(C_9–C_{10}, 0.03 Å) is in agreement with the description of the charge-delocalized nature of I which predicts that C_9–C_{10} should have considerable double bond character.

Selected least-squares planes are presented in Table V. The molecular plane (plane 5, Table V) composed of ring atoms reveals the approximate planarity of the ring system. Table VI lists the intermolecular contacts, <3.60 Å. The shortest contact observed (3.15 Å) involves C_{13} and O_1. This contact compares to the calculated value of 3.40 Å which results from the sum of the van der Waals radii of the oxygen atom and the methyl group.[28]

Table VIII lists h, k, l $10|F_o|$ and $10|F_c|$ for the 1997 data collected.[18]

Acknowledgment. The authors wish to thank the University of Arizona Computer Center for generous financial assistance.

Nuclear Magnetic Resonance Studies of the Conformations of 1,2-Dicarboxy-1,2,3,6-tetrahydropyridazines

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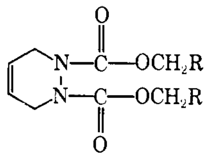
Abstract: Variable-temperature proton and fluorine-19 nmr experiments suggest that 1,2-dicarbethoxy-1,2,3,6-tetrahydropyridazine and 1,2-dicarbotrifluorethoxy-1,2,3,6-tetrahydropyridazine exist as at least four distinct conformational isomers. At low temperatures, the rate of equilibration between these isomers becomes slow, and as the sample temperature is raised to about 30°, the changes in the proton or fluorine spectra can be accounted for in terms of processes that have activation free energies of 14–16 kcal/mol. Consideration of the pmr signals from the ring protons indicates that the heterocyclic six-membered ring is conformationally immobile during these changes and that only at much higher temperatures does ring inversion occur at an appreciable rate ($\Delta G^{\ddagger} \sim$ 20–22 kcal/mol). The nature of the low-temperature rate process is discussed.

The stereochemical capabilities of nitrogen have been widely studied by magnetic resonance and recent reviews have admirably summarized the information that has been obtained about the kinetics of stereomutation at nitrogen in both the pyramidal amine state[2,3] and in the planar amide configuration[4,5] by these techniques. Tetrahydropyridazines with carbethoxy (Ia)



Ia, R = CH_3
b, R = CF_3

or carbomethoxy substituents at the nitrogen atoms have been of particular interest in this regard since pmr studies of these and related molecules have indicated that at least two distinct conformational equilibrations can take place in these systems.[4,5] By proper choice of assumptions, either of these processes can be assigned to any one of three types of conformational interchange: (a) inversion of the cyclohexene-like tetrahydropyridazine ring,[6] (b) inversion of trihedral amide nitrogen atoms in analogy to the process found in ammonia,[7] or (c) restricted rotation about the carbamate N—C=O bond system similar to that found in simpler carbamates.[8] These assignments have, therefore, been the source of some controversy.

The first published observations of the unusual conformational properties of tetrahydropyridazines were reported by Breliere and Lehn.[9] These authors interpreted changes in the pmr spectrum of II in terms of a high-temperature interconversion process ($\Delta G^{\ddagger}$ = 18.9 kcal/mol), assigned to inversion of the heterocyclic ring, and a low-temperature process ($\Delta G^{\ddagger}$ = 14.8 kcal/mol) ascribed to rotation about the carbon–nitrogen bond of the carbamate system. A challenge to this interpretation was effectively answered.[10–12] In contrast, Daniels and Roseman offered a rationalization based on inversion of nitrogen for the complex pattern of methoxyl pmr signals that arise from III when the sample temperature is lowered.[13]

Allred, *et al.*, have examined the variable-temperature pmr spectra of bridged tetrahydropyridazines (IV, V) in order to assess the nature of conformational processes that occur in the absence of any possible ring inversion.[14] In the hydrazine (V), the pmr spectral changes

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(1) (a) NDEA Title IV Fellow, 1967–1970.

(2) J. M. Lehn, *Fortsch. Chem. Forsch.*, **15**, 311 (1970).

(3) A. Rauk, L. C. Allen, and K. Mislow, *Angew. Chem., Int. Ed., Engl.*, **9**, 400 (1970).

(4) W. E. Stewart and T. H. Siddall, III, *Chem. Rev.*, **70**, 517 (1970).

(5) G. Binsch, *Top. Stereochem.*, **3**, 97 (1968).

(6) (a) F. A. L. Anet and M. Z. Haq, *J. Amer. Chem. Soc.*, **87**, 3147 (1965); (b) F. R. Jensen and C. H. Bushweller, *ibid.*, **91**, 5774 (1969).

(7) Such a process has been found in *N*-acylaziridines: F. A. L. Anet and J. M. Osyany *ibid.*, **89**, 352 (1967).

(8) E. Lustig, W. R. Benson, and N. Duy, *J. Org. Chem.*, **32**, 851 (1967).

(9) J. C. Breliere and J. M. Lehn, *Chem. Commun.*, 426 (1965).

(10) C. H. Bushweller, *Chem. Commun.*, 80 (1966).

(11) B. J. Price, R. V. Smallman, and I. O. Sutherland, *ibid.*, 319 (1966).

(12) R. Daniels and K. A. Roseman, *ibid.*, 429 (1966).

(13) R. Daniels and K. A. Roseman, *Tetrahedron Lett.*, 1335 (1966).

(14) E. L. Allred, C. L. Anderson, R. L. Miller, and A. L. Johnson, *ibid.*, 525 (1967).

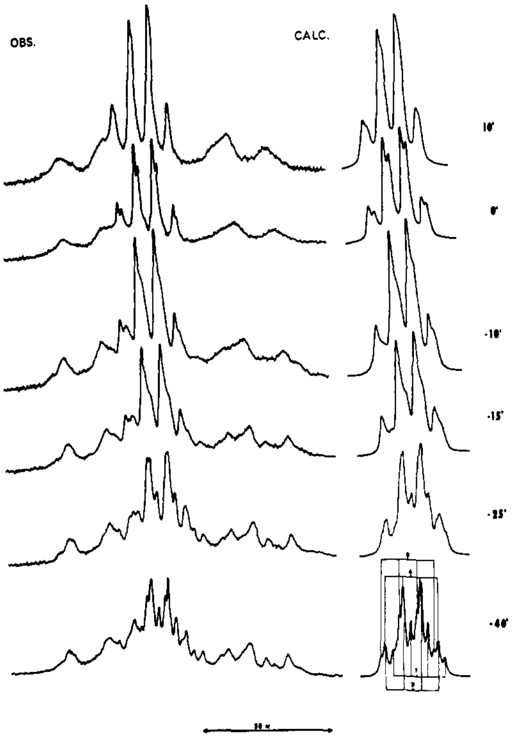
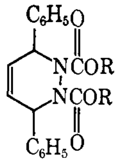
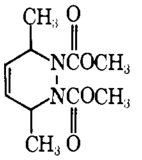


Figure 1. The methylene region of the pmr spectrum of Ia as a function of sample temperature. The sharp lines correspond to the side-chain methylene signals while the broader peaks are assigned to the ring-methylene resonances. The solvent was chloroform. The calculated spectra were prepared as described in the text.

