tered, and evaporated to dryness in vacuo. The residue was washed with Et_2O and recrystallized from MeCN: yield 0.36 g (72%); mp 240 °C dec.

Anal. Calcd for $C_5H_5N_5S$: C, 35.92; H, 3.01; N, 41.89. Found: C, 36.18; H, 3.10; N, 41.81.

Acknowledgments. The authors are indebted to Dr. W. C. Coburn, Jr., and members of the Molecular Spectroscopy Section of Southern Research Institute, who performed most of the microanalytical and spectral determinations.

Registry No.—**1**, 53995-21-4; **2**, 6506-86-1; **3**, 40497-64-1; **4**, 60282-67-9; **5**, 60282-68-0; **6**, 60282-69-1; **7** 2HCl, 60282-70-4; **8** 2HCl, 60282-71-5; **10**, 60282-72-6; **10** urethane derivative, 60282-73-7; **11** 1.8HCl, 60282-74-8; **12** 1.25HCl, 60282-75-9; **13** HCl, 60282-76-0; **14**, 60282-77-1; **15**, 60282-78-2; **16**, 60282-79-3; **17** 2HCl, 60282-80-6; **18**, 60282-81-7; **19** 2HCl, 60282-82-8; **21** 1.8HCl, 60282-83-9; **25**, 38359-74-9; 2-(2,4,6-trimethylbenzyl)-2-thiopseudourea HCl, 60282-84-0; 2,4,6-trimethylbenzyl chloride, 1585-16-6; thiourea, 62-56-6; 2,4,6-trimethyl-α-toluenethiol, 21411-42-7; 2-(diphenylmethyl)-2-thiopseudourea HCl, 60282-85-1; diphenylmethyl chloride, 90-99-3; (diphenylmethyl)thiol Na salt, 60282-86-2.

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(1) This investigation was supported by the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare, Contract N01-CM-43762.
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Stereochemistry in Trivalent Nitrogen Compounds. 31. Conformational Preferences and Torsional Barriers in *N*-Acylimidazoles[1]

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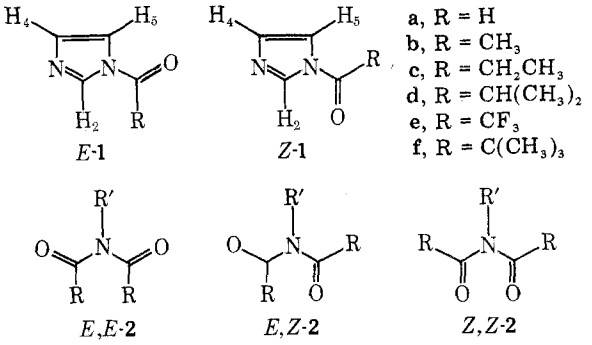
The low temperature ^1H NMR spectra of a series of *N*-acylimidazoles have been examined. All but one exhibited doubling of the resonances of H-2 and H-5 at low temperature reflecting the presence of two diastereomers which differ in configuration at the carbonyl to nitrogen (amide) bond. In all cases, the predominant diastereomer was assigned the *E* configuration. The configurational assignment involved the use of NMR chemical shifts and coupling constants, CNDO/2 calculations, solvent effects, and analogy to imides. Equilibrium constants and free energies of activation for isomerization were determined using variable temperature NMR spectroscopy in methylene chloride: *N*-formylimidazole, 4.6, 11.6 kcal/mol; *N*-acetylimidazole, 1.9, 10.5 kcal/mol; *N*-propionylimidazole, 1.5, 9.9 kcal/mol; *N*-(2-methylpropionyl)imidazole, 1.6, 9.9 kcal/mol; *N*-trifluoroacetylimidazole, 2.2, 10.2 kcal/mol; *N*-trimethylacetylimidazole, no splitting observed. The behavior of the first two of these compounds in three other solvents was also examined and the effects of solvent on NMR chemical shifts, the isomerization equilibrium constant, and the barrier to stereomutation are discussed. The relation between data for *N*-acylimidazoles and those for imides and *N,N*-dimethylamides is discussed.

Among the most informative amide torsional barriers are those for compounds in which the nitrogen lone pair forms part of an aromatic π system. The torsional barriers in such compounds are lower than in the corresponding *N,N*-dialkylamides, and the extent to which the barrier is lowered is related to the delocalization of the nitrogen lone pair and hence to the aromaticity of the heterocyclic ring. Although torsional barriers in amides have been intensively studied over the past 20 years,[3] only few studies have been made on amides of aromatic heterocyclic amines.[4-7] This paper reports our investigation of the variable temperature NMR spectra of a series of *N*-acylimidazoles, **1**, a system which had received no attention when our investigation was begun.

