Geometric Isomerism in the Phenylhydrazones of Some α-Dicarbonyl Compounds

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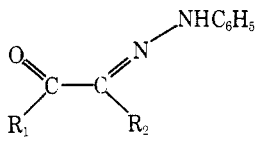
The structures of the phenylhydrazones of four α-dicarbonyl compounds were determined from the IR and NMR spectra of the ^{14}N and ^{15}N isotopomers. The compounds exist only in the phenylhydrazone tautomeric form and, except for the phenylhydrazone of phenylglyoxal in solution, primarily as the geometric isomer with the NHC_6H_5 group oriented away from the carbonyl. The effect of solvent on the composition of the geometric isomerism equilibria is discussed.

The structures of the phenylhydrazones of dicarbonyl compounds have been the subject of a variety of studies since the turn of the century. Many of these compounds have been reported in several, often interconvertible, forms. For monophenylhydrazones of α-dicarbonyl compounds, three tautomeric forms are possible,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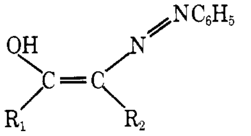
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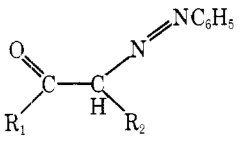
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and for each tautomeric form at least two geometric isomers are possible. Previous studies of compounds of this type have indicated, for example, that different geometric isomers of the hydrazone form A ($R_1 = CH_3$, $R_2 = H$) can be obtained by different methods of preparation,[1] that the form of at least one compound ($R_1 = C_6H_5$, $R_2 = H$) can be altered by the action of solvents,[2,3] and, recently, that the phenylhydrazone of phenylglyoxal ($R_1 = C_6H_5$, $R_2 = H$) exists as a mixture of hydrazone (A) and enol (B) forms in pyridine.[4]

The present spectroscopic study of the ^{14}N and ^{15}N isotopomers of the phenylhydrazones of a series of simple α-dicarbonyl compounds was designed to determine unambiguously the structures of some model phenylhydrazones.

Results and Discussion

The compounds (I, $R_1 = CH_3$, $R_2 = H$; II, $R_1 = R_2 = CH_3$; III, $R_1 = C_6H_5$, $R_2 = H$; IV, $R_1 = R_2 = C_6H_5$) were prepared by condensation of phenylhydrazine hydrochloride with the appropriate α-dicarbonyl compound in water or aqueous ethanol. Compounds I, II, and III were also prepared by the Japp–Klingemann reaction of diazotized aniline with acetoacetic acid, ethyl α-methylacetoacetate, and potassium benzoylacetate, respectively. The ^{15}N isotopomers of II, III, and IV were obtained by the condensation reaction, while that of I was made by the Japp–Klingemann method. The physical and spectroscopic properties of the compounds prepared by both the condensation and Japp–Klingemann methods were identical; however, the condensation product of I required careful purification.

The melting points of the compounds were determined on both a melting point block and by differential scanning calorimetry (DSC). The endotherms observed were found to be reversible and reproducible for all compounds. For compound III the melting point varied with the method used to purify the compound, and it ranged from 101–102 °C for material recrystallized from benzene to 152–153 °C after repeated recrystallization from ethanol. Moreover, the DSC scans for unrecrystallized samples of III showed two endotherms at 101 and 118 °C. However, the IR spectra (Nujol) of all samples of III were identical, as were the NMR spectra in $CDCl_3$ (vide infra). The melting points of the ^{14}N and ^{15}N isotopomers were identical. Melting points and NMR chemical shifts for both ^{14}N and ^{15}N isotopomers are reported in Table I.

The NMR spectrum of compound I in $CDCl_3$ contained two peaks of unequal intensity at 2.2 and 2.4 ppm due to the CH_3 groups, a multiplet centered at about 7.3 ppm attributable to the phenyl proton resonance (and also containing the C–H resonance), and two fairly broad low field resonances at 8.7 and 13.8 ppm, which together integrate to 1 proton relative to 3 for the combined CH_3 resonances. The low field resonances could be ascribed to either OH or NH protons, but not to the CH protons of form C. Since the ^{15}N isotopomer contains the ^{15}N isotope ($I = \frac{1}{2}$) directly attached to the benzene ring (the probability of scrambling during diazotization and condensation is low[5]), a proton directly attached to this isotope in the hydrazone form (A) will give rise to a doublet in the absence of fast exchange. As indicated in Table I, both low field resonances in the NMR spectrum of the isotopomer of I are split into doublets with separations characteristic of one-bond ^{15}N–^{1}H couplings.[6] Therefore, the two methyl resonances and the two low field resonances must be assigned to the two geometric isomers of the hydrazone from A. In one isomer the NHC_6H_5 group is oriented toward the carbonyl (hereafter referred to as the cis form) and the NH proton is very likely hydrogen bonded to the carbonyl. Hydrogen bonding generally results in downfield shifts, as previously documented for phenylazopyrazolones[7] and phenylhydrazones of pyruvic ester,[8] and hence the less abundant isomer, which has the low field peak at 13.8 ppm, is probably the cis form.

