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Spectrometric Studies of Carbonyl–Hydrogen Interactions in Different Steric Environments

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The weak interactions between carbonyl groups and electron-accepting substances have been investigated by nuclear magnetic resonance (n.m.r.) and ultraviolet measurements. The n.m.r. chemical shifts and the ultraviolet band shifts indicate there is steric hindrance to hydrogen bonding if a tertiary butyl group is next to the carbonyl group and there is some increased interaction if electron-releasing groups which do not interfere sterically are present. Long paraffinic chains next to the carbonyl group also make for a steric hindrance, presumably on a statistical basis. In general, the H-bonding tendencies run parallel to the known chemical reactivity in oximation, etc. Ultraviolet difference spectra are obtained and found to be about as sensitive to the existence of weak interactions as the former methods. Certain complicating factors must be carefully controlled if quantitative information is to be derived from the difference spectra.

Introduction

The interactions of carbonyl groups with secondary amino groups and other electron acceptors of the H-bonding type are very important to the study of the stability of the various conformations of proteins and polypeptides. Amides are frequently investigated as model compounds for these polymers,[1-3] but the H-bonding behavior of ketones or secondary amines as such is known only to a very limited extent. In general, the study of these latter compounds is particularly promising because they are capable essentially only of either donating or accepting electrons. Hence self-association and the formation of H-bonded oligomers of various types are suppressed.[4] The single electron donor–electron acceptor equilibrium of interest can then be assessed with some confidence, and one may hope to discern even small differences that may exist. A second reason for studying carbonyl compounds lies in that some of their condensation reactions, like oximation, are known or suspected to be distinctly affected by the steric environment of the carbonyl groups.[5] It will be interesting to seek correlations between the chemical reactivity and the H-bonding tendency. The steric environment of the carbonyl group can be expected to affect strongly the quality or strength of the H-bonds that are formed, and hence the stability of certain secondary structures of polypeptides and proteins. Bamford, *et al.*,[6] have ably reviewed the work done in this area. Theoretical calculations[7] do not seem to allow a clear decision as to the relative stability of various possible forms and experimental approaches are consequently very desirable.

In a few instances, the molecular shapes of the H-bonding species were thought to explain the experimental data. For example, the infrared measurements of Bellamy and Williams,[8] showing diisopropyl ketone to be somewhat less H-bonded than acetone, were interpreted in this fashion. In later work the same authors saw pronounced differences in the spectra of certain *cis*- and *trans*-nitrites.[9] Forbes[10] postulated steric interactions to explain the H-bonding of *o*-nitrobenzaldehyde, taken to be an intermolecular effect.

In any case, sensitive methods are necessary for a study of this type; ultraviolet shift measurements and difference spectra, and nuclear magnetic resonance (n.m.r.) measurements, were used in this work because they are known or expected to give reliable indications of even weak interactions.[11-14] Pimentel has shown that the shifts observed in the ultraviolet spectra due to H-bonding are usually much larger than those due to other causes.[15] In addition, there are a number of infrared studies on carbonyl compounds reported in the literature[8,9,16] while there is a paucity of ultraviolet and n.m.r. data in this area. It seems desirable to get such data and thereby assess the relative merits of the different experimental methods for the detection and classification of weak interactions of the H-bond type.

Experimental Method and Procedure

Materials.—Table I shows the origin and physical characteristics of the solutes and solvents used. The residual moisture, as found by Karl Fischer titrations, is also reported.

N.m.r. Measurements.—The modified side-band technique first described by Tiers[17] was found to be most suitable for the present purposes. It is very precise. Tetramethylsilane is used as an internal reference, and a side band is produced downfield from the signal of interest. The moment the side band is recorded and before the signal of interest appears, the side-band amplitude is reduced to zero. Right after the signal peak is obtained, the side-band amplitude is reset, and the frequency is changed such that a second side band is produced on the other side of the signal. The standard deviation of this procedure is quite low and the accuracy is as high as that of the frequency meter used (Hewlett Packard, Electronic Counter, Model 521). The Varian Associates A-60 console in conjunction with a 12-in. magnet was used for these measurements.

