indication of any sigmoidal pH dependency (Figure 3, ref 8) for the slow reactivation process and hence do not require the participation of His-57 as a general base. The sigmoidal pH–rate profile claimed by Bender and Wedler[31] relies heavily on data obtained for the deacylation of methoxycarbonyl chymotrypsin obtained either using methyl *p*-nitrophenyl carbonate as a substrate, or by transesterification of 4-nitrophenylcarbonyl chymotrypsin with methanol. Ethoxycarbonyl,[18,19,21] 2,2,2-trichloroethylcarbonyl,[18] and 2,2,2-trifluoroethylcarbonyl chymotrypsins (this paper) all behave normally, the respective substrates giving true "turnover" reactions with dissimilar rate constants. Hence, it seems highly probable that methoxycarbonyl chymotrypsin deacylates by the normal general base catalyzed process, and not by that shown by Bender and Wedler (k_5 step in their Scheme II). Similarities in rate constants obtained for deacylation of this species and for reactivation of E–OCO–X in the pH range 5–9 are most likely coincidental, a possibility admitted by these authors. No evidence is presented for an inhibited enzyme resulting from the reaction of methyl *p*-nitrophenyl carbonate and the enzyme in equivalent amounts after both *p*-nitrophenolate ion and methanol are released.

Results obtained by us in ref 8 and in this paper regarding the return of enzymatic activity from the acyl enzyme in two separable stages and the very limited "turnover" found with bis(4-nitrophenyl) carbonate cannot be explained by Scheme II of Bender and Wedler. We are, however, in agreement over the existence of a species E–OCO–X, but derived only from bis(4-nitrophenyl) carbonate. Bender and Wedler suggest that His-57 participates in the rate-determining step of "aging" but do not give any explanation as to how nucleophilic attack occurs in a subsequent product-determining step. Attack by X on the carbonate monoester or its anion, or carboxyl group attack assisted in a general base manner by His-57, are unattractive possibilities. The sigmoidal pH–rate profile ($pK_{app} = 7$) obtained for the combined $k_n + k_{gb}$ process and hence for its component parts (the ratio ($k_n/k_n + k_{gb}$) is pH independent in the range 5–8), plus the absorbance at 245 nm for E–OCO–X, indicate that the unknown "X" is most likely the closest and most powerful nucleophile, His-57. The presence of general base catalyzed deacylation concurrent with the process leading to the inactive enzyme species is demanded by the rapid return of part of the enzymatic activity from the acyl enzyme, by the limited turnover observed under conditions of excess substrate, and by the experiments with methanol described by Bender and Wedler.[31]

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Directions of the Dipole Moments of Aromatic Heterocyclopentadienes

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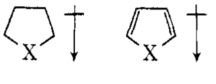
Abstract: The orientational influence of dipolar solutes on the aromatic solvents, benzene and hexafluorobenzene, as reflected by nmr chemical shifts, has been used to determine the direction of the dipole moments of thiophene, furan, pyrrole, and *N*-methylpyrrole. The direction for pyrroles with nitrogen at the positive end was confirmed. Contrary to popular belief, the direction of the dipole moments of the chalcogen heterocycles was found not to be reversed from their saturated analogs but to maintain the direction, placing the heteroatom at the negative end.

Among the major evidence for aromaticity in heterocyclopentadienes is the reversal of dipole moment direction in going from the saturated to the totally unsaturated systems. It is generally accepted[1] that the dipole moments of furan, pyrrole, and thiophene are such that the heteroatom is at the *positive* end.



Since the experimental measurement of dipole moments provides only an absolute number and *not* the direction, we became curious as to the source of this idea. The most often quoted references are those of Brown[2] and Lumbroso.[3] However, Brown's papers clearly indicate the opposite dipole direction for pyrrole[2a] (*i.e.*, with nitrogen at the negative end as in pyrrolidine) and while he originally placed oxygen at the negative pole of furan,[2a] this was later reversed.[4] Indeed, the direction of dipole moment is not a subject of Lumbroso's paper, which is devoted to a study of various solvent interactions with pyrroles using dipole moments as a probe. The definitive work on this subject is found in a report[5] by Kofod, *et al.* (1952). These

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[1] (a) L. A. Paquette, "Principles of Modern Heterocyclic Chemistry," W. A. Benjamin, New York, N. Y., 1968, p 104; (b) R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds," 2nd ed, Interscience, New York, N. Y., 1967, pp 65, 95, 143; (c) M. H. Palmer, "The Structure and Reactions of Heterocyclic Compounds," Edward Arnold, London, 1967, p 254.