The infrared spectrum of I in $CHCl_3$ offers support for these assignments. Two peaks appear in the NH regions: a relatively sharp absorption at 3326 cm^{-1} and a broader absorption at 3260 cm^{-1}. In the ^{15}N isotopomer these absorptions appear at 3320 and 3250 cm^{-1}, respectively, due to the effect of the ^{15}N on the reduced mass of the NH group. The sharp absorption can be attributed, therefore, to the stretching vibration of the non-hydrogen-bonded NH group in the trans isomer, and the broader peak is a result of the NH stretch in the hydrogen-bonded cis form. The infrared spectrum also contains a medium intensity absorption at 1660 cm^{-1} with a high frequency shoulder, which can be attributed to C=O stretching vibrations. These peaks are insensitive to isotopic substitution. Two other peaks in the spectrum shift by more than 5 cm^{-1} on substitution with ^{15}N. These sharp peaks appear at 1513 and 1180 cm^{-1} in the ^{14}N derivative and at 1502 and 1172 cm^{-1} in the ^{15}N derivative. The IR spectrum of I in

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Table I. Melting Points and Chemical Shifts

Compd	Recrystallized from	Melting point, °C Obsd.	Melting point, °C Lit.	Chemical shifts, ppm (*J*, Hz) Solvent	^{14}N	^{15}N[a]
I	Methanol	153–154	148–150[10]	CDCl$_3$	2.23, 2.41, 6.8–7.8, 8.7,[b] 13.8	8.7 (d, J = 92), 13.8 (d, J = 95)
				Me$_2$SO-d_6	2.33, 6.7–7.9, 11.15	11.15 (d, J = 94)
II	–	135–136	133[11]	CDCl$_3$	1.96, 2.46, 6.7–7.5, 7.8	7.8 (d, J = 90)
				Me$_2$SO-d_6	1.98, 2.38, 6.5–7.5, 9.9	9.9 (d, J = 95)
III	95% ethanol	152–153	116–118,[2] 146[2]	CDCl$_3$	6.7–8.2, 8.7, 14.35[b]	8.7 (d, J = 94), 14.3 (d, J = 94)
	Benzene	101–102		Me$_2$SO	6.7–8.2, 11.3,[b] 14.1	11.3 (d, J = 94), 14.1 (d, J = 94)
				C$_5$H$_5$N	*c*, 11.1,[b] 14.5	11.1 (d, J = 95), 14.5 (d, J = 95)
IV	95% ethanol	136–137	135[12]	CDCl$_3$	6.6–8.1, 8.2,[b] 12.1	8.2 (d, J = 92), 12.1 (d, J = 95)
				Me$_2$SO-d_6	6.6–8.2, 10.0	10.0 (d, J = 94)

[a] Spectra of ^{15}N derivatives are identical to those of ^{14}N except for peaks noted d (doublet). [b] The more intense low field peak. [c] Phenyl region observed by solvent.

Nujol exhibits only one sharp peak in the NH region. This may indicate the existence of only the trans form in the solid state.

If the NMR spectrum of I is taken within several minutes of preparing the solution in CDCl$_3$, the relative intensity of the methyl peaks and the low field NH peaks are different than the relative intensities after several hours (when equilibrium has been established). During this time the higher field methyl resonance and the lower field NH resonance increase until at equilibrium the relative intensities of the higher to lower field NH resonance are about 2:1, respectively. Thus, dissolution in CDCl$_3$ produces a relatively slow conversion from the trans isomer in the solid state to a mixture of about 65% trans isomer, 35% cis isomer in solution.

The NMR spectrum of I in Me$_2$SO contains only one methyl and one NH resonance (a doublet in the ^{15}N isotopomer). Because the NH proton would hydrogen bond more strongly to Me$_2$SO than to CDCl$_3$, the NH resonance, which appears at a lower field than the trans isomer in CDCl$_3$ (but at higher field than the cis isomer in CDCl$_3$), can be assigned to the trans form since the resonance for the intramolecularly hydrogen-bonded cis form should be relatively insensitive to solvent effects. Thus, compound I exists solely in the trans-hydrazone form in the solid state and Me$_2$SO and as a mixture of the trans and cis forms in CDCl$_3$.

