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Conformational Analysis. LXXXI. γ-Piperidone and Related Compounds[1-3]

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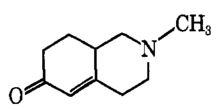
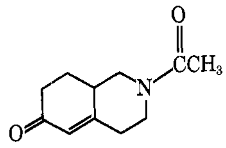
The conformations of *N*-methyl-γ-piperidone and *N*-acetyl-γ-piperidone have been studied by means of *Z* value correlations with $n \rightarrow \pi^*$ spectra, by dipole moments, and by infrared methods. It is concluded that earlier interpretations of the *Z* value correlations are incorrect. All of the molecules examined appear to have the ring in an ordinary chair conformation.

The study of conformational analysis was originally developed from a consideration of cyclohexane rings,[5] and only during the last several years has there been an appreciable amount of work done on heterocyclic rings.[6] The piperidine ring, in particular, has been the subject of a substantial number of recent papers. The equilibrium between the chair and boat forms in this system has not yet been measured directly but is doubtlessly similar to that in cyclohexane. Much discussion has appeared in the literature concerning the orientational preference of a substituent on the nitrogen in piperidine, and not all of the experimental work is in agreement. For example, Lambert has indicated, from a study of the chemical shifts of the α protons in the nmr spectrum, that the proton on nitrogen in piperidine must be largely axial, and the data which he cites in support of this viewpoint seem quite convincing.[7] On the other hand, from a study of the band shapes of the C–H stretching vibrations in the infrared spectrum (a method utilized much earlier by Larnaudie[8]) Katritzky has found that the hydrogen on nitrogen in piperidine is mainly equatorial.[9] These data also seem to be quite convincing. Additional data of various kinds are equally inconsistent.[10-20] Katritzky has said[20] that, while some people believe the hydrogen is equatorial, and some believe it is axial, others have "hedged their winning bets." We feel that one should believe only that which experiment or theory tells us to be true. As the results of new experiments and theories become available, one should really be prepared to modify one's earlier viewpoint if the facts indicate such a modification is in order. Our current feeling is that the answer to this particular problem cannot be said to be known beyond doubt.

Boat forms in six-membered rings were for a long time of great interest, because they seem to be nonexistent, or at least very rare.[5] The first ring which appeared to have a boat conformation was uncovered by Barton in 1957, and this paper[21] was followed by a flurry of work directed at a study of boat and supposed boat forms.[22] An unusual example of the boat form in a piperidine-type ring system was proposed by Kosower (he referred to the structure as a "folded form").[23] He found that the transition energy or wavelength for the $\pi \rightarrow \pi^*$ transition of compound I was quite sensitive to the *Z* value of the solvent (the polarity) in which the measurement was made; in fact, there was a linear relationship between the two. However, in compound II, the relationship was much less pronounced, indeed, apparently nonexistent. The transition energies varied over a range of about 2 kcal/mol, but this variation seemed to be independent of the *Z* value of the solvent. Kosower therefore suggested that, while I was normal (a half-chair–chair conformation), compound II had the piperidine ring in a folded (boat) form, the acetyl group interacting with the conjugated carbonyl system to produce the unexpected observed result.

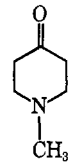


I

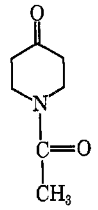


II

In the present work a study of 1-methyl-4-piperidone (III) and the corresponding acetyl derivative IV was undertaken. Whatever forces were acting in com-



III



IV

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[2] Taken from the thesis submitted to Wayne State University, Oct 1962, by S. P. J. in partial fulfillment of the requirements for the M.S. Degree.

[3] This work was supported by Grant GP 15263 from the National Science Foundation.

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pounds I and II and whatever conformational situations developed, there should be analogous forces and conformations in compounds III and IV, and these were more amenable to study. In this case the spectroscopic transitions accessible were n → π*.

