963).

(21) L. Pauling, R. Corey, and H. Branson, *Proc. Nat. Acad. Sci., U. S.*, 37, 205 (1951).

(22) J. Horwitz, E. H. Stickland, and C. Billups, *J. Amer. Chem. Soc.*, **92**, 2119 (1970).

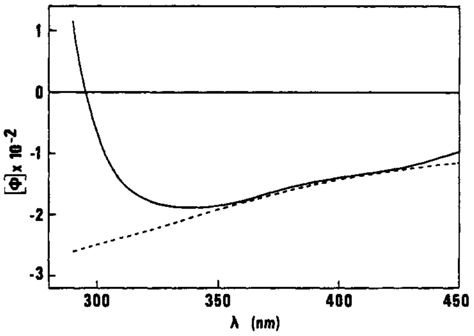

Figure 7. ORD curves of (2*R*)-*N*-benzoyl-2-amino-4-methylpentane (**1**) in methanol (- - -) and dioxane (—).

maxima from 272 and 278 nm in the same solvents (Table I).

The strong CD band of **17** at 227 nm (methanol) can be attributed to the n → π* transition of the amide group. As in the case of the *o*-methyl derivative **16**, the band occurs at shorter wavelengths than in the case of the *N*-monosubstituted benzamides, about 235 nm *vs.* 255 nm in dioxane. The origin of the positive asymmetry in the long wavelength wing of this band in nonpolar media (Figure 5) is unclear. Another CD band associated with the shoulder observed in absorption (Figure 5) may be located near 250 nm, or the asymmetry may be due to distortion produced by a strong negative band below 220 nm.

In conclusion, we suggest that the gross features and solvent effects in the CD spectra of benzamides **1–21** can be best explained by assuming that the n → π* transition of the benzamido chromophore is optically active and, except for **11–13**, is located between the B_{1u} and B_{2u} transitions. The CD solvent changes of benzamides **1–8** do not suggest that tautomerism or mesomerism effects are operative as have past ORD studies conducted on similar molecules.[6] These ORD studies were carried out between 600 and 300 nm, and the sign reversal of the plain curve for some molecules was attributed to a change in electronic structure of the amide portion of the molecule with solvent. We also notice such a "sign reversal" in the ORD of **1** in the wavelength range 450–290 nm (Figure 7). The curve is negative in methanol and, although the rotations near 400 nm begin negative in dioxane, the final result in dioxane is a plain positive curve. The ORD behavior of **1** is easily understood from the CD of **1**. The sign of the plain curve depends upon which of the three CD bands dominates in the ORD between 450 and 290 nm. According to our interpretation, the positive n → π* band determines the sign in dioxane because of a shift to longer wavelength, while the negative B_{1u} or B_{2u} bands dominate the ORD in methanol. In the case of *N*-benzoyl-2-aminobutane (**5**), the ORD sign reversal was not observed (**6b**). According to the CD of **5** (Table I), this is because the n → π* transition is weak and does not significantly distort the long wavelength ORD tail of the B_{1u} transition in any solvent. It is conceivable that the peculiar ORD solvent effects of other *N*-benzoyl derivatives of amines observed in the past could be explained in the same way.

Acknowledgments. We wish to acknowledge helpful discussions concerning the nmr spectra of some molecules with Dr. George Slomp and Dr. B. V. Cheney.

The Microbiological Oxygenation of Acyclic *N*-Alkylbenzamides[1]

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Contribution from the Research Laboratories, The Upjohn Company,
Kalamazoo, Michigan 49001. Received October 27, 1970

Abstract: In searching for new classes of substrates that are oxygenated by *Sporotrichum sulfurescens*, acyclic *N*-alkylbenzamides of four to seven carbon chain length have been found to give a variety of oxygenated products. In general, the longer chain length substrates are oxygenated primarily at the subterminal carbon farthest from the benzamido group. Substrates of shorter chain length are oxygenated at either the terminal or the subterminal carbon atom. The chiral center at the benzamido carbon exerts an influence on the stereochemical course of the reaction in several cases, suggesting an "active" role for the benzamido group in the oxygenation process.

Microbial oxygenations of acyclic compounds have received considerable attention, largely in the hands of microbiologists whose primary interest has been in the metabolic fate of hydrocarbon molecules.[2] Once the hydrophobic barrier of the hydrocarbon chains has been successfully breached by an initial oxidative attack, the oxygenated products generally are much more susceptible to further metabolism as an energy source for the microorganism, thereby precluding any substantial accumulation of useful chemical intermediates. Only when this further metabolism has been effectively blocked have significant quantities of the initially formed products been obtained. As an example, fermentation of hydrocarbons with *Torulopsis apicola*[3] or *T. gropengiesseri*[4] was found to give insoluble glycolipids, into which the oxygenated intermediates were incorporated. Hydrolysis of the glycolipids released

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(1) Stereochemistry of Microbiological Hydroxylation, Part VI.

(2) *Cf.* E. J. McKenna and R. E. Kallio, *Annu. Rev. Microbiol.*, **19**, 183 (1965); A. C. van der Linden and G. J. E. Thijsee, *Advan. Enzymol.*, 27, 469 (1965).

(3) A. P. Tulloch, J. F. T. Spencer, and P. A. J. Gorin, *Can. J. Chem.*, **40**, 1326 (1962).

(4) D. F. Jones and R. Howe, *J. Chem. Soc. C*, 2801 (1968).