The *N*-acylimidazoles represented an interesting subject for study for another reason as well. The *N*-acylimidazoles can be considered as analogues of imides, a class of compounds whose torsional barriers and configurational preferences have been of interest in our laboratory.[8] Two labile configurational isomers are possible for *N*-acylimidazoles, *E*-**1** and *Z*-**1**, which can be interconverted by torsion about the carbon–nitrogen partial double bond. These two configurations are electronically related to the *E,E* and *E,Z* configurations of the imides **2**. Most imides prefer one of these two configurations when in solution in nonpolar solvents.[8,9] While the parent imide, diformamide, and its *N*-methyl derivative (**2a**, R′ = H, CH_3) prefer the *E,E* configuration, the higher homologues diacetamide and dipropionamide and their *N*-methyl derivatives (**2b**, R′ = H, CH_3 and **2c**, R′ = H, CH_3) adopt the *E,Z* configuration. The unsymmetrical imide *N*-acetylpropionamide



exists as a mixture of the two possible E,Z forms. The reversal in configurational preference between diformamide and its higher homologues was interpreted by considering a balancing between opposing steric and coulombic factors. The E,E configuration preferred by **2a** corresponds to the form with the minimum dipole moment and its greater stability seemed to be associated with the decrease in repulsive coulombic interactions reflected in the lower dipole moment. However, the E,E form brings the two R groups into close proximity and this leads to significant destabilizing interactions when R is methyl or a larger alkyl group. It was, therefore, of interest to examine configurational preferences in a system in which steric factors could be controlled. We wished to determine whether the preference for the E,E configuration in diformamide and N-methyldiformamide was the result of coulombic factors alone or whether an H–H attractive interaction might be important. We also wished to learn whether the reversal in configurational preference when R is changed from hydrogen to alkyl might involve coulombic as well as steric factors.

The N-acylimidazole system can be considered as a model system for imides in which steric factors are controlled. While the two configurations E-**1** and Z-**1** are electronically related to E,E-**2** and E,Z-**2,** steric differences between the two acylimidazole diastereomers are minimized. Thus, the steric interaction between H_2 and R in E-**1** is comparable to that between H_5 and R in Z-**1.** As a consequence, electrostatic interactions should be the dominant factor controlling the configurational equilibrium in acylimidazoles, **1.**

Results

The ambient and low temperature spectra of acylimidazoles **1** were obtained in methylene chloride solvent. In addition, spectra of **1a** and **1b** were also obtained in tetrahydrofuran, acetone-d_6, $CDCl_3$ (for **1a**), and $CFCl_3$–$CDCl_3$ (for **1b**). The ambient temperature spectra, in all cases, feature three multiplets for the ring protons at nearly the same chemical shifts, ca. δ 8.2, 7.5, and 7.1.[10] Assignment of these three multiplets is relatively straightforward and has been reported by several groups for N-acetylimidazole.[7,11,12] The lowest field multiplet derives from H_2, the multiplet at ca. δ 7.5, derives from H_5, while H_4 gives rise to the high-field resonance. Change of solvent from methylene chloride to acetone effects only small changes in the ambient temperature chemical shifts. In **1b** downfield shifts of −0.14 and −0.12 ppm were observed for H_2 and H_5, respectively, the protons flanking the acyl group, as well as for the acetylmethyl group −0.09 ppm. The ring proton furthest away from the acyl group suffered an upfield shift (+0.05 ppm). Very similar behavior was observed for **1a.** Changing the solvent to tetrahydrofuran produced shifts in much the same directions but of much smaller magnitudes. Much larger solvent shifts were observed in the low temperature spectra (vide infra) but they were largely averaged out by rapid torsion about the amide bond in the room temperature spectra.

When the temperature is lowered, two of the resonances derived from the ring protons (those from H_2 and H_5) in **1a–e** broaden and split into pairs of unequally intense peaks (Figure 1) reflecting the presence of two diastereomers, in a ratio of 65/35 for **1b,** which interconvert only slowly on the NMR time scale. The resonance corresponding to H_4, which lies furthest from the acyl group, did not exhibit an observable difference in chemical shift corresponding to the difference in configuration at the amide partial double bond. Of the acylimidazoles **1** examined only the trimethylacetyl (pivaloyl) derivative **1f** failed to exhibit nonequivalence at the lowest temperature at which it was examined (−120 °C).[13]

In the spectrum of **1b** in dichloromethane at −94 −C (Figure 1), the resonance derived from H_5 in the major isomer

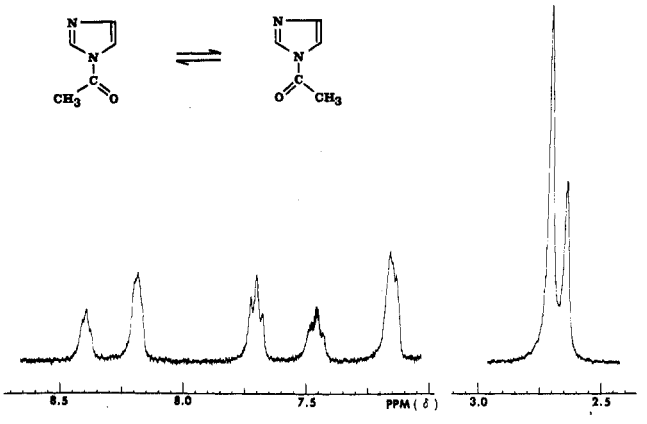


Figure 1. Low temperature (−94 °C) ^{1}H NMR spectrum of N-acetylimidazole (**1b**) in methylene chloride solvent.

appears at lower field (δ 7.69) when compared with that derived from the minor isomer (δ 7.47). By contrast, the multiplet derived from H_2 appears at higher field in the major isomer (δ 8.19) as compared with the minor isomer (δ 8.39). The same qualitative behavior was observed for the other compounds: H_2 always appeared upfield and H_5 always appeared downfield in the major isomer (Table I).