Results

To ascertain that the system under examination (III and IV) was indeed similar to that studied by Kosower, we first looked at the transition energies for the n → π* transitions as a function of the *Z* value of the solvent and, indeed, found trends analogous to those reported for π → π* transitions in the more complicated case. These data are given in Tables I and II and summarized in Figure 1. Thus, compound III shows a transition energy which varies in an essentially linear manner over a range of about 8 kcal/mol with variation in *Z*. On the other hand, compound IV shows a much smaller variation in the transition energy with *Z*, about 2 kcal/mol, and there is no apparent correlation between *Z* and the transition energy in the latter case. Following Kosower, the interpretation would be that III exists in a normal chair form, while IV exists in the boat form (IVb) shown. The torsional arrangement about the carbonyl C–N bond in IVb is, as noted by Kosower, quite unfavorable. The other forces acting, especially the electrostatic attraction, would have to be sufficient to overcome the poor torsional arrangements, both here and with the eclipsing of the ethane type in the ring.

Table I

Uv Spectral Data for 1-Methyl-4-piperidone[a]

Z value	Solvent	λ_{max}, mμ	ε	E_T (n → π*), kcal mol^{-1}
60.1	Isooctane	294.0	18	97.3
62.3	Dioxane	296.5	18	96.5
64.2	Methylene chloride	300[c]		95.2
71.3	Acetonitrile	301[c]		95.0
86.9[b]	50% dioxane	329.5	8	87.7
94.6[b]	25% dioxane	332.0	8	86.1
96.7[b]	Water	333.0	6	85.9

[a] Concentrations approximately 10^{-2} *M*. [b] *Z* values were determined taking cyclohexanone as standard, others were taken from literature: E. M. Kosower, *J. Amer. Chem. Soc.*, **80**, 3253 (1958). [c] Because of strong end absorption, these absorptions appear only as shoulders, and the position of the maximum is poorly defined.

Table II

Uv Spectral Data for 1-Acetyl-4-piperidone[a]

Z value	Solvent	λ_{max}, mμ	ε	E_T (n → π*), kcal mol^{-1}
62.3	Dioxane	282.5	49	101.2
64.2	Methylene	287.0		99.7
71.3	Acetonitrile	284.5	43	100.5
76.3	2-Propanol	286.5	42	99.8
79.6	Ethanol	288.5	33	99.1
96.7	Water	284.5	37	100.5

[a] Concentrations approximately 10^{-2} *M*.

There are a good many physical techniques that can be used in studying conformations. The present study is concerned primarily with dipole moment measurements, supplemented by an examination of the infrared spectra of the compounds. Finally, we want to rationalize the observed facts in terms of current theory.

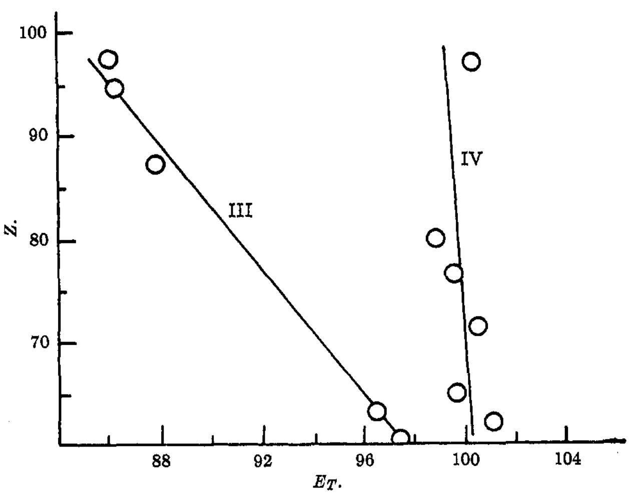
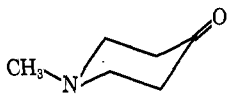
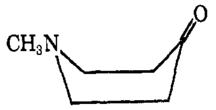


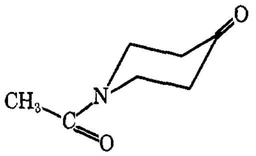
Figure 1.—The dependence of the n → π* transition energy on *Z* for compounds III and IV.