[2] (a) I. M. Bassett, R. D. Brown, and A. Penfold, *Chem. Ind.* (*London*), 892 (1956); (b) R. D. Brown and B. A. W. Coller, *Aust. J. Chem.*, 12, 152 (1959); (c) R. D. Brown and M. L. Heffernan, *ibid.*, 12, 319 (1959); (d) *ibid.*, 12, 330 (1959); (e) R. D. Brown and B. A. W. Coller, *Theor. Chim. Acta*, 7, 259 (1967).

[3] M. Gomel and H. Lumbroso, *Bull. Soc. Chim. Fr.*, 2200 (1962).

[4] Reference 2b, footnote on p 155.

[5] H. Kofod, L. E. Sutton, and J. Jackson, *J. Chem. Soc.*, 1467 (1952).

Table I. Dipole Moments of Five-Membered Ring Heterocycles[a,b] (D)

Heterocycle	Dipole moment, D
Tetrahydrofuran	1.75
Furan	0.71
Tetrahydrothiophene	1.90
Thiophene	0.52
Pyrrolidine	1.58[c]
Pyrrole	1.80
N-Methylpyrrolidine	1.10[d]
N-Methylpyrrole	1.92

[a] Benzene solution at 25°. [b] Reference 8. [c] At 20°. [d] D. Mazet, W. D. Weringa, and H. Lumbroso, *C. R. Acad. Sci., Paris, Ser. C*, **270**, 1537 (1970).

authors studied the dipole moments of a large number of substituted pyrroles, especially para-substituted *N*-phenylpyrroles, and drew the unassailable conclusion that the dipole moment of pyrrole was inverted from that of pyrrolidine. This confirmed the original suggestion of Coulson and Longuet-Higgins,[6] who made their assignment on the basis of a molecular orbital treatment of pyrrole.

A search of the literature leads one to the conclusion that the reversal of dipole moment direction for furan and thiophene is *not* assumed by most research workers involved in dipole moment studies both experimental and theoretical.[7]

As there seems to be no compelling reason why this reversal of dipole moment direction must be true also for furan and thiophene, it appears that this widespread[1] belief is a result solely of analogy with pyrrole. Certainly the situation is quite different for thiophene and furan, as both oxygen and sulfur still possess a nonbonding electron pair after donation of an electron pair to the ring through resonance. The dipole moments of these molecules (Table I) can certainly be interpreted as simply a decrease in magnitude without reversal of direction. Indeed, the examination of dipole moment data for variously substituted heterocyclopentadienes leads to the conclusion that pyrrole and thiophene moments do not have the same sign. For example, the dipole moment of 3-methylthiophene (0.82 D) is larger than that of thiophene (0.52 D), while 2,5-dimethylpyrrole possesses a larger dipole moment than the parent pyrrole (2.08 D *vs.* 1.80 D).[8]

In fact, a relatively simple method is available to determine the direction of dipole moment in these systems. The basis for this method lies in the orientational influence of dipolar solutes on solvents such as benzene and hexafluorobenzene. Benzene has been shown to induce upfield shifts of protons at the positive end of a solute dipole and downfield shifts at the negative end, while hexafluorobenzene displays the reverse effect.[9–12]