We have assigned the E configuration to the major isomer for **1a–e** on several bases. Based upon the analogy with imides we would expect the isomer with the lower dipole moment to be favored. Semiempirical molecular orbital calculations (CNDO/2) indicate that the E isomer has a lower dipole moment than the Z isomer, supporting the validity of the analogy between E-**1** and E,E-**2** and between Z-**1** and E,Z-**2.** The calculated moments for N-formylimidazole were E-**1a,** 1.76 D; Z-**1a,** 3.45 D. The corresponding calculated moments[8] in N-methyldiformamide (**2a,** R = CH_3) are strikingly similar considering the differences in the two compounds: E,E, 1.75 D; E,Z, 3.49 D. The calculated dipole moments in the imide series seemed to agree fairly well with estimates based upon the experimentally obtained dipole moments in imides with known (or fixed) configurations. In analogy with the CNDO/2 calculations for N-methylformamide, the difference in energy between E-**1a** and Z-**1a** was found to be very small.

The chemical shift differences between the resonances for H_2 and H_5 in the two isomers provide further support for our assignment. The reversal of the chemical shift differences for H_2 and H_5, and the negligible difference observed for H_4 indicate that the anisotropy of the acyl group is responsible for the chemical shift difference. The dependence of the ring proton chemical shifts as a function of the R group in the acyl function was relatively small supporting the idea that the configurationally dependent changes in the chemical shifts of H_2 and H_5 are associated with proximity to the acyl oxygen rather than the R group.

Models for the effect of an acyl oxygen in this kind of orientation can be found in the imide series. In diformamide (**2a,** R′ = H), the two diastereotopic formyl protons in the E,Z form can be definitively assigned on the basis of the vicinal coupling constants.[8] The formyl proton closest to the carbonyl oxygen atom of the other acyl group appears at lowest field. The low temperature ^{1}H NMR spectrum of N-acetylpropionamide provides a second example.[14] This compound exists as a mixture of two E,Z diastereomers. In the major isomer the methyl group is in the more sterically hindered position close to the oxygen atom of the propionyl moiety. It exhibits a downfield shift of 0.65 ppm relative to the resonance of the minor isomer. The propionyl methylene group of the minor diastereomer, which is in a comparable orientation near the acetyl oxygen atom, also appears downfield with respect to the

Table I. Low Temperature NMR Data for *N*-Acylimidazoles, 1

Registry no.	Compd	R	Solvent	Chemical shifts, δ: *E* isomer R	H_2	H_4[b]	H_5	*Z* isomer R	H_2	H_4[b]	H_5	Equilibrium constant (*E*:*Z*)[a]	Temp °C
3197-61-3	**1a**	H	$CDCl_3$	9.32	8.27	7.27	7.68	9.21	8.44	7.27	7.52	78/22	−70
			Tetrahydrofuran	9.33	8.47	7.21	7.85	9.21	8.47	7.21	7.85	87/13	−94
			CH_2Cl_2	9.29	8.27	7.23	7.69	9.19	8.41	7.23	7.56	82/18	−94
			Acetone-d_6	9.54	8.62	7.35	7.93	9.44	8.62	7.35	7.93	88/12	−94
2466-76-4	**1b**	CH_3	$CFCl_3$-$CDCl_3$ (2:1)	2.76	8.14	7.17	7.67	2.68	8.41	7.17	7.34	72/28[c]	−94
			Tetrahydrofuran	[e]	8.43	7.07	7.72	[e]	8.35	7.07	7.80	~3/1[f]	−94
			CH_2Cl_2	2.70	8.19	7.16	7.69	2.64	8.39	7.16	7.47	65/35	−94
			Acetone-d_6	2.82	8.68	7.23	7.80	2.73	8.48	7.23	7.96	78/22[d]	−94
4122-52-5	**1c**	CH_2CH_3	CH_2Cl_2		8.20	7.15	7.71		8.39	7.15	7.48	60/40	−93
4122-53-6	**1d**	$CH(CH_3)$	CH_2Cl_2		8.26	7.16	7.69		8.38	7.16	7.53	61/39	−97
1546-79-8	**1e**	CF_3	CH_2Cl_2		8.26	7.26	7.78		8.52	7.26	7.55	69/31	−98

[a] These equilibrium constants are estimated to be accurate to ±2%. The *E* form is favored in all cases. [b] None of the compounds examined exhibited observable chemical shift nonequivalence for H_4. [c] Reported to have an equilibrium constant of 63/37 in $CHFCl_2$. [d] Reported to have an equilibrium constant of 25/75 favoring the *Z* isomer.[7b] The error of this assignment is discussed in text. [e] The solvent peak obscured this resonance. [f] Small chemical shift differences prevented precise determination of the equilibrium constant.

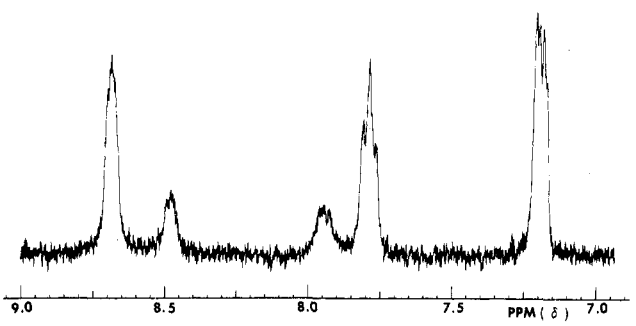
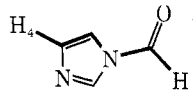


Figure 2. Low temperature (−94 °C) ^1H NMR spectrum of *N*-acetylimidazole (**1b**) in acetone solvent.