Ultraviolet Measurements.—A Cary Model 14 spectrophotometer was used with matched quartz cells of 10-mm. path lengths. Whenever desirable, the cells were fitted with matched quartz blocks so as to reduce the path length to 1 mm. The differential spectra reported below were obtained by a new method, designed to render harmless the minute mismatching of the pairs of quartz cells. First, two solutions of the same solute in two different solvents were placed in the sample and reference beam of the instrument, respectively. Then a second trace was obtained after refilling the cells such that the quartz cells were in interchanged positions but the solutions still in the same positions. The average of the two traces obtained is independent of the mismatching present in every pair of "matched" cells, even for rather high concentrations of the absorbing solute. Next, a solvent trace was obtained in an analogous fashion and finally the difference spectrum was computed as the difference between the average solute and average solvent traces. The difference spectral amplitudes are, in many cases, about one-hundredth of the actual spectral amplitudes, yet the reproducibility of the procedure was found to be quite satisfactory.

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(9) L. J. Bellamy, C. P. Conduit, R. J. Pace, and R. L. Williams, *ibid.*, **55**, 1677 (1959).
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(12) H. A. Scheraga, "Protein Structure," Academic Press, Inc., New York, N. Y., 1961, pp. 217 and 238.
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(17) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

TABLE I

SOLVENT AND SOLUTE PROPERTIES

Solvent or solute	Origin and grade	$n^{25}D$ Exptl.	$n^{25}D$ Lit.[a]	H_2O content, mg./l.[c]
Methanol	Matheson, Coleman and Bell Spectroquality	1.3281	1.3276 1.3257	~870
Isopropyl alcohol	Matheson, Coleman and Bell Spectroquality	1.3763	1.3747[b]	~90
Butanol	Fisher, certified reagent	1.3986	1.3972[b]	~165[d]
p-Dioxane	Matheson, Coleman and Bell Spectroquality	1.4206	1.4203[b]	~165
Chloroform	Fisher, certified reagent	1.4435	1.4436	~120
2,2,4-Trimethylpentane	Matheson, Coleman and Bell Spectroquality	1.3887	1.3890	~80
Cyclohexane	Matheson, Coleman and Bell Spectroquality			~20
Methylcyclohexane	Matheson, Coleman and Bell Spectroquality			~20
Acetone	Matheson, Coleman and Bell Spectroquality	1.3563	1.3568	~2000 ~0[d]
3,3-Dimethylpentanone-3	Aldrich Chemical Co.	1.3945	1.3933	
3-Nonanone	K & K Laboratories Lot 19520	1.4192		
5-Nonanone	K & K Laboratories Lot 28713	1.4176	1.416	
2,2,4,4-Tetramethylpentanone-3	K & K Laboratories Lot 38607	1.4147	1.4160	
3-Tetradecanone	K & K Laboratories Lot 36200	33	34	
Di-*n*-decyl ketone	Fluka A.G., Switzerland Purum	59.0–61.6	60–62	
d-Camphor	Eastman	177.4	176.7	
Benzil	Eastman	94.8–95.4	95	
Benzophenone	Fisher, certified reagent	48–49.1	49	
Di-*o*-tolyl ketone	K & K Laboratories Lot 21481	70.4–71.2	72	

[a] I. M. Heilbron, Ed., "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1936, unless otherwise noted. [b] A. Weissberger, E. S. Proskauer, Ed., "Organic Solvents," Interscience Publishers, Inc., New York, N. Y., 1955. [c] By Karl Fischer titrations. [d] After drying with calcium sulfate.

Results

Table II shows the chemical shifts of the chloroform proton in mixtures with the respective ketones ranging from chloroform mole fraction of about 0.04 to 1.0.