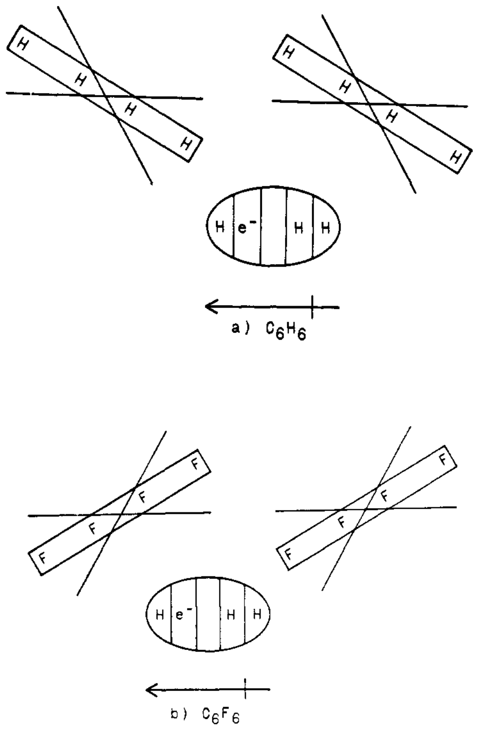

Figure 1. Schematic representation of the interactions of benzene (a) and hexafluorobenzene (b) with a dipolar solute.

The opposite induced shifts of these two solvents have been rationalized[9] in terms of collision complexes in which the solute orientation with respect to the solvent environment is reversed (Figure 1). In benzene, shielding arises from the attraction between the positive region of the dipole and the negative charge in the solvent π cloud, while deshielding stems from the attraction of the relatively positive periphery of the benzene molecules for lone-pair electron density near the affected proton[9,10] or for a proton which is hydridic.[12] In the case of hexafluorobenzene, deshielding of the positive end originates in the attraction of the solute for the fluorine periphery which is now apparently more negative than the π cloud.[9–12] At the negative end of the solute the relatively positive carbon ring of C_6F_6 is likewise attracted.[9,10]

It seemed reasonable to assume from the above that the proton shifts in unsaturated five-membered ring heterocycles by C_6H_6 and C_6F_6 would provide data from which the directions of their dipole moments along the C_{2v} axes could be deduced. From the evidence cited earlier[5] there can be little doubt that the dipole moments of pyrrole and *N*-methylpyrrole are such that the nitrogen is positive relative to the carbon portion of the rings. This suggests that the protons on the β positions should be deshielded in C_6H_6 and shielded in C_6F_6. This is indeed found to be the case (Table II). The upfield shifts of the α protons in both solute molecules arise then from the "flat-on" approach of C_6H_6 molecules occasioned by the positive nitrogen region (Figure 2a). The stronger shielding in the case of pyrrole probably originates in the smaller steric requirement of an N-hydrogen compared with the *N*-methyl group. The strong shielding of the β protons in C_6F_6 confirms this portion of the ring as the negative region of the molecular dipole (Figure 2b). The larger steric interactions provided by the fluorine periphery of C_6F_6 may well be

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(7) M. T. Rogers and T. W. Campbell, *J. Amer. Chem. Soc.*, **77**, 4527 (1955); H. Lumbroso and C. Carpanelli, *Bull. Soc. Chim. Fr.*, 3198 (1964); V. N. Novikov, *Mater. Chetvertogo Nauch. Konf. Aspir. Sb.*, 112 (1962); *Chem. Abstr.*, **60**, 10518a (1964).

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(10) J. A. Mosbo and J. G. Verkade, *J. Magn. Resonance*, **8**, 250 (1972).

(11) J. A. Mosbo, J. R. Pipal, and J. G. Verkade, *ibid.*, **8**, 243 (1972).

(12) A. H. Cowley, M. C. Damasco, J. A. Mosbo, and J. G. Verkade, *J. Amer. Chem. Soc.*, **94**, 6715 (1972).