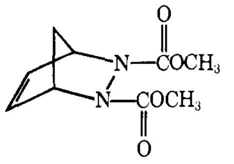
that occur can only be assigned to nitrogen inversion. Since the free energies of activation for conformational exchange in IV and V are similar (15–16 kcal/mol), these authors concluded that nitrogen inversion is also the dominant process in systems analogous to IV. Anderson and Lehn examined these and related bicyclic systems and concluded that restricted rotation at the carbonyl–nitrogen bond is responsible for the spectral changes observed.[15] Finally, Moriarity *et al.*, have reported infrared spectral data which may be consistent with a sterically unusual environment for the carbamyl group; on these grounds these authors suggested that nonplanar, pyramidal (invertible) nitrogen atoms were a possibility in the 1,2-dicarbethoxy-1,2,3,6-tetrahydropyridazine systems.[16]



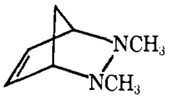
IIa, R = CH_3
b, R = CH_3CH_2



III



IV



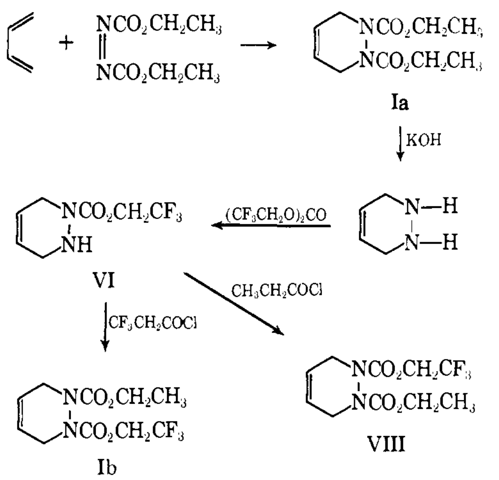
V

Prior investigations have, therefore, not unambiguously characterized the nature of the conformational isomerizations in these molecules. Since most of the previous conclusions have been based on spectra obtained at 60 MHz, we felt that it would be of value to examine the parent system at 100 MHz, where the enhanced chemical-shift effects at the higher filed might reveal additional features in the spectrum at low temperatures. In this same spirit, we have examined a trifluoromethylated analog (Ib) since the large chemical shifts associated with fluorine magnetic resonance spectroscopy have been of value in other studies of conformational processes.[17] We describe here the results of these experiments as well as those obtained from the investigation of model compounds.

Results

Synthesis. The reaction sequence used for the preparation of Ia and Ib is outlined in Chart I.

Chart I



1,2-Dicarbethoxy-1,2,3,6-tetrahydropyridazine. As expected from the prior work described above, the character of the pmr spectrum of 1,2-dicarbethoxy-1,2,3,6-tetrahydropyridazine (Ia) was highly sensitive to the sample temperature. With deuteriochloroform as solvent, the triplet and quartet patterns for the ethyl side chains appeared to be slightly broadened at ambient probe temperature (~34°). These signals sharpened somewhat but underwent no further fundamental change when the sample temperature was increased. Essentially the same effects were noted when toluene or acetic acid was utilized as the solvent. Upon decreasing the temperature of the deuteriochloroform solution below room temperature, the ethyl resonances broadened further and finally evolved into a complex set of signals. Consideration of the methylene signals arising from the ethyl side chains at −50° indicated that *four* overlapping quartet patterns were contained within this multiplet. As indicated in Figure 1, a computer-simulated line shape consisting of four quartets ($J \approx 7.0$ Hz) with relative abundances of 1 : 1 : 1 : 1 could account fairly well for the complex spectrum observed at low temperatures. The methyl multiplet also evolves into a complex pattern that appears to be three overlapping triplets at low temperature. Since the results from the analysis of the methylene signals make it reasonably clear that four different

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[15] J. E. Anderson and J. M. Lehn, *Tetrahedron*, **24**, 123, 137 (1968).

[16] R. M. Moriarity, M. R. Murphy, S. J. Druck, and L. May, *Tetrahedron Lett*., 1603 (1967).

[17] J. D. Roberts, *Chem. Brit.*, **2**, 529 (1966).

magnetic environments are available to the ethyl fragment of Ia, there are probably two chemical-shift degenerate triplets contained within this multiplet.

Signals from the ring methylene groups appear as a somewhat broadened AB quartet (apparent $\delta_{AB} = 0.56$ ppm, apparent $J_{AB} = 15.5$ Hz) at room temperature. As the signals from the side-chain methylene group are developing into the quartet of quartets pattern, the ring methylene signals (some of which apparently lie under the side-chain methyl resonances) become more complex. We have not attempted a line-shape analysis of these changes but, given the appearance of the spectrum at −55°, it is fairly easy to accept the proposition that this multiplet, originally AB-like at room temperature, has evolved into at least four overlapping AB quartets. When the sample temperature was increased, the ring-methylene AB quartet broadened and eventually coalesced into a singlet. These spectral changes were analyzed for the rate of the interconversion process that brings about this change by comparing computer-generated curves to the experimental line shapes and are illustrated in Figure 2. The activation parameters for the process obtained in this way are summarized in Table I. The high value for the activation free energy is in accord with what other investigators have found for "high-temperature" processes in similar systems.[4] It is especially noteworthy that changing the solvent to acetic acid, a strongly hydrogen-bonding medium, does not affect the kinetics of this interchange significantly.

Table I. Activation Parameters for the High-Temperature Process in Ia and Ib

Compd	Solvent	$\Delta G^{\ddagger}_{25}$, kcal/mol	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
Ia	Cyclohexane	20.5	20.7 ± 1.4	0.6
	Acetic acid	21.1	22.9 ± 1.2	6.0
	Mesitylene	20[a]		
Ib	Mesitylene	20[a]		

[a] Estimated from the coalescence temperature of the AB quartet; *cf.* R. J. Kurland, M. B. Rubin, and W. E. Wise, *J. Chem. Phys.*, **40**, 2426 (1964).

The vinyl protons of Ia give rise to an apparent doublet, $J = 2$ Hz, at room temperature (Figure 2). The separation of the doublet is virtually the same at both 60 and 100 MHz, so that it primarily represents a coupling constant. The vinyl protons therefore are characterized by the same chemical shift and it is likely that the ring skeleton has sufficient symmetry at this temperature, either because of its inherent nature or because it is undergoing conformational interconversion rapidly, such that the six-ring hydrogen nuclei define an AA′BB′XX′ system. Complete analysis of the experimental spectra for all of the parameters which would characterize this spectrum is impractical given the lack of resolution in spectra and we shall assume for the discussion which follows that the vinyl and ring methylene signals may be treated approximately as an ABX system.

The vinyl region of the pmr spectrum of Ia undergoes subtle but real changes as a function of sample temperature. Throughout the low-temperature range, during which both sets of methylene signals increase in complexity, the vinyl signals merely broaden slightly. At higher temperatures, the character of the olefinic resonance changes such that at high temperatures a triplet pattern with an apparent splitting of $J = \sim 1$ Hz is observed.

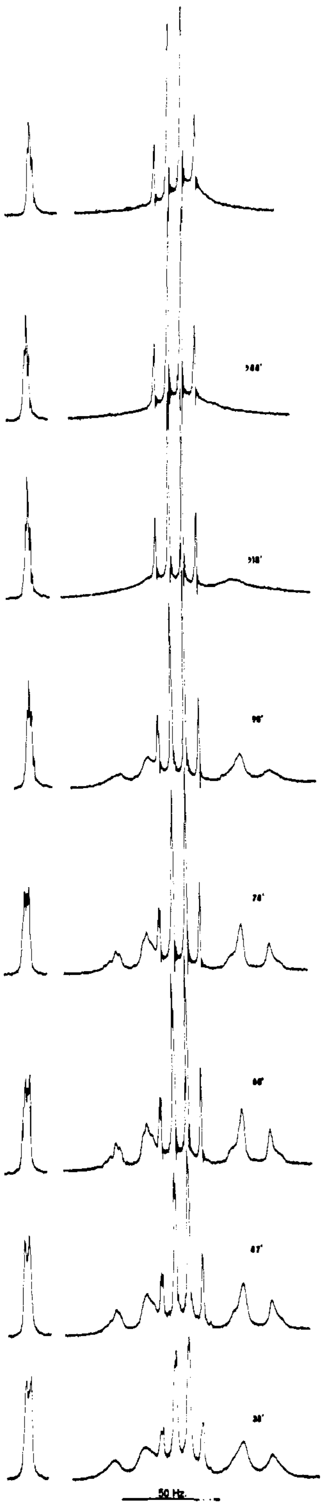

Figure 2. The methylene and vinyl regions of the pmr spectrum of Ia at temperatures above ambient. The solvent was toluene.