Table III summarizes the wave lengths of maximum ultraviolet absorption in 2,2,4-trimethylpentane and the relative shifts in mixtures containing either isopropyl alcohol, butanol, chloroform, or methanol as H-bonding partner for the ketone. The shifts for benzophenone and acetone in methanol relative to the result in a hydrocarbon are in good agreement with the literature values[18,19] if one takes into account the fact that different alcohol and hydrocarbon mixtures were used.

Figure 1 shows the difference spectra obtained on the system acetone–dioxane, in several hydrocarbons, showing the marked differences one can find even in nonpolar solvent systems. Figure 2 shows similar results for acetone in methylcyclohexane, at several concentrations. The difference spectra for acetone and 2,2,4,4-tetramethyl-3-pentanone in the binary solvent consisting of chloroform and a hydrocarbon run against a solution of the ketone in the same hydrocarbon are shown in Fig. 3. Similar data for acetone in strongly hydrogen bonding solvents are presented in Fig. 4. Finally, the difference spectra for two concentrations of acetophenone and benzophenone in chloroform mixtures and in methanol are seen in Fig. 5. Similar curves were obtained on *d*-camphor and *d*-fenchone, but they are not presented here because they are lower than 0.1 absorbance over most of the wave length range used, and they do not, at this time, yield new

TABLE II

CHEMICAL SHIFTS OF THE CHLOROFORM PROTON SIGNAL IN MIXTURES WITH KETONES[a]

Acetone						
Concn., mole %	50.2	10.79	21.18	41.73	61.58	80.99
Shift, c.p.s.	479.0	477.7	475.3	468.0	458.1	447.1
3-Methyl-2-butanone						
Concn., mole %	4.56	11.14				
Shift, c.p.s.	479.2	477.4				
3,3-Dimethyl-3-pentanone						
Concn., mole %	4.04	9.96	19.89	40.29	60.11	82.93
Shift, c.p.s.	477.8	476.6	473.9	466.8	457.5	445.0
Concn., mole %	5.27					
Shift, c.p.s.	477.0					
2,4-Dimethyl-3-pentanone						
Concn., mole %	4.61	10.64				
Shift, c.p.s.	480.2	479.0				
2,2,4,4-Tetramethyl-3-pentanone						
Concn., mole %	4.58		21.15	34.81	57.46	76.42
Shift, c.p.s.	476.8		472.8	467.6	458.0	448.0
3-Nonanone						
Concn., mole %	4.18	11.23	21.20	37.06	61.20	79.53
Shift, c.p.s.	478.0	475.9	473.4	468.2	456.4	446.8
Concn., mole %	2.82					
Shift, c.p.s.	478.1					
5-Nonanone						
Concn. mole %	5.40					
Shift, c.p.s.	477.6					
2-Heptanone						
Concn. mole %	4.33	11.59				
Shift, c.p.s.	478.2	476.4				

[a] Pure chloroform was found to have a shift of 436.1 c.p.s.

(18) G. J. Brealey and M. Kasha, *J. Am. Chem. Soc.*, **77**, 4462 (1955).
(19) W. S. Bayliss and E. G. McRae, *J. Phys. Chem.*, **58**, 1006 (1954).

TABLE III

WAVE LENGTH OF MAXIMUM ULTRAVIOLET ABSORBANCE FOR n–π* AND π–π* BANDS OF VARIOUS KETONES IN 2,2,4-TRIMETHYLPENTANE AND RELATIVE SHIFTS OF THIS BAND ON CHANGING THE SOLVENT AS INDICATED

