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NMR STUDIES OF RATE PROCESSES AND CONFORMATIONS—X

CONFORMATIONAL RATE PROCESSES IN DI-, TETRA- AND HEXA-HYDROPYRIDAZINE SYSTEMS[1]

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Abstract—The NMR spectra of various pyridazine derivatives containing the —N(COOR)—N(COOR)— fragment have been studied. These spectra are temperature dependent. Free enthalpies of activation have been calculated from the observed spectral changes. These changes have been related to conformational changes in the molecules studied.

Hindered rotation about the N—COOR bonds is present in all compounds studied. A *ring inversion* process is observed in the compounds of the tetra- and hexa-hydro-pyridazine types. A "*ring twisting*" process is found in a dihydropyridazine derivative.

The origin of the potential barriers for these processes is discussed.

The geometrical and energetical analogies observed for a number of rate processes arise from the presence of the —N(COOR)—N(COOR)— fragment in the systems studied. It is suggested that this fragment introduces a "conformational fixation" and may serve as a useful *probe* into molecular dissymetry and conformational changes.

Résumé—Les spectres de R.M.N. de divers dérivés de la pyridazine renfermant le motif structural —N(COOR)—N(COOR)— ont été étudiés. Ces spectres varient en fonction de la température. Les enthalpies libres d'activation ont été calculées à partir des modifications spectrales observées. Celles-ci ont été reliées à des modifications conformationnelles présentes dans les molécules étudiées: *rotation restreinte* autour des liaisons N—COOR présente dans tous les composés étudiés, *inversion du cycle* les composés du type tetra- et hexa-hydropyridazine, *torsion du cycle* dans un dérivé du type dihydropyridazine.

L'origine des barrières de potentiel calculées est discutée.

Les analogies à la fois géométriques et énergétiques que présentent les processus observés dans divers types de composés sont attribuables à la présence du groupement —N(COOR)—N(COOR)—.

Ce groupement peut servir en quelque sorte de "*sonde conformationnelle*" intramoléculaire permettant de détecter les dissymétries et les mouvements moléculaires.

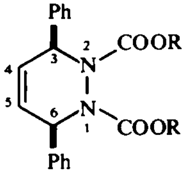
The conformational changes present in the tetrahydropyridazines I and II have been studied[3] using variable temperature NMR spectroscopy.

Other studies of these and similar systems have appeared in recent literature.[4,5]

The temperature dependence of the NMR spectra of I and II has been attributed to two types of rate processes: inversion of the 6-membered ring and rotation about the N—COOR bonds. Hindered N-inversion might also contribute to the observed spectral changes.[4] We have now studied systems in which these different types of rate processes could be investigated separately.

Consecutive N-inversion has been observed in compounds IX and XI.[6]

Hindered rotation about the N—COOR bonds is found in X and XII and a bridge flipping process within the bicyclic system is also present in XII.[1] We report here our results for I–VIII in which ring inversion may occur in addition to the other rate processes present in IX–XII.



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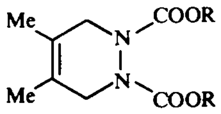
II R = Et



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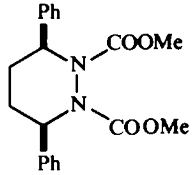
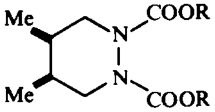
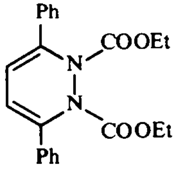
IV R = Et



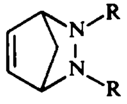
V



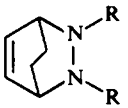
VI R = Me
VII R = Et



VIII



IX R = Me
X R = COOMe



XI R = Me
XII R = COOMe

RESULTS

The compounds studied here have been obtained following established methods (Experimental).

Variable temperature NMR spectra. All compounds I–VIII show temperature dependent NMR spectra. These are described in Table 1 for various temperatures.

The NMR spectrum of I at ca. 30° shows two COOMe peaks of unequal heights but of *equal areas** two octets for the vinylic protons, two broad signals for the allylic protons and a complex peak for the Ph groups (Figs 1b and 2). As the temperature is increased all *pairs* of signals from protons of the same type coalesce and at 130° one observes one COOMe peak, one signal for the vinylic protons, one signal for the allylic protons and a much narrower band for the aromatic protons (Fig. 1a). The chemical shifts of these signals are equal to the mean values calculated from the shifts of the respective pairs of signals observed at 30°. On lowering the temperature, the upfield Me group splits into two signals of unequal heights, the other COOMe peak is somewhat broadened and an other signal of very low intensity seems to appear in this region; at the same time the signals of the other protons become more complex (Fig. 1c).