Since it appears that the interchange of nuclei between four magnetically unique sites is taking place in Ia, we attempted to obtain computer-simulated high-resolution line shapes corresponding to the side-chain methylene signals that would permit an estimate of the rate of exchange. In the general four-site case, a simu-

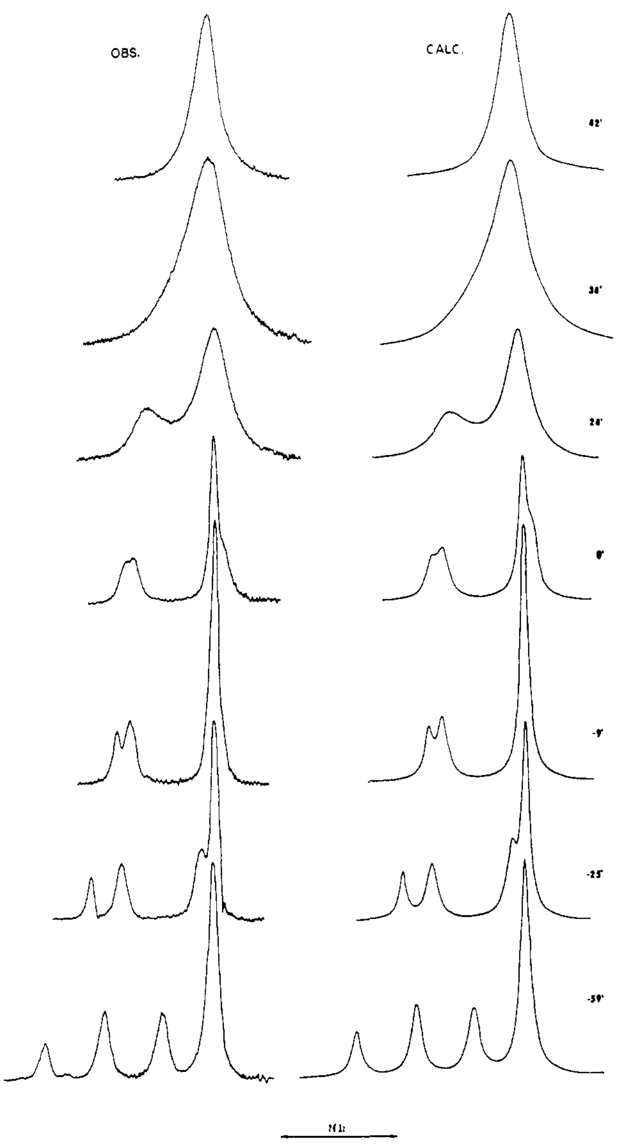

Figure 3. The proton-decoupled fluorine-19 nmr spectrum of Ib as a function of sample temperature. The solvent was chloroform. The theoretical curves were prepared as described in the text.

lation of this nature is characterized by four chemical shifts, four intrinsic transverse relaxation times (T_2), three energy differences related to the relative populations at each site, and six energy barriers which are related to 12 rate constants. A general program which utilizes these data as input was prepared as outlined in the Appendix and was used in our search for a set of parameters that would reproduce the nmr spectral changes observed experimentally. By assuming that the values for the required information are those listed in Table II, it was possible to generate a series of theoretical curves that agreed moderately well with those found in the low-temperature nmr experiments. The interesting feature of these simulations is that two processes with slightly different activation free energies are indicated. However, it must be noted that the number of input parameters required to describe this fairly complex chemical exchange situation is large and it is, therefore, possible that there exists another data set that gives an equally acceptable fit to the experimental data. We have shown, however, that the assumption of random exchange between the four environments does not lead to theoretical pmr curves in reasonable agreement with experiment. The free-energy barrier to exchange between sites 1 and 4 and 2 and 3, as defined in Table II, must be larger than 20 kcal/mol, but the analysis is not sensitive enough to this barrier to permit us to estimate it more exactly.

Table II. Parameters for Conformational Exchange at Low Temperatures

Compd	Site	δ, Hz[a]	J, Hz	$W_{1/2}$, Hz	p[b]
Ia in chloroform[e]	1	0.0	6.8	1.1	0.25
	2	-5.0	7.0	1.1	0.25
	3	-3.1	7.0	1.1	0.25
	4	-3.5	7.0	1.1	0.25
Ib in toluene[c,f]	1	0.0	*d*	1.6	0.47
	2	$-0.9 + 0.08t$	*d*	1.6	0.20
	3	$-13.7 + 0.08t$	*d*	2.0	0.20
	4	$-16.4 \times 0.14t$	*d*	1.6	0.13

[a] Chemical shift of site, relative to that of site 1. Fluorine chemical shifts were linearly dependent on temperature; this dependence is given by the expression shown over the range −50 to +50°. [b] Relative population of each site. [c] Studied by fluorine nmr spectroscopy. [d] Spectra were proton decoupled so that this quantity was not usually measured. [e] $\Delta G^{\ddagger}_{1,2} = \Delta G^{\ddagger}_{3,4} = 15.7$ kcal/mol, $\Delta H^{\ddagger} = 13.7 \pm 1.4$ kcal/mol, $\Delta S^{\ddagger} = -8$ eu, $\Delta G^{\ddagger}_{1,4} = \Delta G^{\ddagger}_{2,3} > 20$ kcal/mol, $\Delta G^{\ddagger}_{1,3} = \Delta G^{\ddagger}_{2,4} = 14.3$ kcal/mol, $\Delta H^{\ddagger} = 11.9 \pm 2.3$ kcal/mol, $\Delta S^{\ddagger} = -9$ eu. [f] $\Delta G^{\ddagger}_{1,2} = \Delta G^{\ddagger}_{3,4} = 16.0$ kcal/mol, $\Delta H^{\ddagger} = 15.6 \pm 1.2$ kcal/mol, $\Delta S^{\ddagger} = -2$ eu, $\Delta G^{\ddagger}_{1,4} = \Delta G^{\ddagger}_{2,3} > 20$ kcal/mol, $\Delta G^{\ddagger}_{1,3} = \Delta G^{\ddagger}_{2,4} = 16.5$ kcal/mol, $\Delta H^{\ddagger} = 18.4 \pm 2.1$ kcal/mol, $\Delta S^{\ddagger} = 6.4$ eu.

1,2-Dicarbotrifluoroethoxy-1,2,3,6-tetrahydropyridazine (Ib). Attention was focused primarily on the fluorine-19 spectrum of Ib, obtained at 94.1 MHz with simultaneous decoupling of protons at 100 MHz. Under these conditions, as indicated in Figure 3, the fluorine-19 spectrum at low temperature consisted of four singlets, present in the relative abundances of 47:20:20:13. No other resonances were found within ±250 Hz of these peaks; given the greater sensitivity of fluorine chemical shifts to molecular environment, this observation confirms the conclusions reached during the investigation of the pmr spectrum of Ia, namely that four distinguishable molecular forms are available to 1,2-dicarbethoxy-1,2,3,6-tetrahydropyridazine.

The behavior of the fluorine signals was also studied using the four-site exchange program mentioned earlier. Unfortunately, it was found that the fluorine chemical shifts appeared to be temperature dependent even in the absence of chemical exchange. This phenomenon, while not uncommon,[18] complicated the analysis. We assumed that the temperature effects on chemical shifts would be linear and that the changes found at low temperatures, where chemical exchange effects will be minimal, could be extrapolated to higher temperatures. Theoretical curves prepared by assuming that interchange between the four molecular environments was not random, but rather proceeded in the same manner as that inferred from the results with Ia, fit the experimental spectra best. The activation parameters so defined for the trifluoromethyl-containing molecule (Ib) are quite similar to those found for the all-hydrogen system (Ia).

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(18) (a) R. A. Newmark and C. H. Sederholm, *J. Chem. Phys.*, **43**, 602 (1965); (b) J. T. Gerig and C. E. Ortiz, *J. Amer. Chem. Soc.*, **92**, 7121 (1970).

