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# *syn-anti* Isomer Determination of 2,4-Dinitrophenylhydrazones and Semicarbazones by N.m.r.

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Proton n.m.r. spectra of thirteen ketone 2,4-dinitrophenylhydrazones (DNP's) and nine ketone semicarbazones were taken in various solvents, and the problem of stereoisomerism about the C=N bond was studied. $\alpha$-Hydrogens *syn* to the anisotropic group are shielded (shifted to higher magnetic fields) while $\beta$ and $\gamma$-hydrogens *syn* to the anisotropic group are deshielded. The magnitude of the chemical shifts between *syn* and *anti* protons is practically independent of the nature (aromatic or aliphatic) of solvent. Use of trifluoroacetic acid as solvent results in serious changes in some spectra; these changes are thought to arise from protonation of the anisotropic group by the acid. Integration of areas under the appropriate n.m.r. signals has afforded evaluation of percentage stereoisomeric (*syn–anti*) composition of these compounds in solution.

## Introduction

We have mentioned previously that the n.m.r. spectra of diethyl ketone 2,4-dinitrophenylhydrazone (DNP) and semicarbazone showed the methylene protons as two quartets and the methyl protons as two triplets[1]; the finding was ascribed to restricted rotation around the C=N bond and the magnetic anisotropy of the groups present in these compounds. Proton n.m.r. has been applied successfully in elucidating problems of structural isomerism involving restricted rotation. Studies which are pertinent to the work described in this paper are those of Phillips and his coworkers on nitrosamines,[2] alkyl nitrites[3] and aldoximes.[4] Recently, Lustig[5] has carried out analogous studies on ketoximes. In all these cases both aldehydic and $\alpha$-hydrogens *syn* to the anisotropic group are deshielded (shifted to lower magnetic fields than the corresponding hydrogens *anti* to the anisotropic group). With the exception of very few cases, $\beta$-hydrogens appear unaffected.

It seemed interesting to apply analogous studies to DNP's and semicarbazones in solution. Structure considerations suggested that these compounds might behave differently from nitrosamines, alkyl nitrites and oximes with respect to the following: (1) Stereoisomeric composition of DNP's and semicarbazones might be strongly controlled by steric effects, not always true in the former compounds, because of the larger size of the substituent. (2) Long range effects of the anisotropic group could be detected. (3) Although predicting the effect of the anisotropic group on the $\alpha$-, $\beta$- and $\gamma$-hydrogens is quite difficult because of the conformational variety available to the molecules and the presence of more than one anisotropic bond, molecular models suggested that $\alpha$-hydrogens *syn* to the anisotropic group, especially in DNP's where they are within the radius of electronic current, might be shielded instead of deshielded as in the case of oximes, nitrosamines and alkyl nitrities. In addition, many conformations indicated that $\beta$- and $\gamma$-hydrogens might be deshielded.

This paper discusses our work with respect to the above questions.

## Results and Discussion

1. **Chemical Shifts.**—The chemical shift differences ($\delta$) between protons of *syn* and *anti*-isomers measured in chloroform and other organic solvents, are summarized in Table I; those measured in trifluoroacetic acid are shown in Table II.

(a) **Direction of Chemical Shifts.**—Since individual stereoisomers, *syn* and *anti*, of a single DNP or semicarbazone in solution were not available, assignment of each of two n.m.r. signals of individual protons to the correct stereoisomer had to be based on some assumption. Taking advantage of unequal isomer concentration in unsymmetrical DNP's and semicarbazones, and according to accepted concepts of steric effects, we have assigned the more intense of the two signals to the *syn*-methyl isomer, *e.g.*, it is reasonable to expect the *syn*-methyl isomer of methyl isopropyl ketone DNP to be favored over the *anti*-methyl isomer. On this assumption $\alpha$-hydrogens are found to be shielded while $\beta$- and $\gamma$-hydrogens are deshielded. As a typical example we analyze the spectrum of butanone DNP (Fig. 1). The $\alpha$-methyl (7.85$\tau$) appears as a doublet of unequal intensity with the more intense signal at higher field. The $\alpha$-methylene (7.53$\tau$) appears as two quartets of unequal intensity with the weaker signal at higher field. Assuming the concentration of the *syn*-methyl isomer as higher than that of the *anti*, the results show that the $\alpha$-hydrogens are shielded. The $\beta$-methyl (8.78$\tau$) appears as two triplets of unequal intensity with the weaker signal at lower field, indicating that the $\beta$-hydrogens are deshielded. The deshielding effect on the $\gamma$-hydrogens was deduced from the spectra of the derivatives of methyl *n*-propyl ketone; the $\gamma$-methyl appears as two triplets of unequal intensity with the less intense triplet at lower field. We wish to emphasize the fact that while $\alpha$-hydrogens in oximes, nitrosamines and alkyl nitrites are deshielded, $\alpha$-hydrogens in DNP's and semicarbazones are shielded. Also, chemical shift differences between isomers of the latter compounds are much smaller than those of the former.