methylene group in the major isomer. These observations are in accord with the notion that protons adjacent to and in the nodal plane of an imide carbonyl group should suffer downfield shifts, just as protons adjacent to and in the nodal plane of the carbonyl groups of aldehydes and ketones are shifted downfield as a consequence of the anisotropy of the carbonyl group.[15] On this basis the major isomer is assigned the *E* configuration since in this isomer H_5 is shifted downfield, while H_2 is shifted downfield in the minor isomer. This pattern was observed in the low temperature spectra of all of the acylimidazoles, **1a–e,** in methylene chloride solvent and we have assigned the *E* configuration to the major isomer in all cases. While the chemical shifts were not greatly affected by the nature of the R group, a slightly larger variation in chemical shifts was observed for the protons in closest proximity to the R group (H_2 in *E*-**1** and H_5 in *Z*-1), except in the case of **1e.** In this compound, the chemical shifts of these hydrogens show little effect from the replacement of an alkyl group by trifluoromethyl while the other two ring hydrogens (furthest from the CF_3 group) suffer comparable downfield shifts, possibly as the result of the inductive effect of CF_3.

Further evidence supporting the assignment of the *Z* configuration to the minor isomer of *N*-trifluoromethylimidazole (**1e**) was obtained by examination of widths at half height in the low temperature spectrum. The H_2 proton in the major isomer and the H_5 proton in the minor isomer showed extra broadening ($W_{1/2}$ of 5.8 and 7.5 Hz, respectively, as compared with the corresponding protons in the other isomers, $W_{1/2}$ 3.8 and 3.9 Hz), probably due to long-range coupling with the fluorine atoms ($^5J_{HF}$). The through-space mechanism for long-range HF coupling allows the prediction that the proton nearer to the trifluoromethyl group will exhibit the larger coupling constant. In *N,N*-dimethyltrifluoroacetamide, the lower field methyl signal has a larger $^5J_{HF}$ coupling (1.60 Hz) than does the methyl resonance at higher field (0.65 Hz).[18-21] Signal assignment has been controversial,[19,20] but the most recent study[21] using lanthanide shift reagents clearly indicated that the lower field signal should be assigned to the methyl group cis to the trifluoromethyl group supporting the operation of through-space coupling for hydrogen and fluorine atoms in this type of system.

Additional broadening was also observed in the spectrum of **1a.** The formyl proton resonance in the major isomer has a greater half width (2.5 Hz) than that in the minor isomer (1.3 Hz). This may be a reflection of long range (5-bond) coupling with H_5, which has a "zig-zag" relationship,[22,23] **3,** with the



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formyl proton only in the *E* configuration. A similar argument based on long-range (5-bond) coupling has been used by Elguero and co-workers[7d] to assign the configuration at the amide bond in *N*-formylindole.

The appearance of the low temperature (−94 °C) spectrum of **1b** in acetone (or tetrahydrofuran) is quite different (Figure 2). The H_2 proton of the major isomer now appears at lower field and the H_5 proton appears at higher field with respect to the resonances of the corresponding protons in the minor isomer, although the ratio of intensities of major to minor resonances was not greatly changed (Table I). This reversal was also noted by Sandstrom and Elguero and co-workers,[7b,c] who concluded that there is a reversal of configurational preference in this solvent rather than attributing the difference to solvent induced changes in chemical shifts.[24] That the explanation based upon reversal of configurational preference is incorrect can be easily demonstrated by examination of spectra in mixtures of dichloromethane and acetone as solvent. Such spectra are expected to be intermediate in either peak intensities or chemical shifts between the extremes recorded in the pure solvents. The spectra in intermediate solvent mixtures show clearly that the ratio of intensities does

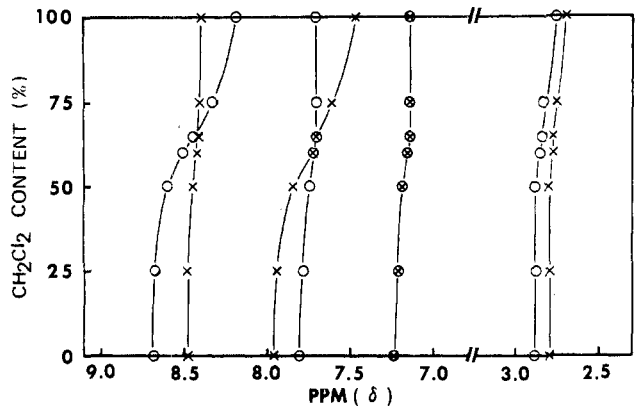
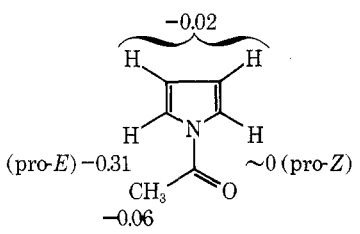


Figure 3. Plot of chemical shifts in N-acetylimidazole (**1b**) in mixtures of methylene chloride and acetone as a function of solvent composition: ×, chemical shifts of resonances in Z-**1b**; ○, chemical shifts of resonances in E-**1b**; the symbol ⊗ indicates that the resonances of the two configurations could not be resolved because of overlap.