Table III. Kinetic Parameters for Model Compounds

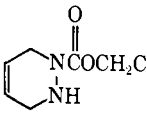
Compd	Solvent	ΔV, Hz[a]	P[b]	$\Delta G^{\neq}$, kcal/mol[c]	$\Delta H^{\neq}$, kcal/mol	$\Delta S^{\neq}$, eu
VI	Chloroform	$34.3-0.32t$	53/47	14.2	11.2	−11
VII	Chloroform	20	32/68	14.8	14.6	1.0

[a] Fluorine chemical-shift difference at 94.1 MHz. [b] Population ratios for the two peaks observed; the signal at low field is given first. [c] Barriers to conversion of the first conformer to the second.

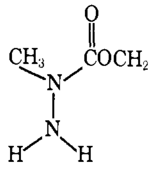
The appearance of the ring methylene and vinyl signals in the pmr spectrum of Ib was very similar to that reported above for Ia (Figure 2). The four-ring methylene protons gave rise to an apparent AB quartet (δ 0.63 ppm, J = 16 Hz) that slowly evolved to an A_2 singlet as the sample temperature was elevated. From the coalescence of the quartet it was estimated that the free energy of activation for the kinetic process that brings about this spectral change is about 20 kcal/mol, in reasonable agreement with the barrier found with Ia for this process (Table I).

The vinyl proton signal in Ib also appeared as an apparent doublet, J = 2.0 Hz at 100 MHz, and was virtually unchanged when observed at an operating frequency of 60 MHz. This multiplet changed to a triplet ($J \approx$ 1 Hz) at high temperature.

Model Compounds. In order to obtain an appreciation for the properties of a tetrahydropyridazine that is substituted at only one nitrogen atom, proton and fluorine nmr spectra of the synthetic intermediate VI were obtained. The proton spectrum of VI at 28° consisted of two broad equally intense signals at 3.3 and 3.9 ppm relative to TMS for the ring methylene protons and broad peak at lower field, assigned to the vinyl protons, in addition to the methylene quartet for the side chain. The ring methylene groups are expected to be magnetically distinguishable because of the asymmetry of VI; it is important to note than an AB pattern was not observed for either of these groups.



VI



VII

The fluorine nmr spectrum, observed with simultaneous proton irradiation, evidenced a single line at room temperature. As the sample temperature was lowered, this singlet broadened and finally evolved into a doublet of nearly equally intense lines; repeated integrations of decoupled spectra at −60° indicated that the intensity ratio of the low-field component to the high-field member was 53:47. An analysis of the changes in spectral line shape with temperature for the exchange rates was carried out and afforded the activation parameters listed in Table III. Again, the fluorine chemical-shift difference was found to be strongly temperature dependent.

Consideration of molecular models indicates that if the nitrogen atom bearing the carbotrifluorethoxy group in VI is significantly nonplanar (*i.e.*, pyramidal), then the pmr signal from the ring methylene group adjacent to this nitrogen should be an AB quartet when nitrogen inversion in this pyramid is slow. The expectation is not realized and it seems reasonable to conclude that in this compound the process which interchanges the fluorine atoms between the two accessible environments is rotation about the urethane carbon–nitrogen bond even though the magnitude of the activation free energy observed (14 kcal/mol) could equally be consistent with inversion of configuration of the urethane nitrogen atom.

An acyclic analog of compound VI, 1-methyl-1-carbotrifluorethoxyhydrazine (VII), was also studied. The fluorine-19 magnetic resonance spectrum of VII in chloroform showed a sharp triplet when the sample temperature was 60°; this multiplet collapsed to a singlet upon double irradiation of protons at 100 MHz. As the sample temperature was lowered, this signal broadened and finally split into two signals of relative areas 0.32 and 0.68. A line-shape analysis was employed to estimate the rate of exchange between the two sites so delineated; the activation parameters which describe the process are listed in Table III.

Lastly, a preliminary examination of the fluorine and proton spectra of the mixed tetrahydropyridazine (VIII) was made; both of these were qualitatively very similar to those obtained for the doubly trifluoromethyl-substituted material Ib.

Discussion

In the discussion that follows we shall assume that, at least qualitatively, the methyl- and trifluoromethyl-substituted materials, Ia, Ib, and VIII, are conformationally similar. The parallelism in the appearance of the pmr spectra for these molecules, coupled with the similar values found for corresponding activation parameters, argues in favor of this assumption; we have seen no indication that fluorine substitution drastically alters the conformational properties of the dicarbethoxy-substituted tetrahydropyridazine.

Because of its cyclohexene-like nature, the six-membered ring system of nonbridged tetrahydropyridazines has generally been assumed to take the half-chair conformation. A justification for this assumption, generated by employing approximate relationships between vicinal coupling constants and dihedral angles proposed by Garbisch,[19] has been offered by Anderson and Lehn.[15] The doublet pattern observed for the vinyl proton signal of Ia and Ib is consistent with this analysis, also. From consideration of Fieser or Dreiding models of the half-chair conformation of cyclohexene, it is estimated that the dihedral angles between a vinyl hydrogen and the adjacent ring methylene protons in I are ~90° and ~40°. Using the Karplus relation, these angles correspond to vicinal coupling constants of ~0 and 2–4 Hz.[20] Thus, if the tetrahydro-

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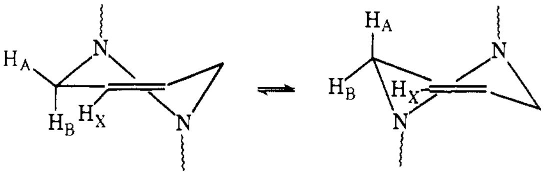
(19) E. W. Garbisch, *J. Amer. Chem. Soc.*, **86**, 5501 (1964).

(20) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, Elmsford, N. Y., 1969, p 284.

pyridazine ring is in a symmetrical conformation analogous to that taken by half-chair cyclohexene, the vinyl protons should appear roughly as a doublet pattern with $J_{AX} \simeq 2$ Hz and $J_{BX} \approx 0$ Hz if the conformation is rigid as indicated in the sketch below.[21] In



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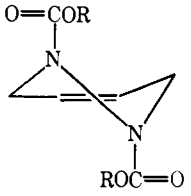
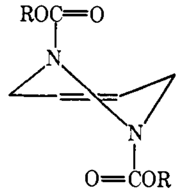
this rigid structure, methylene hydrogens H_A and H_B are magnetically nonequivalent and will, therefore, give rise to an AB pattern in the pmr spectrum. As the rate of half-chair–half-chair interconversion becomes rapid, two effects should be noted in the pmr spectrum: the apparent AB quartet for the methylene groups should change to an A_2 singlet and the splitting of the vinyl signal should become the *average* of J_{AX} and J_{BX}—in this case, about 1 Hz. It is precisely these spectral changes that are observed when samples of Ia or Ib are heated and, on this basis, we assign the "high-temperature" rate process to inversion of the tetrahydropyridazine ring, in agreement with most previous authors.[15,23] A disturbing facet of this conclusion is the very large energy barrier, ~21 kcal/mol, that must be associated with this transformation since typically the activation free energies for cyclohexene ring inversion are 5–8 kcal/mol.[6] Space-filling models suggest that the carbethoxy or carbotrifluoroethoxy groups of Ia or Ib, being quite bulky, can interact strongly in these compounds. Repulsive interaction of the carbonyl dipoles may also play a role and it seems that a considerable degree of cooperativity in the motions of these groups would be required to permit inversion of the configuration of the tetrahydropyridazine ring. We note that in the monosubstituted material, VI, the pmr spectrum of the hydrogen nuclei of the heterocyclic ring is most consistent with the ring being involved in rapid conformational equilibration. Both the methylene group adjacent to the carbotrifluoroethoxy substituent and the one distant from it appear as singlets in the spectrum; they retain this (averaged) character even at −60° in chloroform. The behavior of VI is more typical of a cyclohexene-like molecule and reinforces the notion that interactions between the side chains in the disubstituted tetrahydropyridazine are responsible for the much increased energy barrier to ring flexion in I.