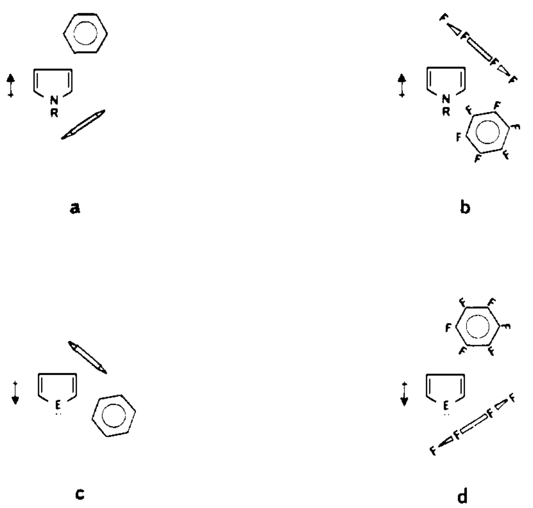

Figure 2. Schematic representations of C_6H_6 and C_6F_6 solvent orientation possibilities with respect to the molecular dipoles of the pyrolles (R = H, Me) and the chalcogen cyclopentadienes (E = O, S). Nothing is implied in these figures about the precise solvent–solute configuration nor of the number of solvent molecules involved.

Table II. Chemical Shifts of Heterocyclopentadienes in CCl_4, C_6D_6, and C_6F_6 at 100 Hz[a–c]

Solute[e]		CCl_4[e]	C_6D_6[e]	C_6F_6[e]
Tetrahydrofuran	β	179.4	143.3 $\overrightarrow{(36.1)}$[d]	184.5 $\overleftarrow{(5.1)}$
	α	361.9	357.3 $\overrightarrow{(4.6)}$	351.4 $\overrightarrow{(10.5)}$
Furan	β	629.9	608.4 $\overrightarrow{(21.5)}$	628.3 $\overrightarrow{(1.6)}$
	α	736.3	713.5 $\overrightarrow{(22.8)}$	725.4 $\overrightarrow{(10.9)}$
Tetrahydrothiophene	β	191.5	147.9 $\overrightarrow{(43.6)}$	199.8 $\overleftarrow{(8.3)}$
	α	275.2	254.7 $\overrightarrow{(20.5)}$	271.4 $\overrightarrow{(3.8)}$
Thiophene	β	706.4	684.7 $\overrightarrow{(21.7)}$	702.8 $\overrightarrow{(3.6)}$
	α	722.1	690.5 $\overrightarrow{(31.6)}$	716.7 $\overrightarrow{(5.4)}$
Pyrrolidine	β	162.5	139.6 $\overrightarrow{(22.9)}$	173.8 $\overleftarrow{(11.3)}$
	α	277.2	264.8 $\overrightarrow{(12.4)}$	280.9 $\overleftarrow{(3.7)}$
Pyrrole	β	608.7	631.4 $\overleftarrow{(22.7)}$	588.5 $\overrightarrow{(20.2)}$
	α	660.6	638.1 $\overleftarrow{(22.5)}$	661.0 $\overleftarrow{(0.4)}$
N-Methylpyrrolidine	β	171.9	160.9 $\overrightarrow{(11.0)}$	171.9 (0)
	α	236.4	231.9 $\overrightarrow{(4.5)}$	233.5 $\overrightarrow{(1.9)}$
	Me	224.1	222.6 $\overrightarrow{(1.5)}$	221.5 $\overrightarrow{(2.6)}$
N-Methylpyrrole	β	592.5	629.5 $\overleftarrow{(37.0)}$	567.8 $\overrightarrow{(24.7)}$
	α	640.7	633.5 $\overrightarrow{(7.2)}$	635.1 $\overrightarrow{(5.6)}$
	Me	362.9	287.7 $\overrightarrow{(75.2)}$	374.3 $\overleftarrow{(11.4)}$

[a] Values in Hz recorded on a Varian HA-100 instrument. [b] *Ca.* 3% wt/vol solutions. [c] As $J_{\alpha,\beta}$ was found not to vary with solvent changes, the numbers given are actually those of the most prominent peak in the multiplet. [d] The values in parentheses are shifts (Hz) in the direction of the arrow relative to CCl_4. [e] All solvents and solutes were freshly distilled.

responsible for the lack of consistency in and the relatively small magnitude of the α-proton shifts. The upfield and downfield shifts of the *N*-methyl protons in C_6H_6 and C_6F_6, respectively, are also consonant with location of the positive end of the solute dipole near this group. The upfield shifts in benzene of the α and β protons of pyrrolidine and *N*-methylpyrrolidine, as well as the *N*-methyl protons of the latter molecule, are indicative of the presence of C → N bond moments. While the 11.3-Hz upfield shift of the β hydrogens of pyrrolidine in C_6F_6 is as expected, little can be said about the small shifts of the α protons or for any of the protons in the *N*-methyl analog. Solvent steric effects coupled with the rapidly inverting nonplanar conformation may discourage orientation effects.