Solute	Wave length of max. absorbance in 2,2,4-trimethylpentane, solv. 1, mμ	Shift (in mμ) of absorbance peak, rel. to position in solv. 1, in a mixt. with vol. fractions, v_2, of solv. 2				Solvent 2
		V_2 = 0.25	0.50	0.75	1.00	
Acetone	278.1	−2.9	−4.0	−5.0	−5.4	Isopropyl alc.
2,2,4,4-Tetramethyl-3-pentanone	295.5	−0.4	−0.9	−1.7	−1.6	Isopropyl alc.
3-Tetradecanone	280.8	−0.5	−1.1	−1.1	−2.0	Isopropyl alc.
Di-*n*-decyl ketone	281.7[c]	...	...	...	1.0	Isopropyl alc.
d-Camphor	291.8	−1.0	−1.0	−1.3	−1.8	Isopropyl alc.
d-Fenchone	289.3	−0.6	−1.0	−1.5	−2.2	Isopropyl alc.
		v_2 ≈ 0.225	0.45	0.675	0.90	
Benzophenone	247.7	1.2	3.1	3.7	4.3	Isopropyl alc.
	346.8	...	...	...	−12.7	Isopropyl alc.
Di-*o*-tolyl ketone	341.1[a]	...	...	...	7.4,[a] 0 to −5[c]	Isopropyl alc.
Benzil	256.9	0.9	1.4	1.7	2.1	Isopropyl alc.
Benzophenone	247.6	+2.0	+3.5	+4.0	+5.8	Butanol
		v_2 = 0.25	0.50	0.75	1.00	
Acetone	278.1	−1.1	−1.6	−1.8	−2.0	Chloroform
3-Tetradecanone	280.8,[a] 282.2[b]	...	...	...	0.8,[a] −1.0[b]	Chloroform
Acetone	278.1	...	...	...	−7.7	Methanol
2,2,4,4-Tetramethyl-3-pentanone	295.5	...	...	...	−2.0	Methanol
3-Tetradecanone	280.8,[a] 282.2[b]	...	...	...	1.3,[a] −0.5[b]	Methanol
d-Camphor	291.8	...	...	...	−2.4	Methanol
d-Fenchone	289.3	...	...	...	−4.8	Methanol

[a] Actual peak positions. [b] Peak position after subtraction of the background and overlap. [c] Position of the intersection of two lines fitted to the inflection points in the vicinity of the peak.

information, beyond what can be inferred from Table III.

Discussion

(a) **Steric Effects.**—The ultraviolet and n.m.r. data given in Tables II and III show that 2,2,4,4-tetramethyl-3-pentanone is less capable of H-bonding than, for example, acetone. 3,3-Dimethyl-3-pentanone also

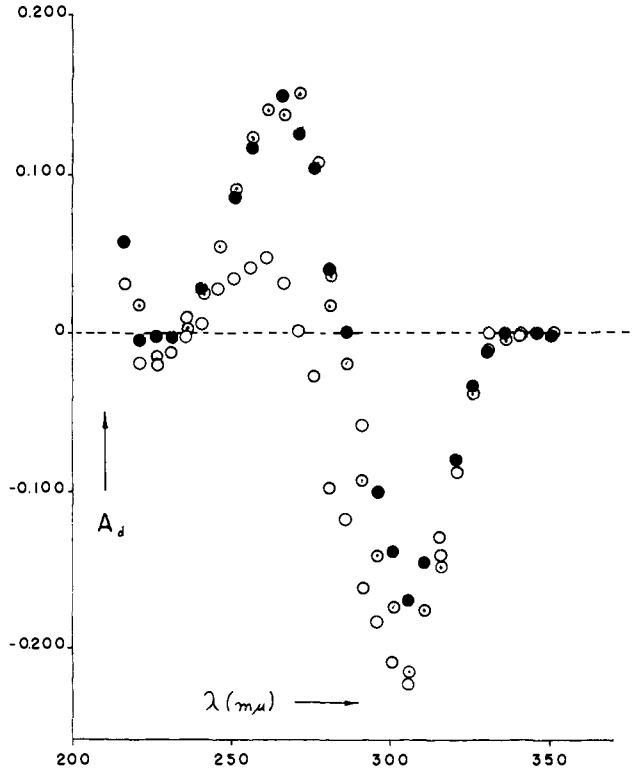

Fig. 1.—Ultraviolet difference spectra, absorbance, A_d, against wave length, λ, for 20% acetone, by volume, in *p*-dioxane run against 20% acetone, by volume, in methylcyclohexane, O; cyclohexane, ⊙; and 2,2,4-trimethylpentane, ●.