Compound II shows a similar temperature dependence for the vinylic, allylic and Ph proton signals. The COOEt protons give rise at −52° to a complex spectrum containing four discernible Me triplets of unequal areas and linewidths and a com-

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* The areas of these two COOMe signals have been measured several times using either the A-60 integrator or a digital voltmeter and a low enough RF field so as to avoid differential saturation effects. The two areas are equal within experimental error. The interpretation given in Ref. 3 has been questioned by Bushweller[7] on the basis of unequal areas for the two COOMe groups of I at 35°C. These criticisms have been answered in two recent communications[7a, 7b] and the present results confirm the earlier interpretation.[3]

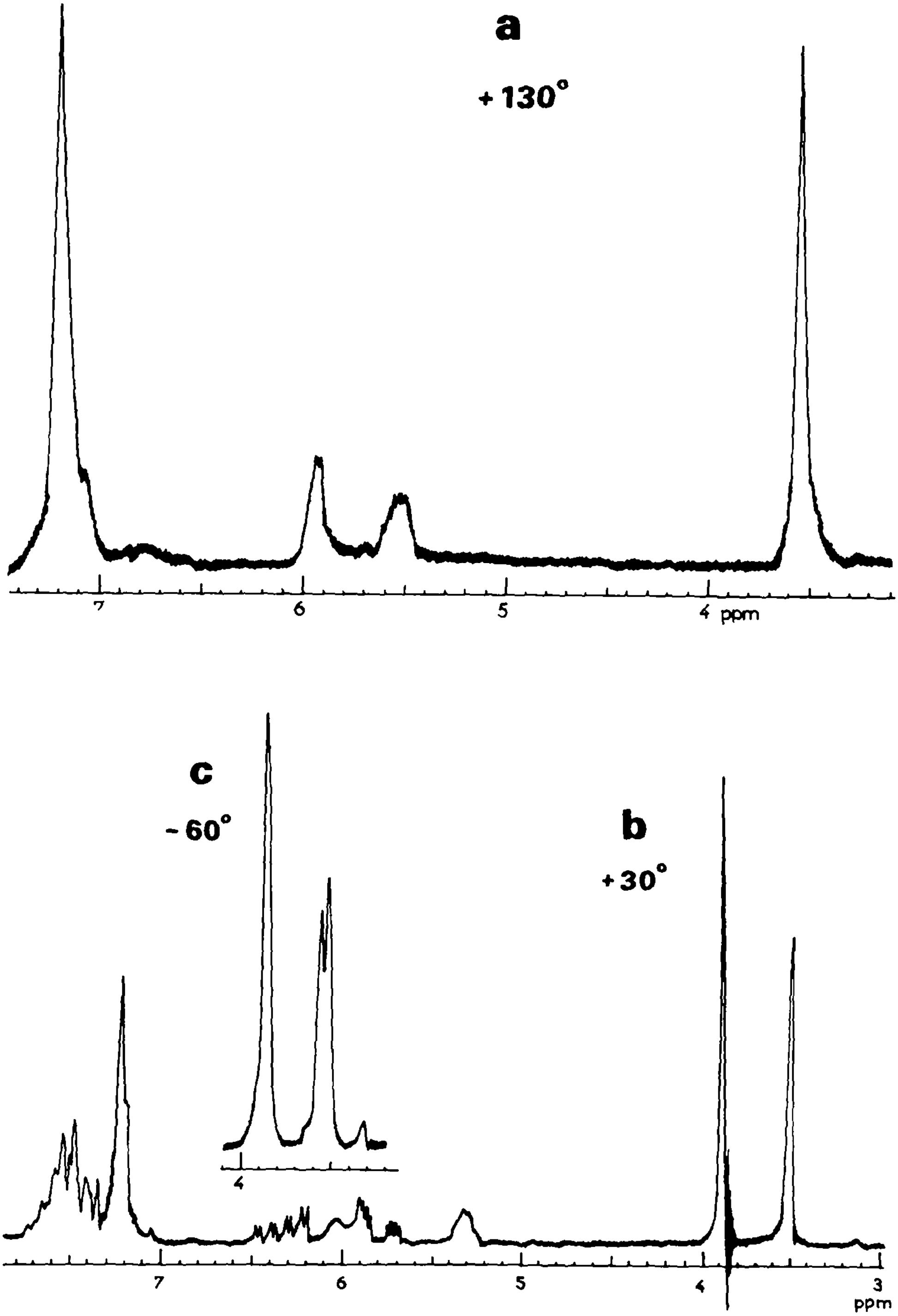

FIG. 1 NMR spectrum of compound I: (a) at 130° in tetrachloroethylene; (b) at 30° in CDCl$_3$; (c) at —60° in CDCl$_3$ at 60 MHz (Spectra taken at different amplifications).

plicated pattern for the CH_2 protons. As the temperature is raised the Me and CH_2 signals coalesce respectively into two triplets and two quartets which, at higher temperatures, coalesce into one triplet and one quartet (Table 1).