(b) **Solvent Effects.**—It was shown[5] that in oximes not having aromatic substituents on the molecule the difference in the chemical shifts of the two isomers depended strongly on the nature of the solvent; it was large in aromatic solvents and

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[1] G. J. Karabatsos, J. D. Graham and F. M. Vane, *J. Am. Chem. Soc.*, in press.

[2] C. E. Looney, W. D. Phillips and E. L. Reilly, *ibid.*, **79**, 6136 (1957).

[3] W. D. Phillips, C. E. Looney and C. P. Spaeth, *J. Mol. Spec.*, **1**, 35 (1957).

[4] W. D. Phillips, *Ann. N. Y. Acad. Sci.*, **70**, 817 (1958).

[5] E. Lustig, *J. Phys. Chem.*, **65**, 491 (1961). For related studies on anisotropic effects see J. B. Hyne, *J. Am. Chem. Soc.*, **81**, 6058 (1959); J. S. Waugh and R. S. Fessenden, *ibid.*, **79**, 846 (1957); D. Y. Curtin, H. Gruen and B. W. Shoulders, *Chemistry & Industry*, 1205 (1958).

Table I

Chemical Shift Differences (δ) of *syn–anti* Isomers of 2,4-Dinitrophenylhydrazones and Semicarbazones in 5–10% Chloroform Solutions

| DNP | δ (p.p.m.)[d] α-Metl | α-Methylene | β-Methyl | γ-Methyl |
|---|---|---|---|---|
| Acetone | 0.08 | | | |
| Butanone | .08(0.08)[a] | 0.03(0.05)[a] | −0.04(0.03)[a] | |
| Diethyl ketone | | .03(0.02)[a] | − .04(0.04)[a] | |
| Methyl *n*-propyl ketone | .09 | | .00(0.00)[a] | −0.1 |
| Pinacolone | .00(0.00)[a] | | .00(0.00)[a] | |
| Diisopropyl ketone | | | − .12 | |
| Methyl isopropyl ketone | .00(0.00)[a] | | .0(0.00)[a] | |
| Ethyl cyclopropyl ketone | | (.12)[a] | − .07(0.1)[a] | |
| *n*-Propyl cyclopropyl ketone | | .03 | | − .1 |
| Isopropyl cyclopropyl ketone | | | − .12(0.1)[a] | |
| Acetophenone | (.01)[a] | | | |
| Phenylacetone | (.40)[a] | (.0)[a] | | |
| Semicarbazone | | | | |
| Acetone | .08 | | | |
| Butanone | .08(0.06)[a]<br>(0.10)[b] | (.03)[a] | − .12(0.03)[a] | |
| Diethyl ketone | | .02 | − .03 | |
| Methyl *n*-propyl ketone | .08(0.08)[c] | .02 | | − .08 |
| Diisopropyl ketone | | | − .03 | |
| Pinacolone | .00 | | .00 | |
| Methyl isopropyl ketone | .01 | | .00 | |

[a] Nitrobenzene solution. [b] Dimethylformamide solution. [c] Dimethyl sulfoxide solution. [d] A positive δ indicates that the *syn* protons are at higher field than the *anti* protons, while a negative δ indicates the reverse.

generally absent in aliphatic ones. DNP's and semicarbazones behave differently. Table I shows that in general there is no appreciable difference between nitrobenzene and chloroform as solvents. In addition, dimethylformamide, dimethyl sulfoxide and methylene chloride do not affect the magnitude of the chemical shift difference.[6] It is interesting to note that δ for α-methyl protons is larger than δ for α-methylene protons, most likely due to conformational differences in the two stereoisomers. The case of phenylacetone DNP (Table I) is quite striking.

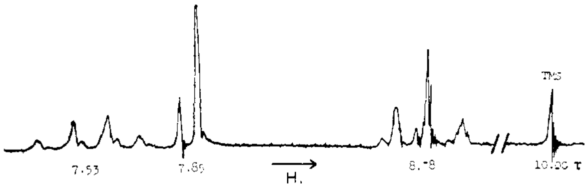

Fig. 1.—Proton n.m.r. spectrum of butanone DNP in nitrobenzene at 60 Mc. Tetramethylsilane (TMS) is the internal reference standard (10.00 τ).