If the above arguments with regard to the nature of the exchange process which occurs at high temperatures are correct, then the cyclohexene-like, tetrahydropyridazine ring may be regarded as being conformationally rigid in the half-chair form at temperatures below 30° and the additional conformational effects evidenced in the proton of fluorine spectra described above must be due to changes in the relative positions or orientation of the carbethoxyl side chains. The existence of four magnetically distinct sites can be rationalized several ways, as discussed below. In this discussion reference will be made only to the spectral behavior noted for the fluorine-19 spectrum of Ib although the arguments are equally applicable to the proton spectrum of Ia.

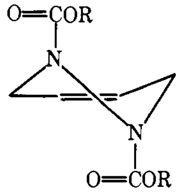
For one interpretation we make the assumption that the acyl carbon–nitrogen bonds have to a high degree the characteristics of the corresponding bond in an amide. That is, we assume that the carbon, nitrogen, and oxygen atoms of a urethane group in I and the first atoms of each of the substituents attached to this bond system are in a common plane. We also assume that the carbon–nitrogen bond will have sufficient double-bond character so that rotation about this axis is not free but rather hindered by an appreciable energy barrier. Under these conditions one can envision three (idealized) arrangements of the diurethane system, **3**, **4**, and **5**. Structures **3** and **4** have sufficient symmetry that they would be expected to each give rise to single fluorine-19 resonance. These conformers could be assigned interchangeably either to the signal at highest field or the one at the extreme low-field position in Figure 3; conformer **4** seems somewhat more favorable and so the high-field resonance is identified with this structure with **3** being assigned to the low-field signal. Isomer **5** should be characterized by two fluorine signals of equal intensity and the two peaks in the center of the low-temperature fluorine spectrum of Ib could be taken to correspond to this form. For this argument we therefore identify site 1 of Table II with **4**, sites 2 and 3 with **5**, and site 4 with **3**. If these materials are amide-like and rotation about C–N bond is the rate process in I which is slowed at −60° as is suggested by the magnitude of the activation parameters, conformational interconversion of **3–5** will most likely occur by rotation of only one urethane function at a time and the interconversion itinerary would follow the scheme sketched in Chart II. The process that changes **4** to **5** should be characterized by the same activation free energy for interchange between trifluoromethyl site 1 and sites 2 and 3. A similar statement holds for the interconversion of **3** and **5**. However, there is no reason to expect the two sets of energy barriers to be equal since the nonbonded interactions in the ground and transition states for these processes are different.[24]



3



4



5

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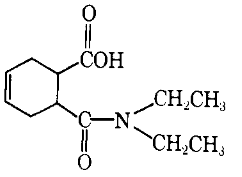
[21] It should be noted that attaching side chains to the cyclohexene ring *via* carbonyl groups does not change the conformation of the cyclohexene ring. Thus, the cyclohexene ring in the compound below is in the half-chair conformation in the solid state.[22]

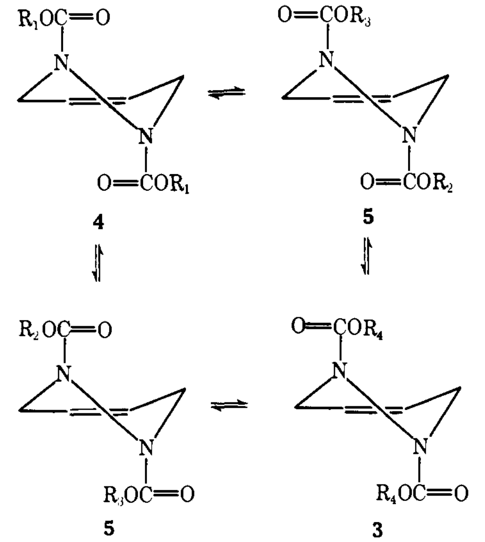


[22] C. Pedone, E. Benedetti, A. Immirizi, and G. Allegra, *J. Amer. Chem. Soc.*, 92, 3549 (1970).

[23] B. Price, I. O. Sutherland, and F. G. Williamson, *Tetrahedron*, 22, 3477 (1966).

[24] The mechanism suggested by Chart II involves the interchange of trifluoromethyl groups between a total of six molecular sites, two of which are doubly degenerate with respect to chemical shift. However, exchange between only four sites needs to be considered in the mathematical treatment used to obtain theoretical nmr line shapes because of

Chart II



(Any important contribution to the overall kinetic picture by conversion of **3** to **4** directly is ruled out by the assumption that concerted rotation of both urethane groups does not occur facilely.) Our experimental results do not agree with this prediction. Instead, the energy barriers between sites 1 and 2 and 3 and 4 appear to be equal while $\Delta G^{\ddagger}_{1,3}$ and $\Delta G^{\ddagger}_{2,4}$ are also equal but slightly different from the first set.

An alternative explanation, based upon inversion of trihedral nitrogen in I, could be put forth to rationalize the changes in the low-temperature nmr spectra of I. The assumption of nonplanar amide nitrogen would seem to carry with it the attendant assumption that the double bond character in the carbonyl carbon–nitrogen bond is greatly reduced so that the rate of rotation about this bond is increased. With these assumptions at hand and presuming a fixed tetrahydropyridazine ring geometry, one can again define three unique molecular conformations for Ib when nitrogen inversion is slow (**6**–**8**). These structures and an interconversion sequence are shown in Chart III. Each of these conformers has a mirror image form that can be obtained by inversion of the six-membered ring.

Chart III

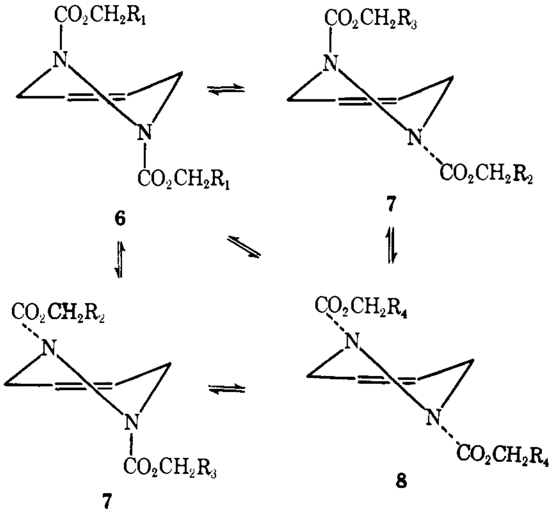
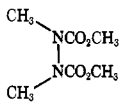
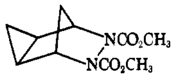


Table IV. Infrared Data for 1,2-Carboalkoxy-1,2,3,6-tetrahydropyridazine and Related Structures[a]

Structure	ν_{C-O}, cm^{-1}	Ref
	1693	*b*
IV	1754, 1713	*b*
	1748, 1704	*b*
Ia	1730 (br), 1650	*c*
VIII	1735 (br)	*c*
Ib	1740 (br), 1650	*c*
VI	1735 (br), 1650	*c*

[a] In carbon tetrachloride solution. [b] Reference 16. [c] This work.