The spectrum of III contains at 30° one sharp COOMe signal, one peak for the vinylic Me groups and a broadened AB pattern for the allylic CH_2 protons. As the temperature is increased the AB pattern coalesces into a single line, the other signals remaining unchanged.

The COOMe groups of compound V give rise to a complex pattern of several overlapping peaks at $-1°$, to two peaks of equal areas 32° and to one peak at 95°. The spectrum of VI shows the following signals: at $-53°$, several overlapping COOMe signals and a very broad band (half-height-width: ca. 10 Hz) for the other Me groups; at $+34°$, a sharp COOMe peak and two doublets for the secondary Me groups; at 119°, a sharp COOMe signal and a single doublet for the secondary Me groups.

Finally the spectrum of VIII shows a singlet for the vinylic protons and an ABC_3 pattern for the COOEt groups (Ref. 1 and Refs therein) at 30°. As the temperature is increased, the ABC_3 pattern changes over to an A_2B_3 pattern at ca. 162°.

Activation parameters. From the spectral parameters ($\Delta\nu = \nu_A - \nu_B$: chemical shift difference; J_{AB}) and from the coalescence temperatures T_c corresponding to the various changes described above, the rate constants k_c at temperature T_c may be calculated for the rate processes involved.

In the case of two uncoupled sites of equal populations one has[8]

$$k_c = \pi\,\Delta\nu/\sqrt{2} \qquad (1)$$

In the case of two coupled, equally populated sites, k_c becomes:[9]

$$k_c = \pi(6J_{AB}^2 + \Delta\nu^2)^{\frac{1}{2}}/\sqrt{2} \qquad (2)$$

The free enthalpy of activation at temperature T, $\Delta G_T^{\ddagger}$, is obtained using Eyrings rate equation and a transmission coefficient of 1:†

$$\Delta G_T^{\ddagger} = 4{\cdot}57T\,[10{\cdot}32 + \log T/k] \qquad (3)$$

ΔG_c^{*} is obtained at temperature T_c using k_c from Eqs (1) and (2).

At temperatures below and above the coalescence temperature T_c, k may be obtained from peak widths at half heights (for a description of the method see Ref. 6).

Plotting log (k/T) as a function of $1/T$ in Eq. (3) yields a straight line whose slope and intercept respectively lead to the enthalpy and entropy of activation, ΔH^* and ΔS^*. Table 1 lists the $\Delta\nu$, J_{AB} and T_c values, as well as the activation parameters calculated for I–VIII.

ΔH^* and ΔS^* values have been obtained only for I and V from the temperature dependence of the COOMe signals above 35°. The other compounds do not present signals suitable for a complete lineshape analysis.

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† A transmission coefficient of 1 has been used for all compounds I–VIII. However, in the case of the hexahydropyridazines V, VI and VII a transmission coefficient of ½ may be more correct as the potential curve of the rate process studied probably contains a valley at the top of the barrier, by analogy with other cyclohexane systems.[10] The first term in brackets in Eq. (3) is then equal to 10·02 and the ΔG^* values for these compounds would be smaller by ca. 0·4 kcal/mole than those given in Table 1. The cyclohexene and cyclohexadiene like I–IV, VIII probably possess a simple potential curve for the rate process studied (see below).

The accuracy of the $\Delta G_c^{\ddagger}$ values for these other compounds is limited as the signals considered are complex and not always well resolved. This is specially valid for the coalescence of several COOMe or COOEt signals, where an exchange between several unequally populated sites is occurring. Some of the $\Delta G_c^{\ddagger}$ values listed in Table 1 are therefore merely used for characterizing the type of rate process and conformational changes involved.

DISCUSSION

From the above description it is apparent that two types of spectral changes occur in the temperature range studied. Very complex patterns are obtained below 0°, especially for the COOR groups. These simplify by coalescence of various signals as the temperature is increased to 30–50°. Then at higher temperatures further coalescences occur and the spectra again simplify. That both changes are not due to the same rate process follows from the very different $\Delta G_c^{\ddagger}$ values obtained from the various coalescences (assuming that there is no very large entropy term (ca. 30 eu) present). Two rate processes seem to be present in I–VIII: a "low temperature" one (changes observed below 0°–10°; $\Delta G_{270}^{\ddagger}$ = ca. 14–15 kcal/mole) and a "high temperature" one (changes observed above 30–50°; $\Delta G_{370-400}^{\ddagger}$ = ca. 18–20 kcal/mole).