not reverse but that the positions of the resonances cross over as the amount of acetone in the solvent mixture is increased. The plot of chemical shifts as a function of solvent composition (Figure 3) indicates that the changes are not linear. Rather, the crossover points, at which the chemical shifts are nearly equivalent, occur with solvent compositions with less than 50% of acetone (about 35% v/v or about 30% when mole percentages are used). This is consistent with the idea, discussed in a succeeding section, that the change is due to specific solvation by acetone rather than a bulk solvent change. Thus, the configuration of the major isomer must be the same in acetone as in dichloromethane. This reversal is caused by very substantial downfield solvent shifts for two protons H_2 in the E isomer and H_5 in the Z isomer. While the other ring protons, H_5 in the E isomer, H_2 in the Z isomer, and H_4, are shifted downfield by only ca. 0.1 ppm, H_2 in the E isomer and H_5 in the Z isomer suffer much greater shifts on the order of 0.5 ppm. Similar but smaller shifts were noted in tetrahydrofuran solvent. The shifts observed in both solvents are illustrated in Figure 4. Formylimidazole (**1a**) also exhibits downfield shifts in these two solvents resulting in coincidence between the resonances in the two diastereomers for all of the ring protons in these solvents. The presence of the two diastereomers is, however, still reflected in the pair of resonances observed for the formyl proton and the population ratio could still be determined by integration of these resonances.

We have observed similar acetone shifts in the low temperature (−61 °C) spectra of N-acetylpyrrole (**4**). While the



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low-field signal of the pair assigned to the α protons exhibits no appreciable shift upon change of solvent from dichloromethane to acetone (δ 7.47), the high-field signal is shifted from δ 7.17 to δ 7.48 at −61 °C. The β protons and the acetyl methyl group exhibit small downfield shifts. On the basis of the similarity of the acetone shifts in acetylpyrrole to those in acetylimidazole and formylimidazole, we can assign the low-field signal to the pro-Z hydrogen and the high-field signal to the pro-E hydrogen. The two groups[4,5] who first investi-

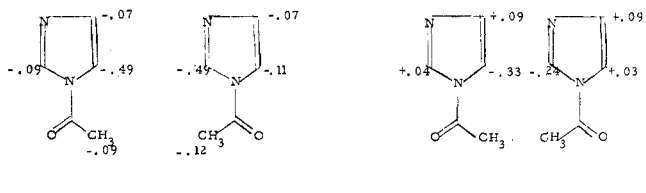


Figure 4. Solvent shifts observed for **1b** in (a) acetone and (b) tetrahydrofuran. Positive shifts (δ units) refer to upfield shifts relative to methylene chloride solvent.

gated slow torsion about the amide bond in N-acetylpyrrole made contradictory tentative assignments of the signals from the α protons on the basis of the supposed anisotropy of the amide carbonyl group. Elguero and co-workers[7d] have examined the problem in greater detail and have made assignments in this and other N-acylazoles using lanthanide induced shifts and comparison with chemical shifts in configurationally fixed model compounds. They concluded that the ring proton closest to the carbonyl oxygen atom appears upfield from that nearest the R group of the acyl function in this and other azoles. Our results provide further support for this conclusion (except when strong solvent shifts occur). While this generalization seems to be valid for a fairly large number of compounds, including the imides as well as N-acylazoles, we agree that assignments of configuration in amides should not be made on the basis of chemical shifts alone.[7d,16]

A small effect of solvent on the configurational equilibrium is evident in the data in Table I. Surprisingly, in the more polar solvents, acetone and tetrahydrofuran, the equilibrium is shifted even further in the direction of the less polar isomer. A rationale for this behavior is discussed in a subsequent section of this paper. It is also surprising that the solvent effects on the equilibrium are so small when one compares the behavior of acylimidazoles with that of furfural where the configuration of more stable isomer changes from E in CF_2Cl_2 or CCl_4 to Z in acetone.[25]

The negligible differences in the equilibrium constants measured in methylene chloride for compounds **1b, 1c,** and **1d** (1.9, 1.5, and 1.6, respectively) bearing methyl, ethyl, and isopropyl groups at the acyl carbon atom, support our contention that steric factors cannot play a significant role affecting the magnitude of the equilibrium constant and that steric interactions are nearly the same in the two diastereomers. If steric interactions were substantially different in the two forms, the equilibrium constant would be expected to change significantly in this series. The much greater equilibrium constant in formylimidazole (**1a**) (4.6 in methylene chloride), then, cannot be ascribed to a decrease in steric bulk of the R group but rather must result from some type of electronic effect. By implication, then, the reversal in the configurational equilibrium in the imide series may not be due solely to changes in steric interactions but may also reflect the same nonsteric factor which is responsible for the differences in the equilibrium constants of **1a** and of **1b, c.** On the other hand, the change in equilibrium constants is much more dramatic in the imide series implying that while steric repulsion may not be the sole factor accounting for the reversal it must certainly be the major factor.