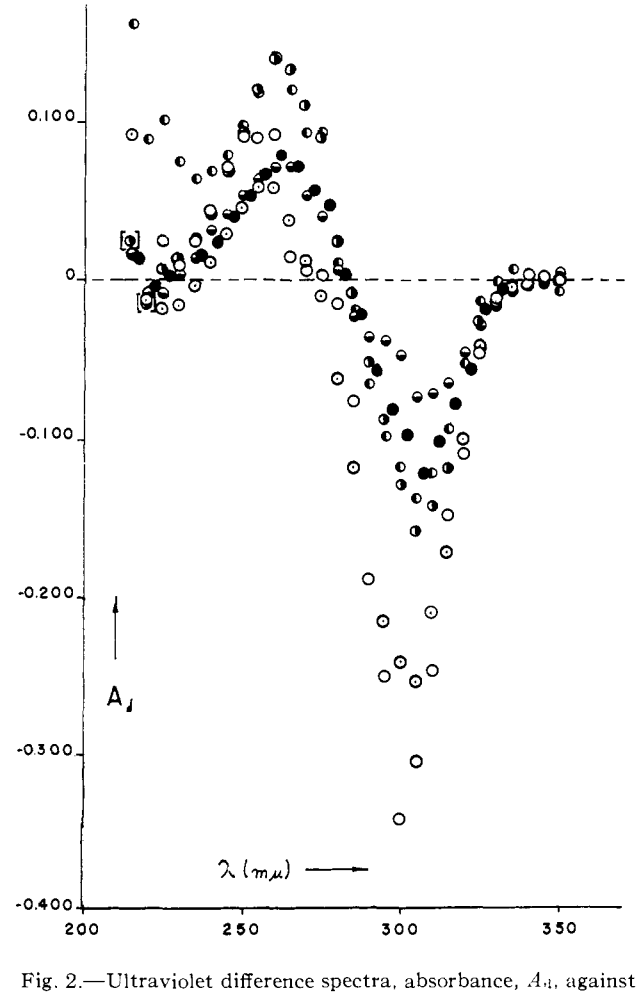

Fig. 2.—Ultraviolet difference spectra, absorbance, A_d, against wave length, λ, for acetone at various concentrations in *p*-dioxane run against acetone, at the same concentration, in 2,2,4-trimethylpentane. The acetone concentrations are, by volume: 5%, ◒; 8%, ●; 10%, ◐; 14%, ◑; 25%, ⊙; and 30%, O.

is at a disadvantage compared to acetone, as judged from the n.m.r. data. Interestingly, the former ketone is known not to react with hydroxylamine and related compounds, while the latter does react. 2,4-Dimethyl-3-pentanone shows shifts which are larger than those of acetone. Obviously, the isopropyl groups attached to the carbonyl group offer little steric hindrance, in contrast to the effect of the *t*-butyl groups noted above. The presence of the methyl groups in the 2- and 4-positions allows some electron release to the carbonyl group[20] and this might be thought to result in the improved H-bonding compared to acetone. 3-Methyl-2-butanone shows shifts very nearly equal to those of acetone. Interestingly, Bellamy and Williams[8] inferred from infrared studies that acetone is a somewhat better proton acceptor than 2,4-dimethyl-3-pentanone. It remains to be seen whether there are many systematic differences between infrared and n.m.r. results. 2,2,4,4-Tetramethyl-3-pentanone and 3,3-dimethyl-3-pentanone could be expected to be proton acceptors superior to acetone, were it not for the steric effect.