Stereochemistry of compounds I *and* II

Conformation of the cyclohexene ring. Stereospecific addition of azodicarboxylic esters to *trans, trans*-1,4-diphenylbutadiene is expected to give the isomer I (or II) with the Ph groups in *cis* relationship. The spectrum of the compound obtained from the Diels-Alder addition shows at 30° different chemical shifts and different vinylic and allylic coupling constants for the four ring protons (Table 1; Fig. 2). This is incompatible with this product being the *trans* adduct (isomer of I) which is expected to have a twofold symmetry axis and to show an AA′ BB′ spectrum for the ring protons. We conclude that addition of azodicarboxylic esters to diene systems is stereospecific and leads to the *cis* adduct I (XIII).[4]

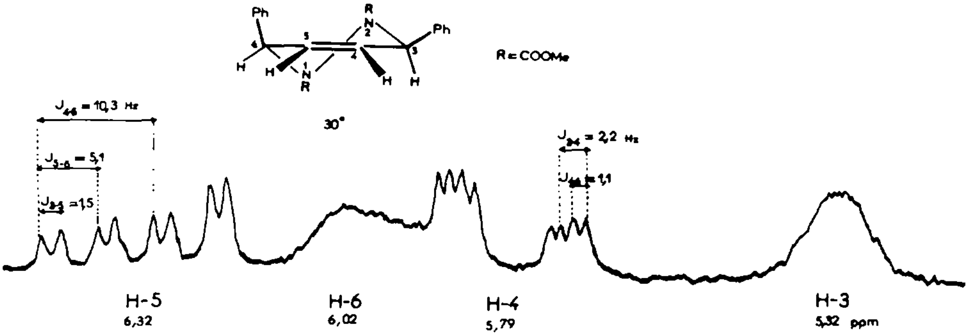
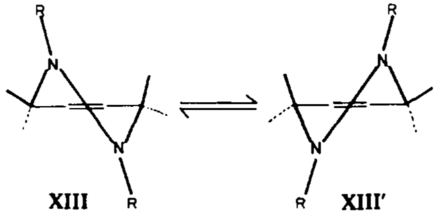


FIG. 2 NMR pattern of the ring protons in compound I at 30° in CDCl (60 MHz); Shifts are downfield from internal TMS.

Garbisch[11] has proposed approximate relationships between vicinal ^3J and allylic ^4J coupling constants and dihedral angles φ for the protons considered. As in the present case two ^3J's and two ^4J's are available for the same set of protons, an estimation of the conformation of the cyclohexene ring in I (XIII) seems possible and may be checked by the mutual compatibility of angles deduced from ^3J and ^4J couplings. The experimental splittings (in a first order approximation) are 5·1, 1·5, 2·2 and 1·1 Hz. The 5·1 splitting is very likely the vicinal coupling corresponding to the smaller dihedral angle, i.e. $^3J_{5-6}$. Then the allylic coupling $^4J_{3-5}$ = 1·5 Hz. As $^4J_{4-6}$ is expected to be smaller than $^4J_{3-5}$,[12] $^4J_{4-6}$ = 1·1 Hz and $^3J_{3-4}$ = 2·2 Hz (see Fig. 2; H-6 is pseudo equatorial and H-3 is pseudo-axial).



XIII XIII′

Assuming that the ^3J couplings are positive and the ^4J couplings negative, and using:[11]

$$^3J_{est} = 6{\cdot}6 \cos^2 \varphi + 2{\cdot}6 \sin^2 \varphi \; (0° \leqslant \varphi \leqslant 90°)$$

$$^4J_{est} = 1{\cdot}3 \cos^2 \varphi - 2{\cdot}6 \sin^2 \varphi \; (0° \leqslant \varphi \leqslant 90°)$$

one obtains:

$$\left.\begin{aligned} {}^3J_{5-6} &= 4{\cdot}8 \pm 0{\cdot}3\,\text{Hz} \\ {}^4J_{4-6} &= -0{\cdot}8 \pm 0{\cdot}3\,\text{Hz} \end{aligned}\right\} \text{ for } \quad \varphi = 45 \pm 5°$$

$$\left.\begin{aligned} {}^3J_{3-4} &= 3{\cdot}3 \pm 0{\cdot}6\,\text{Hz} \\ {}^4J_{3-5} &= -1{\cdot}7 \pm 0{\cdot}5\,\text{Hz} \end{aligned}\right\} \text{ for } \quad \varphi = 65 \pm 10°$$