A solid line has been used in Chart III to denote an axial carbon–nitrogen bond while the dotted lines correspond to an equatorial arrangement. We assign the most intense signals in the fluorine spectrum of Ib to structure **6**, the diaxial form, primarily because it seems this arrangement would be slightly favored by the relief of steric interactions between the carboalkoxyl groups. Because of their symmetry conformers **6** and **8** should each result in a separate, single peak in the proton-decoupled fluorine spectrum while **7** should be characterized by two equally intense signals. This expected pattern of fluorine nmr signals from these conformations is, thus, also in accord with the spectra obtained in the low-temperature spectrum of Ib. Within the framework of this mechanism for conformational interconversion, it would be expected that the free-energy barriers $\Delta G^{\ddagger}_{1,2}$ and $\Delta G^{\ddagger}_{1,3}$ should be equivalent. Similarly, $\Delta G^{\ddagger}_{2,4}$ should equal $\Delta G^{\ddagger}_{3,4}$. We also note that the interconversion of **6** and **8**, by means of simultaneous inversion of two nitrogens, should not be greatly restrained by the steric interaction of the side chains since they need not pass one another during the interconversion. This latter process could thereby make an appreciable contribution to the exchange of carbotrifluoroethoxy groups between the various conformations since the activation energy for this conversion would probably not be much larger than that observed for the processes which involve inversion of configuration at only one nitrogen atom. However, neither of these expectations is supported experimentally and we are forced to reject the nitrogen inversion mechanism as an explanation of our results.

It would be possible to construct a third equilibration scheme based on restricted rotation about the alkyl oxygen–carbonyl carbon bond in order to rationalize the spectral effects observed. Although the energy barriers to rotation about similar bonds in esters are normally very low (1–3 kcal/mol[25]), Moriarity, *et al.*, have suggested that unusual features in the infrared spectrum of molecules such as I may be consistent with the presence of appreciable amounts of double bond character at this position.[16] The assembled infrared data in Table IV for compounds used in this work as well as related structures do show the unusual doubling

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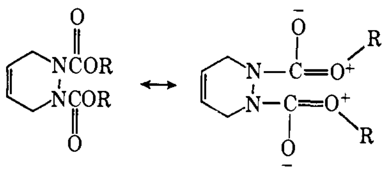
these degeneracies. By reference to Chart II, it can be seen that site populations, chemical shifts, and rate constants experienced by one trifluoromethyl group (say the left one as diagrammed in this chart) are equivalent to those encountered by the other. The simplified, four-site calculations outlined in the Appendix, therefore, provide an adequate description of the spectral changes experimentally observed.

(25) J. P. Lowe, *Progr. Phys. Org. Chem.*, 6, 1 (1968).

of the carbonyl stretching region, as noted by Moriarity, *et al.* However, since the monosubstituted compound, VI, shows nearly the same absorption spectrum as the disubstituted material, Ib, it does not seem likely that this phenomenon can be ascribed to an unusual bonding situation generated by the proximity of two sterically demanding groups. The carbonyl doubling may be due to Fermi resonance;[26] these compounds exhibit a broad envelope of absorptions in the 840–900-cm^{-1} range. In any event the infrared evidence for the contribution of structures analogous to **9** to the ground state of I appears to be equivocal and, because we are unaware of any precedent for assigning energy barriers as large as 15 kcal/mol to rotation of alkoxyl groups in esters or urethanes, we do not consider Moriarity's suggestion a likely one.



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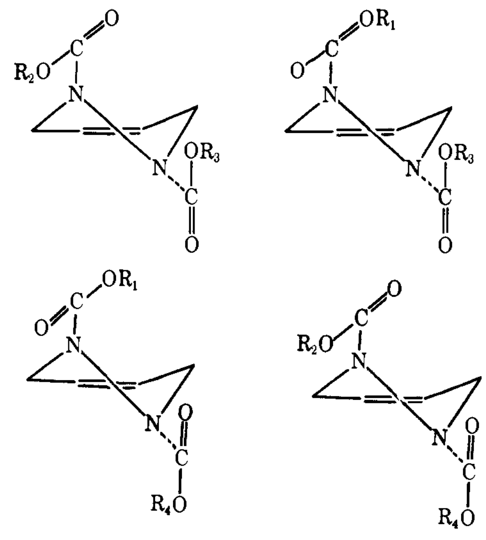
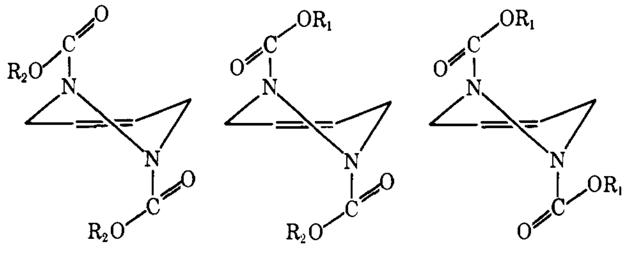
In order to rationalize the low-temperature fluorine nmr spectra of Ib, we must take into account the observation that four magnetically distinguishable sites are involved and that interchanges between these environments apparently occur in a pairwise manner. Thus, two sets of two peaks each coalesce and average as the temperature increases, and then the two (averaged) signals that result merge into a single line. These observations can be accommodated by assuming that the nitrogen atoms of the tetrahydropyridazine ring are sufficiently pyrimidal that the carboalkoxy groups can be found in the equivalent of pseudoaxial or pseudoequatorial positions. If one assumes in addition that rotation about the carbonyl–nitrogen bond is sufficiently restricted, it is possible to write a total of ten conformational isomers for these molecules, neglecting magnetically equivalent mirror image forms. These are sketched in Chart IV. Finally, if it is assumed that the chemical shift of nuclei on a given side chain is determined only by the orientation of the side chain relative to the ring, but *not* by the orientation of its neighboring side chain, then consideration of Chart IV shows that there are four unique environments for carbethoxy side chains in this system: axial side chain in, axial side chain out, equatorial side chain up and equatorial side chain down. These are denoted by the subscripts 1–4, respectively, in the diagram; it can be seen that each position occurs five times so that in the absence of free-energy differences between the conformers, four equally intense sets of side-chain nmr signals would be expected. The observation of unequally populated sites does not necessarily damage this argument; it could merely imply that the symmetrical forms in which both side chains are magnetically equivalent are favored in the equilibrium mixture of conformations. Rotation about the carbon–nitrogen bond that holds the carbethoxy group to the ring would have the effect of averaging the signals for environment 1 with those for environment 2. It would also mix those from sites 3 and 4, but in the absence of any other rate process rotation in this manner would convert the four signals found at slow exchange into two averaged signals. An additional conformational motion, namely nitrogen inversion, would be necessary to average this pair of nmr lines to a single resonance. Alternatively, nitrogen inversion could be the process which, pairwise, collapses the low-temperature spectrum to the averaged set of lines with rotation stepping in to complete the averaging process at higher temperatures. In either case, the predictions of this last model for the low-temperature conformational interchanges in Ib (and Ia) are consistent with the observations we have reported above.

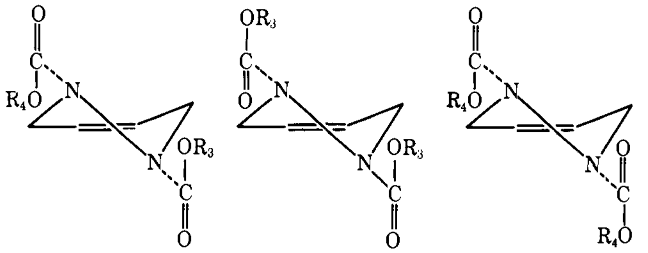
Chart IV



axial—equatorial



axial— axial



equatorial — equatorial

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are reported uncorrected. Mass spectra were recorded on an AEI-MS902 mass spectrometer utilizing a 70-eV ionizing voltage. Routine proton nuclear magnetic resonance spectra were recorded at 60 MHz on a JEOL-60H spectrometer. Ultraviolet and visible absorption spectra were determined with a Cary 15 spectrophotometer; concentrations are specified with the experiments. Infrared spectra were recorded on a Perkin-Elmer

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(26) C. N. R. Rao, "Chemical Applications of Infrared Spectroscopy," Academic Press, New York, N. Y., 1963, p 205.

337 grating infrared spectrophotometer. Vibrational assignments were made for the characteristic absorption frequencies with reference to Silverstein and Bassler.[27] Comparison of the nonfluorinated compound with the corresponding fluorinated compounds indicated that the C–F vibration occurs at approximately 1180 cm^{-1} in these systems.