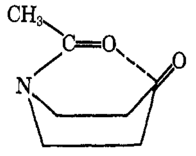
IIIc



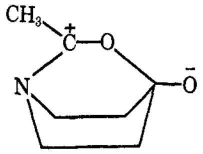
IIIb



IVc



IVb



IVct

The dipole moments were studied, based on the model compounds cyclohexanone (3.06 D), *N*-methylpiperidine (0.95 D), and *N*-acylpiperidine (3.99 D). At the time this work was done it was not clear that the methyl group on nitrogen was equatorial, it having been suggested by LeFevre[10] that the methyl of *N*-methylpiperidine was approximately equally axial and equatorial. Subsequently, additional work has indicated that the methyl is mainly equatorial, although the quantitative amount is still open to discussion. At any rate, using a Drieding model as a model and measuring the angles between the dipoles, it was concluded that the chair form of equatorial methylpiperidone (IIIc) should have a dipole moment of 2.90 D. The axial methyl piperidone should have a dipole moment of 2.39 D, and the boat form (IIIb) shown for the compound would have a moment of 3.94 D. This moment would be reduced if the molecule went into a twist conformation. The experimental value found for compound III was 2.91 D. The agreement for the equatorial methyl chair conformation is fortuitously good, and there could be present a sub-

TABLE III
DIPOLE MOMENTS IN BENZENE SOLUTION AT 25°

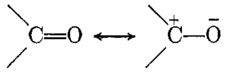
	α	β	ϵ_1	d_1	P_{2_∞}	μ
1-Methyl-4-piperidone	11.481	0.088	2.2745	0.87361	204.5	2.090 ± 0.03 D
N-Methylpiperidine	0.901	0.101	2.2760	0.87355	50.19	0.954 ± 0.04 D
N-Acetylpiperidine	21.597	0.215	2.2758	0.87362	353.7	3.941 ± 0.03 D
N-Acetyl-4-piperidone	12.511	0.434	2.2742	0.87348	218.7	2.987 ± 0.02 D

stantial amount of the axial methyl and perhaps a small amount of the boat or a larger amount of the twist form. However, the most simple interpretation is that the compound exists primarily in the conformation with an equatorial methyl in the chair form.

For the *N*-acyl compound, a rough approximation is to assume that the moment of the amido group lies along the C–O double bond. Actually, it must lie slightly from the nitrogen toward the oxygen, but, using our first approximation, it is calculated that the chair form of the ring with an equatorial acyl group and a planar ring nitrogen would have a moment of 3.59 D. The deviation of the moment from the C=O axis is 20° in formamide[24] away from the nitrogen. Using the same geometry here, the moment is calculated to be 2.51 rather than 3.59 D. The boat form shown (IVb) has a calculated moment of 4.85 D.

The results shown in Table III were obtained in benzene solution at 25°. The experimental dipole moment of *N*-acetyl-γ-piperidone was 2.99 D. This is consistent with a chair form but is clearly far too small to correspond to a boat form or any large amount of boat form in the equilibrium mixture. The reason for suggesting that compound IV might have a stable boat conformation was because of a possible electrostatic interaction between the carbonyl groups in that arrangement. Such an interaction would amount to a charge transfer, which would augment the dipole moment even further. If the charge transfer were complete (as in IVct), the dipole moment would be approximately 20 D. The dipole moment data are quite inconsistent with any such formulation.