Use of trifluoroacetic acid as solvent (Table II) results in serious changes in some spectra. These changes are thought to arise from protonation of the anisotropic group by the solvent.[7] In general, the chemical shift differences between the two isomers have the same magnitude as those observed in the other solvents. The following differences, however, deserve mention. (1) The

Table II

Chemical Shift Differences (δ) of *syn–anti* Isomers of 2,4-Dinitrophenylhydrazones and Semicarbazones in 10–20% Trifluoroacetic Acid Solutions

| DNP | δ (p.p.m.)[a] α-Methyl | α-Methylene | β-Methyl | γ-Methyl |
|---|---|---|---|---|
| Acetone | 0.06 | | | |
| Butanone | .05 | 0.06 | | |
| Diethyl ketone | | .04 | −0.10 | |
| Methyl *n*-propyl ketone | .06 | .05 | | 0.04 |
| Methyl isopropyl ketone | .01 | | | |
| Pinacolone | .00 | | .00 | |
| Diisopropylketone | | | − .11 | |
| Methyl cyclopropyl ketone | .03 | | | |
| Ethyl cyclopropyl ketone | | | − .10 | |
| Isopropyl cyclopropyl ketone | | | − .06 | |
| Phenylacetone | .00 | .00 | | |
| Semicarbazone | | | | |
| Acetone | 0.08 | | | |
| Butanone | .06 | 0.05 | 0.25 | |
| Diethyl ketone | | .02 | .07 | |
| Methyl *n*-propyl ketone | .07 | .04 | | −0.03 |
| Methyl isopropyl ketone | .04 | | .04 | |
| Pinacolone | .00 | | .00 | |
| Diisopropyl ketone | | | .04 | |
| Acetophenone | .07 | | | |
| Phenylacetone | .07 | | | |

[a] A positive δ indicates that the *syn* protons are at higher field than the *anti* protons, while a negative δ indicates the reverse.

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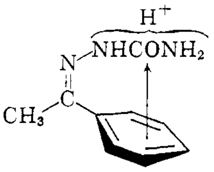
[6] Previous investigators, D. Y. Curtin, J. A. Gourse, W. H. Richardson and K. L. Rinehart, Jr., *J. Org. Chem.*, **24**, 93 (1959), failed to observe any chemical shifts in methylene chloride at 40 Mc. probably because of poor resolution. The low solubility of DNP's and semicarbazones in organic solvents prevented utilization of magnetically isotropic solvents, *e.g.*, carbon tetrachloride.

[7] DNP's and semicarbazones were recovered from trifluoroacetic acid unchanged.

methyl protons of acetophenone and phenylacetone semicarbazones appear as doublets with the less intense signal at ***higher*** magnetic fields. On the assumption that the concentration of the *syn*-methyl isomer is higher than that of the *anti*-methyl isomer, this observation leads to the conclusion that the *syn*-methyl protons of these semicarbazones are deshielded relative to the *anti* ones. Such a conclusion is opposite to the one drawn from the other semicarbazones which show, in trifluoroacetic acid, the less intense signal of the methyl doublets at *lower* magnetic fields; we see no valid reason to justify such a conclusion. We rather favor the explanation that the *syn*-methyl protons are shielded and that the concentration of the *anti*-methyl isomer is higher than that of the *syn*-methyl. Although such an explanation is opposite to predictions of stereoisomeric composition from considerations of DNP results and steric effects, it is not unreasonable. Since we are dealing with protonated species, and the two semicarbazones in question have an aromatic substituent, it is conceivable that the aromatic ring interacts with the protonated group (I) favoring the *anti*-methyl isomer over the *syn*-methyl one. Unsuccessful attempts up to now to find a suitable solvent for these compounds have prevented further elucidation of this point. (2) The γ-hydrogens of methyl *n*-propyl ketone DNP, and the β-hydrogens of butanone and methyl isopropyl ketone semicarbazones are shielded, which is opposite of what was found in the other solvents. (3) In all cyclopropane compounds reported here, including methyl cyclopropyl ketone and dicyclopropyl ketone, the cyclopropane hydrogens are shifted to lower fields by about 1 p.p.m. in trifluoroacetic acid relative to the other solvents; this finding is in accord with the well known nucleophilic character of the cyclopropane ring.