In order to obtain the free energies of activation for torsion about amide bonds in **1a–e,** the coalescence temperatures (T_c) were measured and the rate constants at the coalescence point (k_c) were calculated using computer assisted complete lineshape analysis. The signal broadening due to coupling was simulated by adjusting the relaxation times (T_2). The relative populations and chemical shift differences were assumed to be essentially independent of temperature within the temperature range in which coalescence occurs. The validity of

Table II. Dynamic NMR Data and Torsional Barriers for *N*-Acylimidazoles, 1

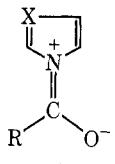
Compd	R	Solvent	Proton obsd	$\Delta\nu$, Hz	T_c, °C	Equilibrium constant (*E*/*Z*)	$\Delta G^{\ddagger}_{E\rightarrow Z}$, kcal/mol	$\Delta G^{\ddagger}_{Z\rightarrow E}$, kcal/mol
1a	H	$CDCl_3$	H_2	9.5	−50	(78/22) = 3.5	12.4	11.8
			H_5	9.8	−50		12.5	11.9
			CHO	6.4	−54		12.3	11.7
		THF	CHO	6.8	−65	(87/13) = 6.7	11.9	11.1
		CH_2Cl_2	H_2	8.2	−56	(82/18) = 4.6	12.2	11.6
			H_5	8.2	−56		12.4	11.7
			CHO	6.2	−59		12.1	11.5
		Acetone-d_6	CHO	6.2	−68	(88/12) = 7.3	11.8	11.0
1b	CH_3	$CFCl_3CDCl_3$ (2:1)	H_2	16.4	−68	(72/28) = 2.6	10.9	10.5
			H_5	19.7	−65		11.0	10.6
			Me	4.6	−76		11.0	10.7
		CH_2Cl_2	H_2	12.1	−73	(65/35) = 1.9	10.6	10.4

Table III. Room Temperature NMR Chemical Shifts (δ) in *N*-Acylimidazoles

		R						
R	Solvent	CH_3	CH_2	CH	H	H_2	H_4	H_5
H	$CDCl_3$				9.16	8.17	7.19	7.53
	THF				9.19	8.20	7.06	7.57
	CH_2Cl_2				9.19	8.16	7.17	7.53
	Acetone-d_6				9.39	8.33	7.14	7.65
CH_3Me	$CFCl_3$–$CDCl_3$	2.57				8.09	7.06	7.44
	THF	2.57				8.22	7.03	7.57
	CH_2Cl_2	2.56				8.12	7.08	7.48
	Acetone-d_6	2.65				8.26	7.03	7.60
CH_2CH_3	CH_2Cl_2	1.29	2.90			8.14	7.07	7.48
$CH(CH_3)_2$	CH_2Cl_2	1.31		3.22		8.17	7.08	7.50
CF_3	CH_2Cl_2					8.24	7.19	7.58
$C(CH_3)_3$	CH_2Cl_2	1.45				8.25	7.02	7.56

this assumption was supported by the finding that changes in $\Delta\nu$ and K_{eq} were within experimental error for **1b** in dichloromethane in the temperature range −80 to −105 °C. In any event, it is well known that moderately large errors in k_c result in errors in the free energy of activation smaller than the error introduced by the experimental uncertainty in the measurement of temperature.[26] The chemical shift differences, coalescence temperatures, and free energies of activation (obtained using the Eyring equation) are collected in Table II. In most cases, the coalescence of more than one set of signals could be used to calculate the torsional barrier. The barriers calculated using signals derived from different protons never differed by more than 0.2 kcal/mol, which is approximately the error derived from the uncertainty in the temperature (about ±2 °C).

The energy barriers for *N*-acetyl- and *N*-formylimidazoles are about 2–3 kcal/mol lower than those for the corresponding pyrrole analogues.[4,5,7] This implies that the ionic canonical structure **5** makes a less important contribution to the structures of imidazoles (X = N) than it does to the structures of the corresponding pyrroles (X = CH). This is in accord with the results of studies on *N*-acylazoles using infrared spectra and molecular orbital calculations.[27,29] The carbonyl stretching absorbtion of the amide group appears at 1734, 1747, 1765, and 1779 cm^{-1} in the *N*-acetyl derivatives of pyrrole, imidazole, triazole, and tetrazole, respectively, and the amide torsional barriers are expected to decrease in this order.



X = CH, N
R = H, CH_3

5

The barriers in the imidazole series are comparable to those in the imide series. Thus the barrier in **1a** (11.8 kcal/mol) is slightly smaller than that in diformamide (12.9 kcal/mol). The replacement of one of the carbonyl oxygen atoms by a less electronegative nitrogen atom would be expected to increase the barrier to torsion about the other amide bond. The aromaticity of the imidazole ring, on the other hand, leads to a lowering of the torsional barrier. Apparently these two factors are nearly balanced and the barrier is not changed appreciably.

The variation of the torsional barriers in compounds **1** parallels that in the corresponding *N*,*N*-dimethylamides, $RCON(CH_3)_2$. A plot of the free energies of activation for the acylimidazoles **1** in methylene chloride as a function of the barriers for the corresponding dimethylamides in nonpolar solvents indicates a good correlation (Figure 5).[30] This suggests that the barriers in both series are dependent on approximately the same mix of steric and electronic effects associated with changes in the acyl moiety.[31] Based upon the correlation illustrated in Figure 5, an approximate torsional barrier for *N*-trimethylacetylimidazole (**1f**) of ca. 7.9 kcal/mol can be predicted. Based on a chemical shift difference of ca. 10 Hz and an equilibrium constant of 1.5, this would correspond to a coalescence temperature of about −130 °C. This prediction is in accord with the failure to detect signal splitting as the result of slow exchange in **1f** at the lowest temperatures attained (−120 °C).