A study of the infrared spectra of these compounds was also carried out. Compound III shows the ketone C=O stretching frequency at 1724 cm^{-1}, whereas the corresponding absorption of IV is at 1730 cm^{-1}. Any sizable electrostatic interaction such as in IVct would greatly reduce the frequency of the acetyl compound, relative to that of the methyl compound, and this is not observed. The frequency is in fact higher. If we consider that the carbonyl group consists primarily of two resonance forms



then the inductive effect of the acetyl would tend to make the double-bonded form more important than the singly bonded form, which would raise the stretching frequency. This is what is observed, although the effect is pretty small. However the evidence is quite inconsistent with a conformation such as IVb, being maintained by electrostatic forces.

The amide carbonyl frequency in 1-acetylpiperidine is observed at 1650 cm^{-1}, while in the corresponding 4-piperidone, the frequency is 1664 cm^{-1}. The inductive effect of the carbonyl on the acetyl should lead to this increase in frequency, just as the inductive effect of the acetyl on the carbonyl led to an increase in the double bond stretching frequency. Thus the observed frequency shift is compatible with a chair form. On the other hand, the electrostatic interaction between the carbonyls should lead to a decrease in frequency. However, in compound IVb, the π orbital of the amide carbonyl is orthogonal to that of the lone pair on nitrogen, and this also should lead to a substantially increased carbonyl frequency. Whether this effect is smaller or larger than the electrostatic effect mentioned is not obvious; so it is not clear what one would predict for the carbonyl frequency of the acetyl group in compound IVb.

Conclusions

In compound III, the dipole moment data indicate that the predominant conformation is the simple chair form with an equatorial methyl. Smaller amounts of other conformations cannot be excluded, but there is no evidence for them.

Compound IV cannot exist in the boat form analogous to that proposed by Kosower to any large extent. The simple chair conformation with an approximately planar nitrogen is consistent with the available data.

The correlation between the transition energies of the n → π* transitions and the polarity of the solvent as measured by the *Z* value is pretty good in the case of the *N*-methyl compound. The points lie near to a straight line of moderate slope. It may be noted that the sign of the slope of the line is opposite to that usually observed[23] for n → π* transition, however. The correlation is not very good in the case of the *N*-acetyl compound. The slope of the line is nearly infinite, indicating only a small random effect of the *Z* value of the solvent on E_T. The ring conformation seems to have nothing to do with the correlation between E_T and *Z*, however. There is no evidence for the ring being anything other than a simple chair in any case. The reason for the lack of a systematic effect of the *Z* value of the solvent on the transition energy is not clear. The scatter of the points can be attributed to the fact that the *Z* value, which is determined by the effect of the solvent on E_T in a specific molecule,[24] does not exactly account for the effect of solvent on E_T in structurally different molecules because of the specificity of solvation on a molecular scale. The nearly infinite slope of the line (Figure 1) in the case of compound IV shows that solvation is equally important in the n → π* excited state and in the ground state. Why this is true in IV, but not in III, is not obvious. It is conceivable that the molecules of IV do not form solutions that are at all ideal, even at low concentrations, but instead tend to dimerize or clump together, particularly in less polar solvents.

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Experimental Section

1-Methyl-4-piperidone (III).—Methyldi(β-carbethoxyethyl)amine was prepared by the Michael addition of methylamine to ethyl acrylate, 78% yield, bp 117–119° (0.5 mm) [lit.[25] reports bp 118–119° (0.5 mm)]. The latter underwent a Dieckmann condensation with potassium *tert*-butoxide to give the cyclic β-keto ester, which upon hydrolysis and decarboxylation yielded 1-methyl-4-piperidone, bp 67–79° (19 mm), $n^{24}\mathrm{D}$ 1.4580 [lit.[26] reports mp 56–58° (11 mm), $n^{25}\mathrm{D}$ 1.4580, yield 58%].

1-Acetyl-4-piperidone.—A Michael addition of ammonia to ethyl acrylate gave di(β-carbethoxyethyl)amine, bp 154–164° (1.5 mm) [lit.[27] bp 150–164° (1–2 mm)]. The *N*-benzoyl derivative was prepared and had bp 192–197° (0.4 mm), $n^{24}\mathrm{D}$ 1.5020 [lit.[27] bp 192–194° (0.4 mm), $n^{25}\mathrm{D}$ 1.5040]. The Dieckmann reaction was then carried out with the aid of sodium and furnished 1-benzoyl-3-carbethoxy-4-piperidone, mp 59–60° (lit.[27] mp 54–56°).