1,2-Dicarbethoxy-1,2,3,6-tetrahydropyridazine (Ia). Diethyl azodicarboxylate (10.0 g, 0.58 mol, Aldrich) was added to a previously weighed bomb. The bomb was sealed and immersed into a Dry Ice–acetone bath. Butadiene (15.9 g, 0.296 mol) was distilled into the bomb. The vessel was sealed and allowed to stand at room temperature for 6 hr. The excess butadiene was removed by distillation into a receiver contained in a Dry Ice–acetone bath and was pure enough for reuse. The residue was distilled *in vacuo* and collected from 120 to 122° (1 mm) (lit. 115° (0.5 mm)[28]). The pmr spectrum in carbon tetrachloride showed a triplet at 1.25 (6 H), two broadened quartets centered at 4.15 (8 H), and a singlet at 5.80 ppm (2 H) relative to internal TMS. The infrared spectrum in carbon tetrachloride showed absorptions at 3050, 2950–2850, 1730, 1650, 1475, 1425, 1400, 1350, 1280, 1230, 1130, 1080, and 1030 cm^{-1}.

1,2,3,6-Tetrahydropyridazine. In a 50-ml round-bottomed flask were placed 3.15 g (0.014 mol) of compound Ia, 12.5 ml of ethanol, and 3.2 g (0.056 mol) of KOH. This solution was refluxed for 1 hr and cooled, and the solid mass was removed by filtration. The filtrate was refluxed again for an additional 2 hr. The ethanol was then evaporated and the residue distilled under reduced pressure. The product (0.23 g, 0.0027 mol, 20%) was collected between 50 and 60° (10 mm). The pmr in CCl_4 showed a singlet at 3.25 (4 H), a singlet at 3.7 (2 H), and a singlet at 5.7 ppm (2 H) for the ring protons, N–H protons, and the vinyl protons, respectively. The compound is unstable to air but can be stored at room temperature under nitrogen. The yield of diamine product can be increased to 40–50% if the solid mass is washed thoroughly with ethanol.

Trifluoroethyl Carbonate. Trifluoroethanol (39.4 g, 0.39 mol) was dissolved in 100 ml of ether. Sodium metal (9.2 g, 0.40 mol) was added in small pieces keeping the flask cold in an ice bath. Meanwhile, phosgene (50.1 g, 0.505 mol) was distilled into a 500-ml flask immersed in a Dry Ice–acetone bath. The flask was equipped with a cold-finger reflux condenser, a dropping funnel, and a thermometer. Two hundred milliliters of ether was then added slowly through the dropping funnel with the temperature not allowed to exceed −50°. The condenser was charged with a Dry Ice–acetone mixture. The ethoxide solution was added to the phosgene solution over a period of 2 hr. After the addition of the ethoxide solution the reaction mixture was permitted to warm up to room temperature and the contents of the cold-finger condenser were changed to ice-water at 0°. A series of three traps were set up, all of which contained toluene and ethanol, and the excess phosgene was allowed to distill into the traps. The cold-finger condenser was replaced by a distilling head and 100 ml of ether was removed at a distillation temperature of 36–36°. This distillate was treated with ethanol to destroy any remaining phosgene. An additional 100 ml of ether was added to the reaction mixture and this procedure was repeated. The residue was filtered and then fractionally distilled at atmospheric pressure. After the solvent, three major fractions were collected, bp 69–72, 76–82, and 82–118°, respectively. Glc analysis of these fractions on a $^1/_4$ in. × 10 ft SE-30 column at 60° afforded the following information. All fractions contained five peaks except the last one which did not contain an ether peak. Of the four remaining peaks, two were assignable to trifluoroethanol and toluene (sodium was stored under toluene before use). The remaining two peaks were expected to be trifluoroethyl chloroformate and trifluoroethyl carbonate. Fraction three (16 g) was almost exclusively (93%) either the chloroformate or carbonate. It did not react violently with aniline nor did it have a characteristic chloroformate odor, whereas the first fraction, which contained both unidentified peaks, had a strong pungent odor. Further support that fraction five was predominantly the trifluoroethyl carbonate came from the proton nmr spectra of fractions one and three. The nmr of fraction one showed two quartets in addition to and shifted downfield from the ether and trifluoroethanol quartets, presumably due to the chloroformate and carbonate. *A priori*, one would expect the chloroformate to be shifted further downfield, and, indeed, the downfield quartet is absent in fraction three. One further indication that fraction three was trifluoroethyl carbonate is the fact that with aniline, no precipitate is formed in ether whereas aniline gives a precipitate with a solution of ethyl chloroformate in ether or with a few drops of fraction one. No further attempt was made to separate these materials; fraction three was used for reactions involving trifluoroethyl carbonate while fraction one was used for syntheses requiring trifluoroethyl chloroformate.

1-Carbotrifluoroethoxy-1,2,3,6-tetrahydropyridazine (VI). To 6.8 g (0.030 mol) of trifluoroethyl carbonate (93% pure, containing 2% of trifluoroethyl chloroformate as described above) in 10 ml of ether was added 1,2,3,6-tetrahydropyridazine (0.9 g, 0.011 mol) in 10 ml of ether over a period of 30 min. A precipitate developed, presumably from formation of the protonated amine from the acid generated by the reaction of the trifluoroethyl chloroformate with the amine. After all of the tetrahydropyridazine solution had been added the reaction mixture was stirred for an additional hour. The solid material was filtered off and dissolved readily in D_2O. The pmr spectrum of the D_2O solution was that which would be anticipated for the protonated amine: ring proton signals at 3.65 (4 H) and vinyl signals at 5.9 ppm (2 H). The filtrate was then evaporated and the residue vacuum distilled. The product was collected at 89–92° (1 mm). Upon standing overnight under nitrogen, the sample crystallized. The pmr spectrum at ambient temperature was consistent with the expected product and consisted of vinyl proton resonances at 5.8 (2 H), a quartet (J = 9.0 Hz) centered at 4.4 (2 H), ring protons, broad singlets at 3.9 and 3.3 (4 H), and the NH proton, a broad singlet at 4.3 ppm (1 H). Mass spectral analysis of this material showed the following major fragments: *m/e* 210, 127, 109, and 83. These peaks were assigned to the molecular ion, the acylium ion $O{=}C^{+}OCH_2CF_3$, the trifluoroethoxonium ion ($^{+}OCH_2CF_3$), and the trifluoroethyl cation, $^{+}CH_2CF_3$, respectively. The infrared spectrum in carbon tetrachloride showed bands at 3350, 3050, 1735, 1650, and 1180 cm^{-1}.

1-Carbotrifluoroethoxy-2-carbethoxy-1,2,3,6-tetrahydropyridazine (VIII). Lutidine, 1.1 g (0.010 mol), was added to a flask containing 10 ml of ether immersed in an ice bath. Then 2.1 g (0.01 mol) of 1-carbotrifluoroethoxy-1,2,3,6-tetrahydropyridazine (VI) was added followed by dropwise addition of a solution of 1.2 g (0.011 mol) of ethyl chloroformate in 15 cm^3 of ether over a period of 1 hr. After the addition of the ethyl chloroformate the reaction was stirred for 1 hr. The mixture was filtered and the ether evaporated. The residue was vacuum distilled and the product collected at 122° (1.8 mm) to give 2.5 g (0.0089 mol, 89%) of VIII. The proton nmr in CCl_4 at room temperature showed the following information: a triplet at 1.3 (3 H), a singlet at 6.0 (2 H), and a multiplet from 3.7 to 5.0 ppm comprising ring protons and OCH_2CF_3, OCH_2CH_3 (8 H). The pmr spectrum is consistent with the assigned structure VII. Mass spectral analysis showed the following major peaks: *m/e* 282, 209, 127, 109, and 83, which were assigned to the molecular ion, the M − OCH_2CH_3 peak, the acylium ion $^{+}O{=}COCH_2CF_3$, the trifluoroethoxonium ion, $^{+}OCH_2CF_3$, and the trifluoroethyl cation, $^{+}CH_2CF_3$, respectively. The infrared spectrum in carbon tetrachloride showed a very broad band centered at 1735 cm^{-1}, which was assigned to both carbonyl groups, and weak bands at 3050 and 1180 cm^{-1} which were assigned to the olefinic C–H and the C–F stretching vibrations, respectively. The remainder of the ir spectrum was similar to compound I.