The NMR spectra of the other derivatives can be similarly analyzed. In each case there is no evidence for the CH form (C). Moreover, the low field resonance(s) observed for the ^{14}N derivatives splits into doublets on substitution of ^{15}N. Each compound therefore exists in solution only in the hydrazone form. Compound II in both CDCl$_3$ and Me$_2$SO exists as only the trans geometric isomer, as evidenced by the single relatively high field (7.84 ppm) NH peak which shifts to a lower field in Me$_2$SO. Compound III exists as a mixture of cis and trans forms in CDCl$_3$, Me$_2$SO, and pyridine. In CDCl$_3$ the cis form predominates in a ratio of about 12:1, in Me$_2$SO the trans form predominates in a ratio of 10:1, and in pyridine the ratio of cis to trans is approximately 1:3. The compound was also examined in mixtures of CDCl$_3$ and Me$_2$SO, and the ratio of cis to trans isomers was found to be dependent on the ratio of CDCl$_3$ to Me$_2$SO. For example, in a 25% by volume solution of Me$_2$SO in CDCl$_3$ the ratio of cis to trans was 1:1, in a 50% solution the ratio was 1:3, and in a 75% solution the ratio was 1:9. Compound IV exists primarily in the trans form in CDCl$_3$ and only in the trans form in Me$_2$SO.

The infrared spectra of compounds II and IV are in general agreement with the structural assignments above. The IR spectrum of the ^{14}N derivative of II in CDCl$_3$ contains two peaks in the NH region: a sharp peak at 3353 cm^{-1} and a broader peak at 3300 cm^{-1}. These peaks shift to 3348 and 3291 cm^{-1} in the ^{15}N isotopomer. A very broad carbonyl peak appears at 1665 cm^{-1} in the spectrum of both isotopomers. Two other peaks shift by more than 5 cm^{-1} on substitution of ^{15}N; these occur at 1497 and 1178 cm^{-1} in the ^{14}N derivative and at 1490 and 1169 cm^{-1} in the ^{15}N derivative. The appearance of two NH absorptions in the IR but only one NH resonance in the NMR may be indicative of exchange between two NH forms. The IR of II in Nujol exhibits only a single sharp NH peak.

The IR spectrum of III in CDCl$_3$ contains two very weak absorptions in the NH region: at 3323 and 3190 cm^{-1} in the ^{14}N isotopomer and at 3308 and 3180 cm^{-1} in the ^{15}N isotopomer. The region from 1635 to 1558 cm^{-1} contains a series of peaks: two shoulders at 1635 and 1608 cm^{-1} and sharp peaks at 1598 and 1588 cm^{-1}. Absorptions at 1428 (weak) and 1146 cm^{-1} (sharp) in the ^{14}N derivative shift to 1417 and 1132 cm^{-1} in the ^{15}N isotopomer. The NH absorptions are not readily apparent in the spectrum of III in Nujol.

The IR spectrum of IV in CDCl$_3$ contains an intense sharp peak at 3315 cm^{-1} and a very weak broad peak at 3268 cm^{-1}. The carbonyl absorption occurs at 1635 cm^{-1}. In the ^{15}N derivative of IV the sharp NH absorption appeared at 3304 cm^{-1}. A shift in the weak peak was difficult to discern. The spectrum of IV in Nujol contained two sharp almost equally intense peaks at 3310 and 3280 cm^{-1}.

Thus, the spectroscopic evidence strongly suggests that only the hydrazone form exists in solution for each of the compounds studied. All but III in CDCl$_3$ exist solely or primarily in the trans geometric isomer. For those that exist as mixtures in CDCl$_3$ (I, III, and IV), the trans form is favored by more basic solvents (Me$_2$SO, pyridine), presumably because of hydrogen-bonding interactions with the solvent that are unlikely in the cis form. The trans form is also apparently favored in the solid state. Since the equilibrium between the geometric isomers in solution is apparently established rather rapidly for all but I, it is not surprising that the spectroscopic solution data indicate that the same forms or mixtures are obtained by both synthetic routes. Moreover, since this equilibrium is clearly solvent dependent, it is likely that reaction conditions, solvents, and recrystallization media are more influential on product composition than on synthetic route. Clearly, the conditions used for the condensation and Japp–Klingemann reactions reported here resulted in compounds with identical physical properties.