4-Piperidone hydrochloride was prepared by hydrolysis of the previous compound by refluxing with 6 *N* hydrochloric acid until carbon dioxide evolution ceased. The solution was filtered to remove the benzoic acid, and the product was taken up in ether. The ether solution was evaporated to dryness and the product was decolorized with charcoal and crystallized from ethanol–ether. It was then taken up in acetic acid–sodium acetate and acetylated with acetic anhydride, bp 135–136° (0.3 mm), $n^{25}\mathrm{D}$ 1.5016 [lit.[28] reports bp 124–128° (0.2 mm), $n^{25}\mathrm{D}$ 1.5023].

Dipole Moments.—The apparatus and method[29] and the details of the computations[30] have all been described previously, no allowance for atomic polarization being made in line with earlier conclusions.[31]

Registry No.—III, 1445-73-4; IV, 32161-06-1; *N*-methylpiperidine, 626-67-5; *N*-acetylpiperidine, 618-42-8.

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Notes

Friedel–Crafts Acylation of 10-Methylphenothiazine

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As part of the preparation of a compound containing the 3-(10-methylphenothiazinyl) group, it was necessary to use a Friedel–Crafts acylation in one of the synthetic steps. Although hundreds of phenothiazine compounds have been reported we were unable to find a high-yield procedure for the Friedel–Crafts acylation of 10-methylphenothiazine.

The literature reports that *N*-alkylphenothiazine is 3,7 directing and *N*-acylphenothiazine is 2,8 directing in Friedel–Crafts acylation.[1–6] Both mono- and disubstituted products are formed but were not separated in the reported crude yields. Acylation takes place with higher yields with *N*-acylphenothiazine than with *N*-alkylphenothiazine.

For example, when 1 mol of 10-methylphenothiazine was acylated with 1 mol of acetyl chloride in carbon disulfide with aluminum chloride, the crude yield of 3-acetyl product was 25% (reported as the hydrate) with 42.5% utilization of 10-methylphenothiazine.[1] In a recent attempt to duplicate the reaction, the major product found was the 3,7-diacetyl derivative.[2] With 2.5 mol of acetic anhydride, the yield of 3,7-diacetyl product was 39%.[3]

Acylation of 10-acetylphenothiazine with 1 mol of β-carbomethoxypropionyl chloride in carbon disulfide with aluminum chloride gave 58% of crude 2-acylated product.[5] A 94% yield of the 2-acetyl product was obtained using 1 mol of acetic anhydride,[6] while the 2,8-diacetyl derivative was obtained in 52% yield using 4 mol of acetyl chloride.[3]

Results and Discussion

In this laboratory, it was found that the aluminum chloride–carbon disulfide system gave rather poor yields of monosubstituted product in the acylation of 10-methylphenothiazine with β-carbomethoxypropionyl chloride. The effect of solvent and catalyst on the reaction was therefore investigated; the results are summarized in Tables I and II and Chart I.

The 3 position of the substituent is assigned by analogy to related cases[1,3,7] and the nmr spectra. The chemical shift of the aromatic protons in **4** (τ 2.18, 2.27, 3.14 for a_1, a_2, and b) agree well with those calculated for a 3-acyl-, 5-alkylthio-, 6 dialkylamino-substituted benzene (τ 2.19, 2.22, 3.34), using a recent table of aromatic chemical shifts,[8] but not for the corresponding 2-acyl derivative (τ 2.70, 2.72, 2.77).

Product **5** presumably arises by acylation of a second mole of phenothiazine by the monosubstituted product, leading to the tertiary alcohol which dehydrates to **5**. Compound **5** gave a single peak in thin

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