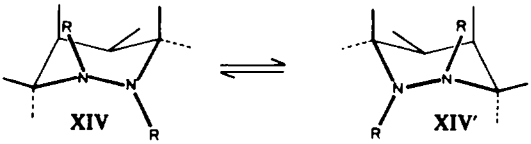
These angles give an estimate of the pseudo-equatorial and pseudo-axial position on the cyclohexene ring in the present compounds. They are similar to those which may be estimated from Dreiding models; however the "calculated" $^3J_{3-4}$ is quite different from the measured first order splitting. In any case one should not expect to obtain very accurate geometrical data from the angular dependence of coupling constants, as many factors other than dihedral angles affect the values of J.[13]

Nature of the "low temperature" rate process (changes observed below 0–20°). The spectral modifications observed below 0° for the COOR groups of the present compounds are very similar to those present in the bridged systems X and XII at similar temperatures.[1,5] They may be ascribed to the same rate process in both cases: i.e. *hindered rotation about the N—COOR bond.*[1,5] The di-urethane system —N(COOR)—N(COOR)— may exist in three different rotameric forms.[1] In the symmetrical (twofold axis) III, IV, a maximum of four COOR signals is expected at low temperatures, whereas eight such signals are expected for I, II, V, VI, VII. This results in very complex spectra at −60° for these compounds (see Table 1). As many signals overlap and identification of the signals from the different rotameric forms is problematic, no attempt was made to study the low temperature spectra in more detail.

Nature of the "high temperature" rate process (changes observed above 30°–50°). The different chemical shifts as well as the different vinylic and allylic coupling constants observed for the ring protons of I at 30° indicate that the cyclohexene ring is conformationally frozen (on the NMR time scale) at this temperature. The changes observed as the temperature is increased require that all pairs of protons of the same type exchange between the two sites observed in the spectrum at 30°. Chemical shifts and coupling constants are averaged out between two equally populated sites by a process in which the molecule takes part as a whole. At 130° the equilibrating species is in effect symmetrical. Such a process corresponds to *ring inversion* interconverting the two enantiomeric half-chair forms XIII $\rightleftharpoons$ XIII'.

The same result is valid for the AB → A_2 change observed for the ring CH_2 signals in the spectrum of III and IV. The breadth and the lack of resolution of the signals of the allylic protons (next to the diurethane site) in I and II may be due to a tail effect of the low temperature rate process.

The temperature dependent spectral changes described above for compounds V and VI may similarly be accounted for by the presence of a ring inversion process of the type XIV $\rightleftharpoons$ XIV', which at ca. 100–120° averages out the signals observed at 30° for the two sites (Table 1).



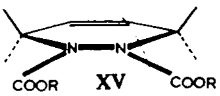
Mechanism of the ring inversion process and origin of the potential barrier. The N-sites in the —N(COOR)—N(COOR)— group in the compounds studied here are distorted from the pure pyramidal state towards the planar state by conjugation of the N lone pair with the CO groups (see discussion in Ref. 1). The presence of a high barrier to rotation about the N—COOR bonds (Table 2) is a consequence of this conjugation,[1] as is also the case in amides.[8]

The ring inversion processes XIII $\rightleftharpoons$ XIII' and XIV $\rightleftharpoons$ XIV' show very high activation energies (Table 1) as compared to cyclohexene[14] ($\Delta H^* = 5{\cdot}3$ kcal/mole; $\Delta S^* = 1{\cdot}3$ e.u.[14]) and to cyclohexane[15] ($\Delta H^* = 10{\cdot}8$ kcal/mole; $\Delta S^* = 2{\cdot}8$ e.u.). Furthermore, the inversion barriers for cyclohexene and cyclohexane are very different, whereas the tetrahydropyridazines (I–IV) and the piperidazines (V–VII) show similar barriers. Both pecularities of the present systems point to the fact that their potential barriers to ring inversion are determined in an important fashion by factors which are absent in cyclohexene and in cyclohexane.

Among the factors which may contribute significantly to these potential barriers, in addition to those present in cyclohexene and in cyclohexane, we may consider the following:

(1) The COOR groups are eclipsed in the transition state and may therefore interact strongly (as in XV for instance).

(2) Ring inversion is not possible without rotation about the N—N bond. A high barrier to internal rotation has recently been calculated for hydrazine (11·5 kcal/mole).[16]



XV

Although the electronic structure of the diurethane system is very different from that of hydrazine, appreciable torsional strain may be present in the planar arrangement of the transition state (XV) and may contribute significantly to the ring inversion barrier.

(3) The ΔG^* values also contain an entropy barrier, as shown by the negative ΔS^* values obtained for I and V (Table 2).