Experimental Section

All condensation reactions were carried out by the reaction of phenylhydrazine hydrochloride with the appropriate α-dicarbonyl compound in aqueous ethanol (except for compound I which was prepared from hot water, thoroughly washed with cold 95% ethanol, and then recrystallized from absolute methanol). Recrystallization solvents for the other compounds are given in Table I. For the preparation of the ^{15}N isotopomers by the condensation method the phenylhydrazine-^{15}N hydrochloride was prepared[9] from 98% isotopically pure aniline-^{15}N (Prochem, Inc.). The Japp–Klingemann procedures described by Reynolds and Van Allan[10] were used for the preparation of I and II, while the method of Bamberger and Schmidt[2] was followed for III.

Solvents for spectroscopic studies were dried over molecular sieves, except for chloroform which was shaken with alumina. Compounds were vacuum-dried. Solution concentrations for both NMR and IR studies were 10–20% by weight.

NMR spectra were obtained on a Varian A-60D spectrometer. Infrared spectra were taken on a Perkin-Elmer 621 spectrophotometer. Melting points were obtained under nitrogen on a Perkin-Elmer DSC-1 differential scanning calorimeter and on a Fisher-Johns melting point block.

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Registry No.—*cis*-I, 64840-28-4; *trans*-I, 27843-96-5; *trans*-II, 15385-07-6; *cis*-III, 15823-87-7; *trans*-III, 15808-13-6; *trans*-IV, 64840-29-5; 2-oxopropanal, 78-98-8; 2,3-butanedione, 431-03-8; α-oxobenzeneacetaldehyde, 1074-12-0; benzil, 134-81-6; phenylhydrazine hydrochloride, 59-88-1.

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Analysis of Carbon-13 Nuclear Magnetic Resonance for Monohydroxy Steroids Incorporating Geometric Distortions[1a]

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For a given molecule, deviations between its observed ^{13}C NMR spectrum and its spectrum predicted from a set of empirical ^{13}C NMR rules is often explained in terms of geometric distortions. Allinger's[2,3] molecular force field is used to study geometric distortions in monohydroxy-$5\alpha,14\alpha$-androstanes. The net effect of many types of slight geometric distortions on the ^{13}C shift are examined in terms of the nonbonded interactions. The Δ_α and Δ_β effects could be characterized in a few terms suggested by the nonbonded interactions. Caution should be used in explaining ^{13}C chemical shifts with geometric distortion arguments without obtaining some evidence of existing geometric changes and exploring other substructural arrangements which might be important.

Introduction

Within the past decade considerable effort has focused upon deriving empirical ^{13}C NMR rules. One of the standard methods for rationalizing a ^{13}C nuclear magnetic resonance spectrum has been to equate the C-13 shift of a particular carbon atom to contributions from structural features in the molecule.[4–9] The structural features chosen are presumed to give linearly independent contributions to the shift. The subject of some recent work[9] has focused on systems which are skeletally rigid and thus provide ideal systems to study the influence of geometrical and stereochemical features.

The method of structural parameterization has been applied to monohydroxy steroids by Eggert et al.[9] The steroids considered in this work consisted of all trans ring junctions and thus could be classified as rigid systems. Deviations between the observed shifts and shifts calculated by the structural parameterization method have been observed. For instance, C-1 in $5\alpha,14\alpha$-androstan-1β-ol has an observed substituent effect, Δ_α, of 40.1 ppm compared to the calculated value of 45.0 ppm. The structural parameters considered in the work of Eggert[9] for the explanation of Δ_α were the number, n, of γ gauche carbons possessing hydrogen atoms able to interact with the hydroxyl group and the number of skew pentane interactions, p, of the hydroxyl group with carbon atoms. The Δ_α substituent effect is given as Δ_α (ppm) = 45.0 + 3.5p − 3.5n. The explanation of Δ_β was given in terms of q, the number of γ-gauche interactions of the hydroxyl group with the γ carbon atom connected to the β carbon atom in question. The equation for Δ_β is Δ_β)ppm) = 9.3 − 2.4q.

Geometric distortions in a structural framework leading to changes in local electronic environments of the nuclei have been advanced as one possible explanation of the deviations between observed and calculated shifts. Kollman et al.[10] have looked at long-range effects in cortisol by molecular-orbital calculations and have shown that conformational changes were accompanied by changes in charge densities which often outweigh direct inductive electronic effects. Charge densities have been related to C-13 shifts by various authors.[11,12] Geometric distortions can result in other effects which might influence the C-13 shift. Changes in distances between atoms in the molecule can result in varying steric and electric-field

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