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2. ***syn-anti* Composition of DNP's and Semicarbazones in Solution.**—The question of stereoisomerism of DNP's about the C=N bond has received some attention in the past. Isolation of pure stereoisomers has been achieved in special cases where one of the stereoisomers is hydrogen bonded internally.[8] Ramirez has shown that sufficient differences exist in the infrared and ultraviolet spectra of the two stereoisomeric DNP's of various cyclic ketones to enable one to assign one or the other structure.[9] The above studies, however, are not general and cannot be applied successfully to simple ketone DNP's. The n.m.r. method outlined above, analogous to the one for oximes,[5] promises to be quite general and useful not only for DNP's and semicarbazones, but also for phenylhydrazones.[10] The isomeric composition of ten DNP's and six semicarbazones, evaluated from integration of the areas under the appropriate n.m.r. signals, is shown in Table III.

TABLE III

*syn–anti* COMPOSITION OF 2,4-DINITROPHENYLHYDRAZONES AND SEMICARBAZONES IN SOLUTION

| (1) DNP of ketone | % *syn* (methyl) | % *anti* |
|---|---|---|
| Methyl ethyl | 80 | 20 |
| Methyl *n*-propyl | 80 | 20 |
| Methyl isopropyl | $90^a$ | $10^a$ |
| Methyl cyclopropyl | $92^a$ | $8^a$ |
| Methyl *t*-butyl | 100 | 0 |
| Methyl phenyl | 63 | 37 |
| Methyl benzyl | 79 | 21 |
| Ethyl cyclopropyl | 65(ethyl) | 35 |
| *n*-Propyl cyclopropyl | 45(*n*-propyl) | 55 |
| Isopropyl cyclopropyl | 55(isopropyl) | 45 |
| (2) Semicarbazone of ketone | | |
| Methyl ethyl | 75 | 25 |
| Methyl *n*-propyl | 82 | 18 |
| Methyl isopropyl | $90(80)^a$ | $10(20)^a$ |
| Methyl *t*-butyl | 100 | 0 |
| Methyl phenyl | $10^a$ | $90^a$ |
| Methyl benzyl | $15^a$ | $85^a$ |

[a] Trifluoroacetic acid solution.

The values given in Table III refer to stereoisomeric composition of DNP's and semicarbazones in solution. The extent to which this composition is reflected in the solid state of these compounds, the question of whether the two stereoisomers are in thermodynamic equilibrium and what the energy of interconversion is, must await further experimentation. It is evident from the data that, as anticipated, the size of the groups attached to the carbon of the C=N group is quite important in determining stereoisomeric composition. In general, excluding cases where internal hydrogen bonding occurs, the isomer *syn* to the smaller group is favored over the other. The extent to which electronic effects, such as electron donating or withdrawing ability of groups attached to the carbon of the C=N group, influence stereoisomeric composition cannot be ascertained from the present data.

## Experimental

1. **Preparation of DNP's and semicarbazones** was accomplished according to well established procedures. Each compound was recrystallized at least twice and melting points were checked against literature values.

2. **All n.m.r. spectra** were taken with a model V4300-2 Varian Associates high resolution n.m.r. spectrometer at 60 Mc. Undegassed solutions of about 5–10% (10–20% in trifluoroacetic acid) in thin-walled Wilmad Glass Co. tubes were used. Chemical shifts were measured using the standard side band technique,[11] a Hewlett–Packard model 200 CD audiofrequency oscillator being employed; tetramethylsilane was the internal reference standard.

**Acknowledgment.**—The authors thank Mr. John S. Fleming for running many of the n.m.r. spectra.

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(8) (a) P. deMayo and A. Stoessl, *Can. J. Chem.*, **38**, 950 (1960); (b) F. A. Isherwood and R. L. Jones, *Nature*, **175**, 419 (1955); (c) H. Van Duin, *Rec. trav. chim.*, **73**, 78 (1954); for an example of a phenylhydrazone case see R. Kuhn, W. Münzing and W. Otting, *Ann.*, **622**, 43 (1954); von D. Schulte-Frohlinde, *ibid.*, **622**, 47 (1954).

(9) F. Ramirez and A. F. Kirby, *J. Am. Chem. Soc.*, **76**, 1037 (1954).

(10) For relative n.m.r. studies on the aromatic hydrogens of the DNP's of ethyl benzoylacetate and acetophenone see R. M. Silverstein and J. N. Shoolery, *J. Org. Chem.*, **25**, 1355 (1960).

(11) J. T. Arnold and M. E. Packard, *J. Chem. Phys.*, **19**, 1608 (1951).