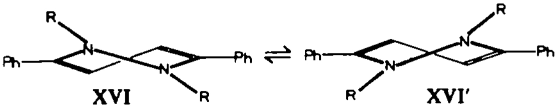
These factors (steric, electronic and entropic) are the same as those discussed for the "bridge flipping" process observed in XII (see discussion in Ref. 1). There is in fact a significant analogy between the present ring inversion process and the bridge flipping process in bicyclic compounds[1] both from the geometrical and from the energetical point of view. It appears that the —N(COOR)—N(COOR)— grouping is the general link between all these compounds (see below).

Nature of the rate process observed for compound VIII. The ABC_3 pattern observed for the COOEt signals of VIII at 33° points to the presence of some kind of dissymetry in the molecule. Its change to an A_2B_3 pattern indicates that a rate process is present which at higher temperatures renders the equilibrating molecule symmetrical on the NMR time scale.

If the molecule were planar, non-equivalente of the CH_2 protons of the COOEt groups would not be expected.[17] Furthermore this non-equivalence is still present at temperatures where rotation about the N—COOR bonds is expected to be very fast.

It is known from microwave data that 1,3-cyclohexadiene exists in a twisted conformation.[18]

Using a similar conformation, VIII may be represented as in XVI. Slow interconversion of the type XVI $\rightleftharpoons$ XVI′ may then lead to an ABC_3 pattern for the COOEt groups. On raising the temperature the rate of interconversion increases and the ABC_3 pattern changes over into an A_2B_3 pattern, the "average species" observed by NMR being then a planar entity. A ΔG^*_c value of 23 ± 1 kcal/mole (at ca. 420° K; Table 2) has been obtained from the coalescence of the different splittings present in the ABC_3 spectrum, and is therefore only a rough estimate of the energy barrier for the interconversion XVI $\rightleftharpoons$ XVI′.†



XVI XVI′

In addition to the factors contributing to the potential barrier for ring inversion discussed above, the very high ΔG^*_{420} obtained for the process XVI $\rightleftharpoons$ XVI′ may also contain an energy term arising from steric interactions between the eclipsed COOEt and Ph groups in the planar transition state. The rate process present in VIII represents a ring inversion or "*ring twisting*" process in a cyclohexadiene like system containing six planar or nearly planar sites.

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† The effect of changes of rotamer populations should also be considered. A more detailed study of this process, as well as the determination of the ΔH^* and ΔS^* values is under way.

TABLE 1. VARIABLE TEMPERATURE NMR SPECTRA OF COMPOUNDS I–VIII[a]

Compound	Temperature	N—COOR	Ring protons	CH_3 at C(4) and C(5)	Aromatic protons
I	130° (TCE)	3·55 (s; 6H) (calc. 3·6)[b]	H_3, H_6: 5·52 (bp; 2H) (calc. 5·54)[b] H_4, H_5: 5·93 (bp; 2H) (calc. 5·98)[b]	--	7·2 (bp; 10H) (calc. 7·2)[b]
	30° (TCE)	3·38 (s; 3H) 3·80 (s; 3H)	H_3: 5·18 (bm; 1H); H_6: 5·90 (bm; 1H) H_4: 5·70 (oc; 10·3, 2·2, 1·1 Hz; 1H) H_5: 6·25 (oc; 10·3, 5·1, 1·5 Hz; 1H)	—	7·05 (bp) 7·40 (bp) (10H for both p)
	30° ($CDCl_3$)	3·50 (s; 3H) 3·88 (s; 3H)	H_3: 5·32; H_6: 6·02; H_4: 5·79 H_5: 6·32. Multiplicity and areas as above	—	7·22; 7·50 (10H)
	−60° ($CDCl_3$)	3·50 and 3·54 (doublet; slightly less than 3H) 3·87 (s; 3H)	H_3: 5·28 (bm; 1H); H_6: 6·00 (bm; 1H) H_4: 5·77 (ill resolved oc; 1H) H_5: 6·30 (ill resolved oc; 1H)	—	7·18; 7·46 (bp; 10H)
II	140° (TCE)	CH_2: 4·0 (q; 7 Hz; 4H) CH_3: 1·1 (t; 7 Hz; 6H)	as for I at 130°	—	as for I at 130°
	30° ($CDCl_3$)	3·90 (q: 7 Hz; 2H) 4·30 (q: 7 Hz; 2H) 1·30 (t: 7 Hz; 3H) 0·95 (bt: 7 Hz; 3H)	as for I at 30°	—	as for I at 30°
	−52° ($CDCl_3$)	3·8–4·5 (several q; 8H) 1·35, 1·15, 0·60 (triplets of different areas and line-widths)	as for I at −60°	—	as for I at −60°
III	154° (HCB)	3·6 (s; 6H)	3·8 (bs; 4H)	1·6 (s; 6H)	—
	30° (TCE)	3·7 (s; 6H)	broad AB pattern at 4·15 and 3·60 (J = 15·9 Hz)	1·6 (s; 6H)	—