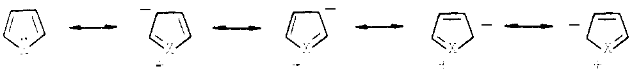

Figure 3. Canonical forms of heterocyclopentadienes.

Because our solvent shift data for the pyrrole systems are entirely consistent with the direction of the molecular dipole determined experimentally by an independent method,[5] the results for furan and thiophene become of singular interest inasmuch as the lore associated with these heterocyclopentadienes states[1] that the dipole direction is the same as in the pyrroles. In benzene, both the α and β protons of furan and thiophene are markedly shifted upfield, which very strongly suggests that the positive region of the dipole is in the carbon portion of the ring, with the negative site in the vicinity of the heteroatom (Figure 2c). The influence of the benzene molecules approaching the negative heteroatom lone pair is subdominant to that of the solvent molecules interacting in a "flat-on" fashion. The smaller upfield shift in the case of the α protons may arise from an attenuation of the "flat-on" interaction by the "edge-on" deshielding effect. Hexafluorobenzene seems to be incapable of completely reversing the solvent shift effect (with respect to benzene) for furan and thiophene. Steric interactions may dictate here that the "flat-on" interaction dominates the "edge-on" approach (Figure 2d) in contrast to the behavior in benzene. This view is supported by the observation of larger shifts for the α protons than for those in the β position.

In benzene, the saturated analogs, tetrahydrofuran (THF) and tetrahydrothiophene (THT), both exhibit upfield shifts for the α and β hydrogens, as do pyrrolidine and *N*-methylpyrrolidine, and our rationale for these data is analogous. The shifts for these systems observed in benzene accord well with those reported earlier by Strom.[13] The shifts for THF and THT in C_6F_6 are better behaved than those observed for the pyrrolidine systems. The greater symmetry and smaller steric requirements resulting from absence of a heteroatom substituent are undoubtedly responsible for this. The shifts in the saturated chalcogen heterocycles are suggestive of simultaneous "flat-on" and "edge-on" interactions, of which the former dominates in the case of THF and the latter is more efficacious for THT.

In summary, the aromatic solvent shift data reported here clearly show the direction of the dipole moment of furan and thiophene not to be in the same direction as pyrrole, but with the heteroatom at the negative end of the dipole. This new information does not negate the idea of electron donation in these systems from the heteroatom to the ring through resonance, as in Figure 3. Indeed, various ring current determinations sup-

(13) E. T. Strom, *et al.*, *J. Org. Chem.*, 33, 2555 (1968).

port this concept.[14] However, the decrease in dipole moment in going from THF or THT to the totally unsaturated molecules is not great (1.03 and 1.37 D, respectively),[8] and would be expected to decrease to some extent simply by the introduction of a π system in the carbon portion of the ring. Thus the resonance forms in Figure 3 (which neglect any thiophene canonical forms arising from sulfur d-orbital participation) do not control the molecular dipole direction of these molecules.

Acknowledgment. We wish to thank the Public Health Service, National Institutes of Health (GM-16689), for generous support of this work.

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Alkyl Shifts in Thermolyses. V.[1] Thermal Epimerization of the 1,4-Dimethylspiropentanes[2]

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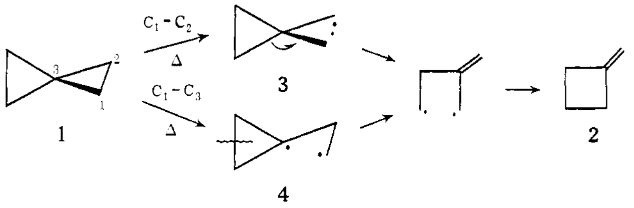
Contribution No. 2133 from the Indiana University,
Bloomington, Indiana 47401. *Received March 21, 1972*