1,2-Dicarbotrifluoroethoxy-1,2,3,6-tetrahydropyridazine (Ib). To 1.53 g (0.0073 mol) of 1-carbotrifluoroethoxy-1,2,3,6-tetrahydropyridazine (VI) and 0.86 g (0.008 mol) of lutidine dissolved in 10 ml of ether was added 1.3 g (0.008 mol) of trifluoroethyl chloroformate (obtained from the trifluoroethyl carbonate preparation) dissolved in 10 ml of ether. The reaction mixture was stirred during the addition period (*ca.* 30 min) with the flask immersed in an ice bath. After the addition was complete, the mixture was allowed to come to room temperature and stand 4 hr. The solvent was evaporated and a 30-ml portion of ether was added which caused the lutidine hydrochloride to separate. This was removed by filtration. The filtrate was then flash evaporated and the residue vacuum distilled. The product (1.8 g, 0.0054 mol, 74%) was collected at 105–112° (1.7 mm). The fluorine-19 magnetic resonance spectrum at 100° showed two sharp CF_3 triplets, one of which had the same chemical shift as that of the starting material. Hence, the mixture was dissolved in 10 ml of ether and extracted 3 times with 10-ml portions of 0.5 *N* HCl, three 5-ml portions of water, two 5-ml portions of sodium bicarbonate, and finally with a 5-ml portion of water. The ether layer was then dried with magnesium sulfate and evaporated. The residue was vacuum distilled and the material collected that boiled in the range 110–112° (1.5 mm). The fluorine-19 magnetic resonance spectrum at 100° now contained

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[27] R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," Wiley, New York, N. Y., 1964, p 49.

[28] P. Baranger and J. Levisalles, *Bull. Soc. Chim. Fr.*, 704 (1957).

only one triplet which did not correspond to the starting material. The proton magnetic resonance in carbon tetrachloride gave a broad signal for the vinyl region at 5.8 (2 H) and a multiplet from 3.7 to 4.9 ppm (8 H) for the ring protons plus the methylene protons of the side chain. Mass spectral analysis showed the following major peaks: *m/e* at 336, 237, 209, 127, and 83 which were assigned to the molecular ion, the $^+M - OCH_2CF_3$ peak, the $^+M - O{=}COCH_2CF_3$ peak, the acylium ion, $O{=}^+COCH_2CF_3$, and the trifluoroethyl cation, $^+CH_2CF_3$, respectively. The infrared spectrum in carbon tetrachloride showed major bands at 3050, 1740, 1650, and 1180 cm^{-1} which were assigned to the olefinic C–H, C=O, and the C–F stretching vibrations, respectively.

1-Methyl-1-carbotrifluoroethoxyhydrazine (VII). Trifluoroethyl carbonate (4.5 g, 0.02 mol) was dissolved in 10 ml of ether. To this solution was added dropwise over a period of 30 min a solution of methylhydrazine (0.92 g, 0.02 mol) in 20 ml of ether. After standing for an additional hour the ether was evaporated and the residue was vacuum distilled. A colorless liquid was collected from 52 to 60° (2.5 mm) which contained presumably both isomers 1-methyl-1-carbotrifluoroethoxyhydrazine and 1-methyl-2-carbotrifluoroethoxyhydrazine. The pmr of the mixture in carbon tetrachloride exhibited two *N*-methyl signals at 3.25 and 2.7 ppm downfield from TMS; the ratio of these signals was 4:1, respectively. Upon microdistillation the first fraction collected contained greater than 95% of the isomer with the low-field chemical shift. Mass spectral analysis showed major peaks at *m/e* 172, 127, and 83 corresponding to the molecular ion, the acylium ion, $^+O{=}COCH_2CF_3$, and the trifluoroethyl cation, respectively. However, mass spectroscopy would not necessarily distinguish between the two possible isomers. It was found that this material would form a hydrazone with *p*-nitrobenzaldehyde[29] and it, therefore, must be the 1-methyl isomer.

Kinetic Studies. Variable-Temperature Nmr. The fluorine-19 spectra have been recorded on a Varian HA-100 spectrometer operating at 94.1 MHz equipped with the Varian variable-temperature accessory and an NMR Specialties HD-60 heteronuclear spin decoupler operating at 100 MHz. Proton magnetic resonance spectra were recorded on the same intrument operating at 100 MHz with the decoupler at 94.1 MHz. All of the solutions for the temperature-dependent nuclear magnetic resonance studies were 10 vol % of sample in either toluene, deuteriochloroform, or mesitylene. For fluorine-19 nmr, ethyl trifluoroacetate (10%) was added as an internal reference. Proton magnetic resonance chemical shifts are reported relative to tetramethylsilane (TMS) which was 5% by volume. Sample temperatures maintained by the Varian V-4343 variable-temperature controller were calibrated using a United Systems Corporation digital thermocouple by inserting the thermocouple into the sample and recording the temperature as a function of the controller setting. Approximately 20 min was allowed for the sample to equilibrate after a change in temperature.

The experimental spectra were analyzed for chemical exchange by visual comparison to theoretical curves generated by an IBM 360/75 computer for various values of the exchange rate(s). For compounds VI and VII a two site exchange program was used to determine rate constants ($1/\tau$) for the interconversion of conformers.[30] For the systems in which exchange between four sites was prevalent, a program based on the considerations given in the Appendix was used. Activation parameters were determined with standard equations.

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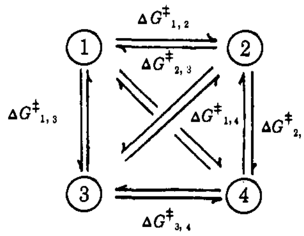
Appendix

We shall assume that a set of four magnetically unique, interconvertible states is available to the molecule of interest and that the nucleus or nuclei under examination for characterization of these states give rise to a singlet resonance. The nmr spectrum of these nuclei is, therefore, characterized by four chemical shifts, four relaxation times (T_2) related to the spectral line width, and the relative population of each state. As the diagram below indicates, a total of six independent rate constants for exchange must be specified to define the system; the rate constants not indicated in the diagram are obtainable from the populations and the six rate constants that are specified.

For the purposes of characterizing the six possible interconversions we define six free-energy barriers, $\Delta G^{\ddagger}_{i,j}$, $i = 1–3$, $j = i + 1–4$, $i \neq j$, for interchange originating at site i and ending at site j. Defining the free energy of site 1 as zero, the populations of the remaining three sites can be specified by three free-energy differences, $\Delta G_{1,j}$, $j = 2–4$, which correspond to the free energy of each site relative to site 1. Following Newmark's procedure,[31] the rate constants for each step in the exchange can be calculated with these nine energies. The rate constant, k_{12}, for exchange from site 1 to site 2 is given by



$$k_{1,2} = \frac{kT}{2\pi h} e^{-(\Delta G^{\ddagger}_{1,2}/RT)} \tag{A-1}$$

while

$$k_{2,1} = \frac{kT}{2\pi h} e^{-(\Delta G^{\ddagger}_{1,2}/RT)} e^{-(\Delta G_{1,2}/RT)}$$

Similar expressions hold for each rate constant. With these values and the other parameters which characterize each site in hand, a set of four coupled differential equations relating the four density matrix elements, ρ_i, $i = 1–4$, can be obtained.[32,33] Making the slow-passage assumption, these equations reduce to a set of simultaneous equations which are solved point-by-point through the frequency range of interest. A program to perform this task and plot the resulting spectrum was prepared; the 17 essential variables described above (four chemical shifts, four T_2 values, nine free energies) are used as input to the program and may be varied independently. Copies of this program are available upon request.

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