TABLE 1.—*continued*

Compound	Temperature (solvent)	N—COOR	Ring protons	CH_3 at C(4) and C(5)	Aromatic protons
IV	163° (HCB)	1·2 (t; 7 Hz; 6H) 4·05 (q; 7 Hz; 4H)	2·75 (bs; 4H)	1·6 (s; 6H)	—
	30° ($CDCl_3$)	1·2 (t; 7 Hz; 6H) 4·05 (q; 7 Hz; 4H)	broad AB pattern at 4·05 and 5·50 (*J* = 15·8 Hz)	1·6 (s; 6H)	—
V	95° (HCB)	3·60 (s; 6H)	H_3, H_6: 5·0–5·3 (bp; 2H) H_4, H_5: 1·8–2·1 (bp; 4H)	—	6·9–7·3 (bp; 10H)
	32° (HCB)	3·45 (bs; 3H) 3·75 (bs; 3H)	H_3, H_6: 4·8–5·2 (bp; 2H) H_4, H_5: 1·7–2·2 (bp; 4H)	—	6·9–7·3 (bp; 10H)
	−1° (HCB)	several overlapping peaks: 3·3–3·9 (6H)	H_3, H_6: 4·8–5·3 (bp; 2H) H_4, H_5: 1·7–2·2 (bp; 4H)	—	6·9–7·3 (bp; 10H)
VI	−53° ($CDCl_3$)	several overlapping peaks: 3·55 (6H)	H_3, H_6: 2·5–4·0 (vbm; 4H) H_4, H_5: 1·5–2·0 (bp; 2H)	0·87 (bp; 6H)	—
	34° (TCE)	3·50 (sharp s; 6H)	H_3, H_6: 2·5–4·0 (vbm; 4H) H_4, H_5: 1·5–2·0 (bp; 2H)	0·82 (d; 6 Hz; 3H) 0·86 (d; 6 Hz; 3H)	—
	119° (TCE)	3·55 (sharp s; 6H)	H_3, H_6: 3–4·0 (vbm; 4H) H_4, H_5: 1·5–2·0 (bp; 2H)	0·83 (d; 6 Hz; 6H)	—
VII	30° (TCE)	1·2 (t; 7 Hz; 6H) 4·1 (q; 7 Hz; 4H)	as for VI at 34°	0·83 (d; 6 Hz; 3H) 0·86 (d; 6 Hz; 3H)	—
	103° (TCE)	1·2 (t; 7 Hz; 6H) 4·2 (q; 7 Hz; 4H)	as for VI at 119°	0·86 (d; 6 Hz; 6H)	
VIII	162° (HCB)	A_2B_3 pattern 1·0 (t; 6H) 4·0 (4H)	H_4, H_5: 6·2 (s; 2H)	—	7·1–7·7 (m; 10H)
	30° (TCE)	1·0 (t; 7 Hz; 6H) 4·0 (q; 7 Hz; 4H)	H_4, H_5: 6·2 (s; 2H)	—	7·1–7·7 (m; 10H)

[a] Shifts are in ppm downfield from internal TMS. Coupling constants are in Hertz (= cycles per second) Hz; s: singlet; d: doublet; t: triplet; q: quartet; oc: octet; b: broad; p: peak; m: multiplet; v: very; TCE: tetrachloroethylene; HCB: hexachlorobutadiene; signal integral is last term in parentheses.

[b] These shifts have been calculated by averaging the shifts of the corresponding protons at 30°.