The barriers for **1a** and **1b** measured in the more polar solvent acetone are somewhat smaller than those in the less polar solvent $CDCl_3$ (or $CFCl_3/CDCl_3$ for **1b**). It might have

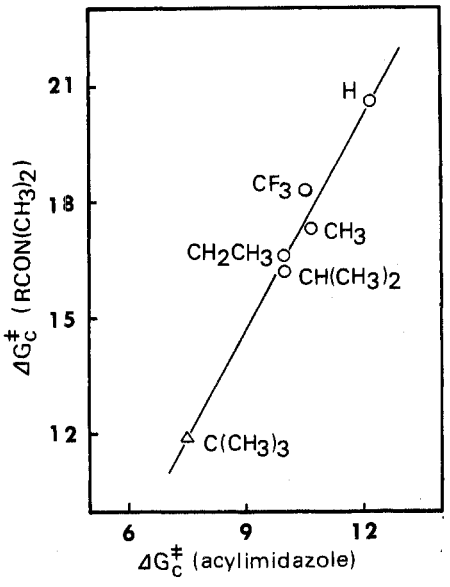


Figure 5. Linear free energy relationship between torsional barriers in N-acylimidazoles ($RCONC_3H_3N$) and those in the corresponding N,N-dimethylamides [$RCON(CH_3)_2$]. The point, △, for R = $C(CH_3)_3$ is not a data point but was extrapolated from the linear least-squares best fit line from the experimental points, O, using the literature value for the barrier in N,N-dimethylpivalamide.

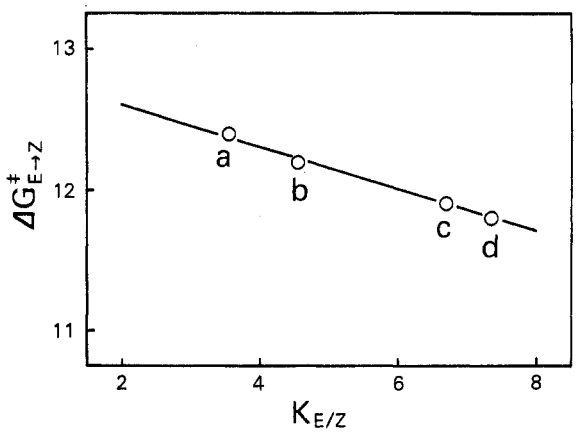


Figure 6. Plot of the free energies of activation for torsion in N-formylimidazole (**1a**) as a function of the configurational equilibrium constant in a series of solvents: a, deuteriochloroform; b, methylene chloride; c, tetrahydrofuran; d, deuterated acetone.

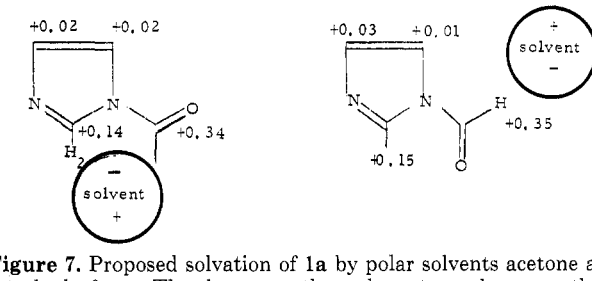


Figure 7. Proposed solvation of **1a** by polar solvents acetone and tetrahydrofuran. The charges on the carbon atoms shown are those obtained by CNDO/2 calculations.

been supposed that polar solvents would stabilize the ground state, in which the polar canonical structure **5** makes a contribution, more than they would in the torsional transition state where amide resonance is not possible. Indeed, this is the direction observed for the simple amides dimethylformamide and dimethylacetamide.[30c] Further, we note that the variations in barriers in **1a** do not correlate quantitatively with solvent bulk dielectric constant. Thus, the barrier for **1a** in tetrahydrofuran (ϵ 10.6 at −60 °C) is considerably lower than that in dichloromethane (ϵ 13.3 at −60 °C), but is not very different from that in acetone (ϵ 30.0 at −60 °C). While we cannot offer a conclusive rationale for this phenomenon, nor for the effect of solvent on the equilibrium constant for the configurational equilibrium, the two may very well be related. A plot of the torsional barrier as a function of the equilibrium constant for **1a** results in a surprisingly good correlation (Figure 6). In those solvents in which the configurational equilibrium is most biased, the torsional barrier is the lowest. If this correlation is not fortuitous, it suggests that the operation of a common factor is involved. The implication is that solvation of a particular region of **1a** by acetone and tetrahydrofuran is more favorable in the E isomer of the ground state than in the Z isomer and more favorable in the transition state than in either ground-state form. The most positively charged carbon atom, according to our CNDO/2 calculations, is the carbonyl carbon atom of the acyl group which bears a charge of +0.35. It seems most reasonable to suppose that solvation of this carbon atom is involved. This postulate provides a rationale for the solvent effects on chemical shifts described earlier (Figure 4). The greatest shifts observed are those for the ring carbon atoms H_5 in the Z isomer and H_2 in the E isomer. The protons would be the closest to solvent molecules interacting with the positive end of the carbonyl bond dipole. This solvation would be more favorable in the E isomer than in the Z isomer, (Figure 7), since solvent is able to interact as well with C_2, which is the most positively charged of the ring carbons, as shown. Solvation even in this form is hindered by the peri-like interaction with H_2 and thus solvation can be more effective in the transition state where this interaction is absent. The more effective solvation of the transition state results in a lowering of the torsional barrier in these solvents.