A similar correlation of the H-bonding capability and chemical reactivity is found for the pair benzophenone and di-*o*-tolyl ketone. The methyl groups in the vicinity of the carbonyl group result in inefficient H-bonding (Table III) and in a very low reactivity to condensation reagents.[5] The activated state in these reactions is thought[21] to involve the H-bonded carbonyl group, or its conjugate acid, and the correlation of reactivity and H-bonding tendency is therefore quite reasonable.

Another pair of ketones of interest is camphor and fenchone. The carbonyl group of the latter compound is probably somewhat shielded by the two methyl groups attached to its neighboring carbon atom. The ultraviolet shifts show fenchone to be at least as good an H-bonding partner as camphor, even though it forms a semicarbazone only with difficulty, in contrast to camphor.[5]

Molecular models do not lead to a resolution of this conflict, and one must conclude that in this case the steric hindrance affects the reactivity more strongly than the H-bonding tendency.

Long chain ketones present a somewhat different situation. The paraffinic chains of 3-tetradecanone are likely to bury the carbonyl group, at least part of the time, judging from the calculations of Taylor.[22] The H-bonding tendency is, accordingly, much lower than that of acetone (Table III). Owing to the intermittent or statistical nature of this hindrance, the chemical reactivity is still quite high.[23] The situation appears to be similar for the higher ketones di-*n*-decylketone or stearon, but the ultraviolet spectra of these latter materials are very difficult to analyze. The n.m.r. shift measurements on 3-heptanone, 3-nonanone, and 5-nonanone confirm this idea of a statistical hindrance.

(b) **Confirmatory Evidence from Ultraviolet Difference Spectra.**—Judging from the work by Scheraga and his co-workers[12] on polypeptide and protein solutions, one may expect the ultraviolet difference spectra to yield much information on weak interactions. Figure 1 demonstrates that spectra obtained in different nonpolar solvents differ slightly. The variations are not readily related to the solvent differences owing to the smallness and complexity of the dispersion terms of the McRae expression for the solvent effects in ultraviolet spectra.[24] The maximum of the difference spectrum is numerically smaller than the minimum in all three cases shown, and particularly so for methylcyclohexane. This could be the result of relatively minor intensity changes in the absorption bands in different solvents, but it is more likely caused by a second difference spectral wave form centered much further in the ultraviolet range which in part superposes the present curve shapes. All three curves lie high at the far-ultraviolet end of the range and presumably the disturbing effect lowers the heights of the difference spectra in the vicinity of their maxima.

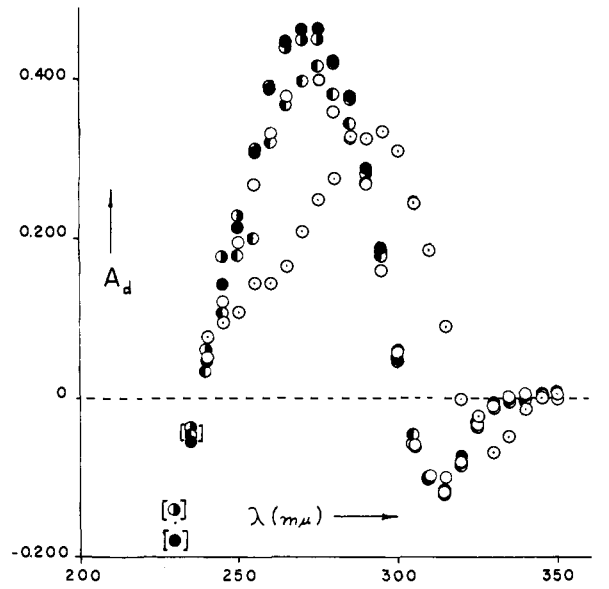

Fig. 3.—Ultraviolet difference spectra, absorbance, A_d, against wave length, λ, for 20% acetone, by volume, in a mixture of equal volumes of chloroform and a hydrocarbon, run against 20% acetone, by volume, in the same hydrocarbon: undried acetone and methylcyclohexane, ○; and 2,2,4-trimethylpentane, ●,◐; dried acetone–2,2,4-trimethylpentane, ◑; similar curve for 15% 2,2,4,4-tetramethyl-3-pentanone and cyclohexane, ⊙.