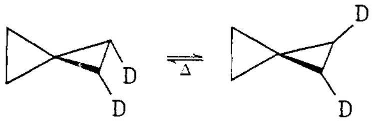
Abstract: In order to ascertain which of the two different types of bonds in spiropentane is reversibly cleaved prior to the thermally induced structural rearrangement to methylenecyclobutane, the proximal, medial, and distal 1,4-dimethylspiropentanes were pyrolyzed in the vapor phase. Geometric isomerization (epimerization) occurred substantially faster than structural isomerization. However, initially, the proximal and distal isomers gave only the medial isomer indicating that reversible cleavage of only the C_1–C_2 (peripheral) bonds occurred. The kinetics of epimerization of the distal compound revealed that the epimerization was first order and that k (sec^{-1}) = $10^{14.7}\exp(-50000/1.987T)$.

The migration of groups to vicinal cationic centers is well known,[4,5a] but examples of the analogous migration to radical[5b] or anionic[5c] sites are rare, especially when the migrating group is a hydrogen or a saturated carbon. The best characterized reaction involving such a migration to a radical site is the cyclopropane to propene rearrangement which is actually a biradical case.[6] The work of Schlag, Rabinovitch, and Wiberg has shown that the rearrangement is preceded by reversible ring opening followed by migration of a hydrogen atom to give propene.[6b,c] It appears, however, that in all the well-characterized cyclopropane pyrolyses alkyl group migration is not an important process.[7]

The rearrangement of spiropentane (**1**) to methylenecyclobutane (**2**) which was first studied by Flowers and Frey[8] and by Burkhardt[9] could be envisioned as a vicinal shift of a methylene group in the second ring after fission of the C_1–C_2 (peripheral) bond in the first. There is an alternate pathway in which the C_1–C_2 (radial) bond breaks first followed by bond breaking in the other ring to give product.



An investigation by Gilbert[10] has shown that *cis*- and *trans*-1,2-dideuteriospiropentanes (**5** and **6**) undergo geometric isomerization about ten times faster than structural isomerization. Thus, there must be some species present on the reaction pathway which allows for cis–trans isomerization; diradical **3** or **4** could be invoked to account for this observation.



Gajewski[11] pyrolyzed the four 4-methylisopropenylspiropentanes **7**, **8**, **9**, and **10** and found that each of the compounds equilibrated relatively rapidly with its C_1 epimer, but interconversion of all four occurred slowly. These results indicate that there was predominant peripheral bond fission since, in principle, radial bond cleavage would allow the interconversion of all four compounds. Further evidence for initial peripheral bond cleavage was the observation of products **11** and **12** from the pyrolysis of isopropenylspiropentane (**15**) and the absence of compounds **13** and **14**. Compounds **11** and **12** can arise only by peripheral fission followed by rearrangement.

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(1) For part IV see J. J. Gajewski and L. T. Burka, *J. Amer. Chem., Soc.*, **94**, 2554 (1972).

(2) Taken from the thesis of L. T. B., submitted in partial fulfillment of the requirements for the Ph.D. degree, Indiana University, Jan 1972.

(3) Fellow of the Alfred P. Sloan Foundation.

(4) D. Bethell and V. Gold, "Carbonium Ions," Academic Press, New York, N. Y., 1967.

(5) (a) "Molecular Rearrangements," P. de Mayo, Ed., Interscience, New York, N. Y., 1963; (b) C. Walling, *ibid.*, Chapter 7; (c) H. E. Zimmerman, *ibid.*, Chapter 6.

(6) (a) T. S. Chambers and G. B. Kistiakowsky, *J. Amer. Chem. Soc.*, **56**, 399 (1934); (b) E. W. Schlag and B. S. Rabinovitch, *ibid.*, **82**, 5996 (1960); (c) E. W. Schlag, B. S. Rabinovitch, and K. Wiberg, *J. Chem. Phys.*, **28**, 506 (1958).

(7) See, for example, the compilation by S. W. Benson and H. E. O'Neal, *J. Phys. Chem.*, 72, 1866 (1968).

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