This model also has the virtue of rationalizing the greater effects on chemical shifts, the equilibrium constant, and free energy of activation of tetrahydrofuran as compared with dichloroethane. While the bulk dielectic constant of tetrahydrofuran is slightly smaller than that of dichloromethane, it is better at solvating positive charge.

Experimental Section

N-Acylimidazoles were synthesized and purified as reported by Staab and his co-workers.[32] Physical and spectroscopic properties were in accord with those reported and the assigned structures. N-Acetylpyrrole was prepared by transacetylation from N-acetylimidazole according to Reddy.[33]

^1H NMR spectra were recorded on a Varian A-60A spectrometer equipped with a V-6040 temperature controller using 2.5 mol % solutions. Temperatures were measured using methanol spectra as described in the Varian users manual and are considered accurate to ±2 °C. Chemical shifts were calibrated by the side band method using a Hewlett-Packard 200CDR audio oscillator, and a Beckman FR 67/U frequency counter.

Molecular orbital calculations (CNDO/2) were carried out using a slightly moiified version of the program given in ref 34. Bond lengths and angles used were taken from x-ray crystallographic data for imidazole[35] and microwave spectroscopic data for formamide[36] (subscript f refers to atoms in the formyl moiety): C_f–O, 1.19 Å; C_f–H_f, 1.102 Å; C_f–N_1, 1.376 Å; N_1–C_2, 1.349 Å; N_1–C_5, 1.369 Å; C_2–N_3, 1.326 Å; N_3–C_4, 1.376 Å; C_4–C_5, 1.358 Å; $C_{2(4,5)}$–H, 1.08 Å; bond angles OC_fN_1, 123.8°; $H_fC_fN_1$, 113.2°; $C_fN_1C_2$, 126.4°; $N_1C_2N_3$, 111.3°; $C_2N_1C_5$, 107.2°; $N_1C_5C_4$, 106.3°.

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(14) M. Raban and R. Keintz, unpublished results.
(15) The situation in simple *N,N*-dialkylamides is more complicated.[3a,16,17] In *N,N*-dimethylamides, $RCON(CH_3)_2$, the methyl group cis to the carbonyl oxygen atom is shifted *upfield* relative to the trans methyl group. The direction of this shift was rationalized by taking into account the placement of methyl protons out of the plane of the carbonyl group and into a region of shielding by the anisotropic amide group. Perhaps the greater planarity in imides and acylimidazoles leads to results which are more consistent with the well-established model of the magnetic anisotropy of the isolated carbonyl group (in ketones and aldehydes) in which protons near the nodal plane of the carbon–oxygen double bond are deshielded. It may be noted that *N*-acylanilides, which have a similar geometry, exhibit consistent downfield shifts for the ortho protons which are cis to the carbonyl group. The methyl group in *N,N*-diethylamides also exhibits a downfield shift for the methyl cis to the amide oxygen.
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Reduction of 1,3-Diphenyl-2,2-dihaloaziridines with Tri-*n*-butyltin Hydride

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1,3-Diphenyl-2,2-dihaloaziridines (**1–5**) were prepared by the addition of dihalocarbene (CClF, CBrF, CClBr, CCl_2, and CBr_2) to *N*-benzylideneaniline in *n*-hexane. These aziridine compounds were reduced with tri-*n*-butyltin hydride in *n*-pentane at room temperature to give the corresponding 1,3-diphenyl-2-haloaziridines (**6–8**). The reduction of **1, 2,** and **3** proceeded stereospecifically, i.e., with retention of configuration, indicating that the intermediate 2-fluoro- and 2-chloro-2-aziridinyl radicals are pyramidal, and configurationally stable enough to abstract hydrogen from tri-*n*-butyltin hydride much more rapidly than invert their configurations.

It is known that the configurational stability of cyclopropyl radicals is strongly dependent on the nature of the α substituent, i.e., the substituent at the radical carbon.[1] The energy barriers for inversion of the cyclopropyl (A), the α-chlorocyclopropyl (B), and the α-fluorocyclopropyl (C) radicals have been calculated to be 0.8, 4.0, and 10.5 kcal/mol, respectively, by use of the CNDO/2 approximation.[2] These calculations indicate that the configurational stability of these radicals increases in the order A < B < C, which is in good agreement with that of the degree of stereospecificity observed in a number of reactions proceeding via these radicals, such as the reduction of cyclopropyl halides with organotin hydrides, the brominative decarboxylation of silver cyclopropanecarboxylates, and the thermal decomposition of cyclopropanepercarboxylic acid esters. Thus, cyclopropyl radical (A)[3] inverts its configuration so fast that it behaves as if it were planar, whereas the α-fluorocyclopropyl radical (C) reacts stereospecifically, i.e., with complete retention of configuration, in many reactions.[1,4,5] The inversion rate of the α-chlorocyclopropyl radical[1,6] is between those of the radicals cited above.

Recently, we have shown that the configurational stability of the α-fluorocyclopropyl radical is also affected by the β substituent.[7] Our findings are again in agreement with the prediction made theoretically by Dewar and Bingham.[8]

As compared with cyclopropyl radicals, however, there have been very few studies on the configurational stability of other three-membered-ring radicals containing a heteroatom in the ring, such as oxiranyl, 2-aziridinyl, and thiiranyl radicals. Altman and his collaborator have shown both theoretically[2] and experimentally[9] that the energy for inversion of the oxiranyl radical is larger than that of the corresponding cyclopropyl radical.

We have now extended our studies to the hitherto unexa-