TABLE 2. SPECTRAL DATA AND ACTIVATION PARAMETERS

Compound	Signals and spectral changes studied	$\Delta\nu$ (at $T°$) Hz	T_c (solvent)	ΔG_c^* kcal/mole (ΔH^*, ΔS^*)^c	Conformational change
I	collapse of low temperature COOMe signals to a doublet	2·5 (−60°)	−3° ($CDCl_3$)	14·8^a	rotation about the N COOMe bonds
	lineshape analysis of COOMe doublet between 60° and 150°	23·5 (30°)	97° (TCE)^b	18·5 ± 0·3 (ΔH^* = 16·4 ± 1) (ΔS^* = −7 ± 3 eu)	ring inversion
II	collapse of several low temperature CH_2 quartets and Me triplets	—	—	—	rotation about N—COOEt bonds
	collapse of two CH_2 quartets	25 (30°)	95 5° (TCE)	18·5 ± 0·5	ring inversion
	collapse of two Me triplets	23 (40°)	95 5° (TCE)	18·5 ± 0·5	ring inversion
III	collapse of ring CH_2 AB pattern	31 (30°) (J = 15·9 Hz)	123° (HCB)^b	19·7 ± 0·5	ring inversion
IV	collapse of ring CH_2 AB pattern	30 (30°) (J = 15·8 Hz)	133° 5° (HCB)	20·3 ± 0·5	ring inversion
V	lineshape analysis of COOMe doublet between 33° and 95°	16·5 (33°)	55° (HCB)	16·7 ± 0·3 (ΔH^* = 15·6 ± 1) (ΔS^* = −3·5 ± 3 eu)	ring inversion
VI	collapse of the two CH—CH_3 doublets	2·3 (34°)	74° (TCE)	19·4 ± 0·4	ring inversion
VII	collapse of the two CH—CH_3 doublets	2·05 (35°)	78°	19·2 ± 0·4	ring inversion
VIII	change of COOEt signals from ABC_3 to A_2B_3	2·4 (30°)	420° (HCB)	23 ± 1	ring twisting

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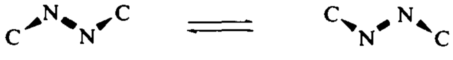
[a] Approximate value due to the presence of an exchange between several sites of different populations.

[b] TCE = tetrachloroethylene; HCB = hexachlorobutadiene.

GENERAL CONCLUSIONS

It should be noted that the "bridge flipping" process found in XII,[1] the ring inversion and the ring twisting processes discussed above, show a number of similarities. This seems to be a consequence of the presence of the —N(COOR)—N(COOR)— structural unit in all compounds studied.

Geometrically, these rate processes represent an interconversion between a right-handed and a left-handed twisted  $\underset{\text{COOR}}{\overset{}{\text{C—N}}}\text{———}\underset{\text{COOR}}{\text{N—C}}$ fragment with rotation about the N—N bond:

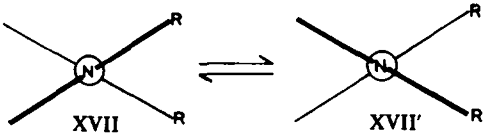


Energetically, the high activation energies found for these rate processes seem to arise for an important part from energy terms inherent to this same fragment (see discussion above and in Ref. 1).

This is also shown by the recent report of high barriers to rotation (of the order of 20–21 kcal/mole for the *cis* eclipsed arrangement) about the N–N bond in tetra-acylhydrazine derivatives.[19]

In addition, a recent X Rays analysis of the crystal structure of N, N′-bisuccinimidyl, shows that in this compound the two ring planes make a dihedral angle of 65°.[20]

It seems then that the acylhydrazine systems strongly prefer a non-eclipsed conformation (of type XVII) about the N—N bond and that the activation energy of a process of the type XVII ⇌ XVII′ is very high.



XVII XVII′

Furthermore, to the extent that replacing a $—CH_2—CH_2—$ structural unit by an —N(COOR)—N(COOR)— fragment does not lead to appreciable changes of the overall shape of the molecule but to *conformational fixation* (on the NMR time scale), this di-urethane fragment may be considered as a useful probe into molecular dissymetry and conformational changes.

EXPERIMENTAL

The spectra have been recorded on a Varian A-60 spectrometer equipped with the Varian variable temp accessory. The general recording conditions and the procedure used for lineshape analysis (in view of determining ΔH^* and ΔS^* in I and V) are described in Ref. 6. Shifts are in ppm downfield from internal TMS; coupling constants are in Hz and have been obtained by a first order analysis.

Preparation of the compounds. Compounds I,[21] II,[21], IV,[22,23] VII[23] and VIII[24] have been prepared by established methods and had physical constants and spectral data in agreement with their structure.

1,2-Dicarbomethoxy-4,5-dimethyl-1,2,3,6-tetrahydropyridazine (III). This was prepared according to the procedure reported for the diethyl ester derivative,[22,23] yield of recrystallised product (from cyclohexane): 70%; sublimed product m.p. 70°. (Found: C, 52·63; H, 7·19; N, 12·45. $C_{10}H_{16}N_2O_4$ requires: C, 52·62; H, 7·07; N, 12·27%.)

1,2-Dicarbomethoxy-4,5-dimethylpiperidazine (VI). This was obtained by catalytic hydrogenation of III using conditions similar to those employed for hydrogenation of the diethyl ester derivatives,[25] yield:

84%, b.p. 60–62°/22 mm. $n_D^{23} = 1{\cdot}471$. (Found: C, 52·34; H, 7·95; N, 12·39. $C_{10}H_{18}N_2O_4$ requires: C, 52·16; H, 7·88; N, 12·17%.)

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