In any case, the curve shapes are definite and outside the experimental errors. This is clear from the series of curves shown in Fig. 2. If one assumes the minima of the difference spectra to be a true measure of the spectral shift, undistorted by the above complication, one should be able to obtain a measure of this shift, and therefore for the strength of the H-bond interaction from the depth of this minimum, divided by the concentration. Ratios obtained in this way for the curves of Fig. 2 are highest for the lowest concentration, and approach a near constant value for the higher concentrations. Thus one must, on the present assumptions, conclude that the weak interactions between acetone and dioxane seen here are dependent on the concentration. The definite "local" dipole moment of dioxane[25] is probably the cause for this interaction.

Figure 3 shows two duplicate curves for undried acetone in a chloroform–2,2,4-trimethylpentane mixture. A curve for dried acetone lies in between these two. All curves show relatively large maxima and low minima and a tendency to point downward in the far-ultraviolet. This strengthens the argument used to explain the asymmetry of the curves of Fig. 1. The curve for acetone in methylcyclohexane is related to those for acetone in 2,2,4-trimethylpentane in a way similar to the corresponding curves of Fig. 1.

The 2,2,4,4-tetramethyl-3-pentanone difference spectrum (Fig. 3) is similar to that for acetone, if one ac-

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(22) W. J. Taylor, *J. Chem. Phys.*, **16**, 257 (1948).

(23) I. M. Heilbron, *et al.*, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1934.

(24) E. G. McRae, *J. Phys. Chem.*, **61**, 562 (1957).

(25) E. Lippert, *Z. Naturforsch.*, **10a**, 541 (1955).

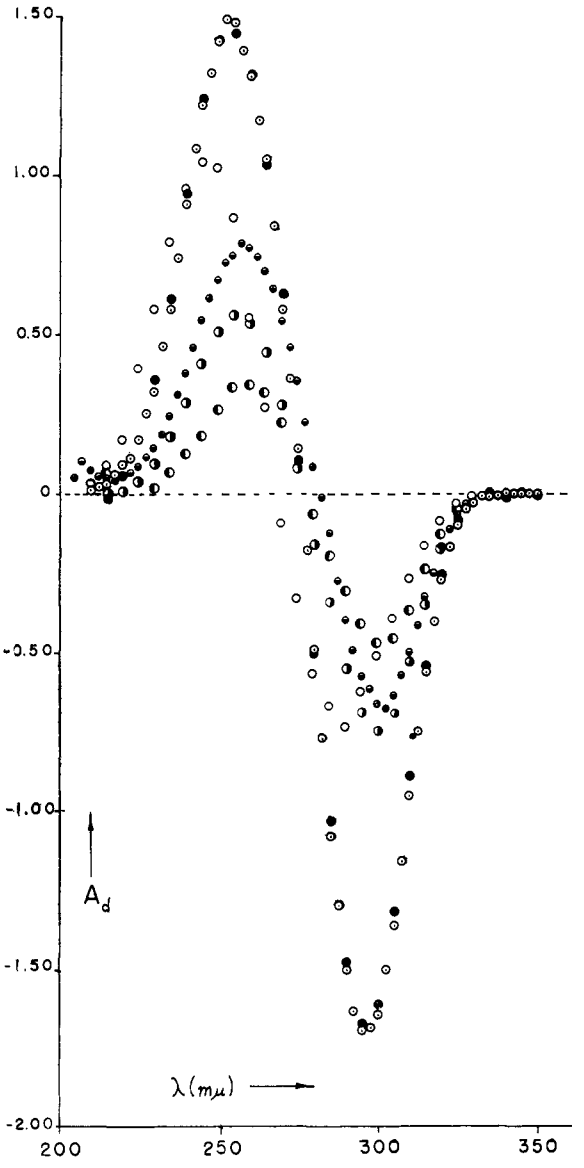

Fig. 4.—Ultraviolet difference spectra, absorbance, A_d, against wave length, λ, for 20% acetone, by volume, in water run against 20% acetone, by volume, in cyclohexane ⊙, and in 2,2,4-trimethylpentane ●. Similar curves for the solvents methanol and cyclohexane ◒, methanol and 2,2,4-trimethylpentane ◑, butanol and 2,2,4-trimethylpentane ◐, and H_3PO_4 and methylcyclohexane O. Acetone concentration for last curve is 5% by volume.

counts for the difference in concentrations. A more thorough analysis must, however, take into account[12] the difference in the molar extinction coefficient of the two ketones, and one finds the bulky 2,2,4,4-tetramethyl ketone to be distinctly less H-bonded than acetone, in agreement with the n.m.r. results cited above.

The difference spectra of Fig. 4 show that somewhat stronger H-bond type interactions can readily

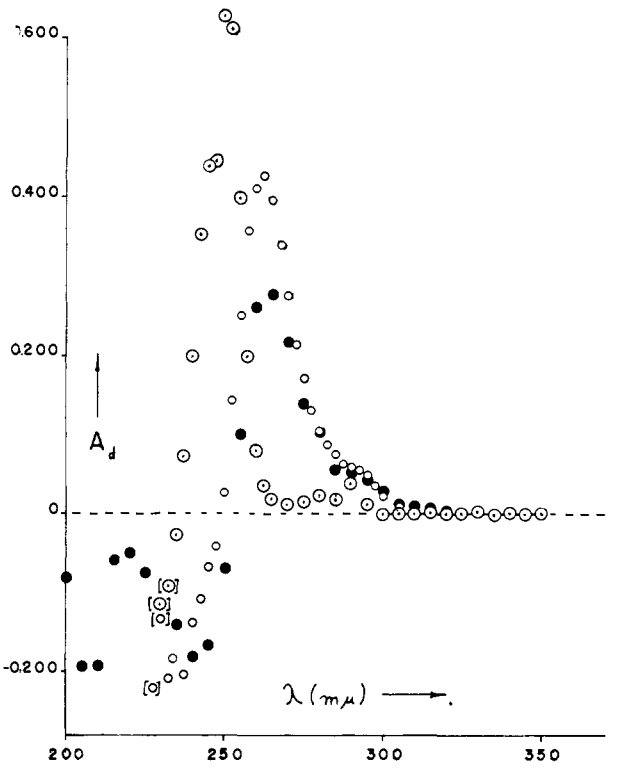

Fig. 5.—Ultraviolet difference spectra, absorbance, A_d, against wave length, λ, for 0.01% benzophenone in methanol run against 0.01% benzophenone in methylcyclohexane, ●; similar curve with equal volumes of chloroform and 2,2,4-trimethylpentane as one solvent and 2,2,4-trimethylpentane as the other, O; same solvents as for O, but 0.01% acetophenone as solute, ⊙.

be assessed by a comparison of the sums of the peak heights of maximum and minimum of each trace. The acetone–water and acetone–methanol systems yield total difference spectral amplitudes in the ratio of 2.14 (uncorrected for differences in the extinction coefficients) while the shifts of the absorption bands, relative to a heptane solution, as measured by Balasubramanian and Rao[11] are in a ratio of 1.72. There is thus semiquantitative agreement.

There are two remarkable features in the benzophenone difference spectra of Fig. 5. For one, the $n-\pi^*$ shift does not show up, for the present low concentrations used, while the $\pi-\pi^*$ shift does. The latter in turn is larger in the chloroform mixture than it is in the methanol solvent and it is also similar to the behavior of the band of acetophenone, even though this band is known to be of the charge-transfer type.[26]

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