1,3-Diphenylcyclobut-2-enyl Cyanide (7, X = CN).—1,3-Dibromo-1,3-diphenylcyclobutane (**6**) (2 g, 5 mmol) was dissolved in acetonitrile (150 ml) and DMSO (60 ml) under a nitrogen atmosphere. Sodium cyanide (2 g) was added to the solution and the mixture was stirred at room temperature for 10 hr. The milky yellow solution was then poured into 1 l. of water and extracted with ether (two 300-ml portions). The ethereal solution was washed with water several times and then with saturated sodium chloride solution and was dried over magnesium sulfate. Evaporation of the solvent yielded a brownish oil which was chromatographed on Florisil. The desired product was eluted with hexane as a yellow oil (1.03 g, 82%): ir (neat) 2220 cm^{-1}; nmr (CCl_4) τ 2.70 (m, 10 H), 3.72 (s, 1 H), 6.79 (A_2B_2 q, J = 13 cps, 2 H); mass spectrum *m/e* 231 (parent peak). The substance decomposed rapidly on standing at room temperature and was not analyzed.

1,3-Diphenylcyclobut-2-ene-1-carboxamide (7, X = $CONH_2$).—Sodium methoxide (commercial powder, 1.2 g, 22 mmol) was dissolved in DMSO (50 ml). Cyanide **7** (X = CN) (1.1 g, 4.7 mmol) in DMSO (5 ml) was added. The solution was stirred at room temperature under a nitrogen atmosphere. After 48 hr, the solution was poured into 800 ml of ice water and extracted with ether. The ether solution was washed with water several times and dried over magnesium sulfate. When the ether solution was concentrated to 15 ml and hexane was added, a white precipitate formed which was filtered and recrystallized from hexane–ether to give 0.872 g (73%) of a white solid: mp 143–145°; ir ($CHCl_3$) 3500, 3360, 1685 cm^{-1}; nmr ($CDCl_3$) τ 2.7 (m, 10 H), 3.31 (s, 1 H), 4.25 (br s, 2 H), 6.68 (A_2B_2 q, J = 13.1 cps, 2 H); mass spectrum *m/e* 249 (parent peak). The compound decomposed rapidly at room temperature and was not analyzed.

1-Methoxy-1,3-diphenylcyclobutene (7, X = OCH_3).—Sodium iodide (3 g) was dissolved in DMSO (50 ml), and absolute methanol (1.5 ml) was added to the solution. Dibromide **6** (1.5 g of the mixture of isomers) was dissolved in 5 ml of DMSO and added to the solution. After a while a yellow color developed which gradually turned red-brown (iodine). After 12 hr the solution was added to ice water (800 ml), and the cloudy solution was extracted with ether. The ether solution was washed with a dilute sodium sulfite solution to remove the iodine and washed several times with water to remove the DMSO. The ether solution was dried and evaporated to give 0.953 g (98.5%) of an oil: ir ($CHCl_3$) 1117 cm^{-1}; nmr (CCl_4) τ 2.75 (m, 10 H), 3.35 (s, 1 H), 6.82 (s, 3 H), 7.02 (A_2B_2 q, J = 13 cps, 2 H) (there were no other peaks evident in the nmr spectrum, and integration ratios were within 15% of the calculated values); mass spectrum *m/e* 236. The compound was unstable at room temperature and was not analyzed.

Registry No.—**1**, 27617-85-2; **2**, 27396-85-6; **3**, 27396-86-7; **4**, 27396-87-8; *trans*-**5** (X = H), 25558-23-0; **5** [X = $N(CH_3)_2$], 19043-28-8; *cis*-**6**, 27396-24-3; *trans*-**6**, 27396-25-4; **7** (X = CN), 27396-88-9; **7** (X = $CONH_2$), 27396-89-0; **7** (X = OMe), 27396-90-3; 1-phenylpentane-1,4-dione, 583-05-1; 3-phenylcyclopent-2-enone, 3810-26-2; 1,4-diphenyl-1,3-cyclopentadiene, 4982-34-7; 3-phenylcyclohex-2-enone, 10345-87-6; 1,3-diphenyl-1,3-cyclohexadiene, 10345-94-5; di-*tert*-butyl pertruxillate, 27396-96-9.

Application of the Linnett Electronic Theory to Organic Chemistry. IV. The SN2 Transition State

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Linnett structures for the SN2 transition state are proposed which differ from conventional dotted-bond structures X·····CR_3·····Y in that the three C–R bonds are weakened by L strain. Valence shell expansion is not required. Walden inversion is accounted for, and the energy price for retention is estimated at 11 kcal/mol for R = H and 16 kcal/mol for R = CH_3. The pattern of activation energies in alkyl halide exchanges is discussed in terms of secondary L strain, which also explains the rate accelerations brought about by conjugated unsaturation, α heteroatoms, and the α effect. The effect of L strain on entering and leaving groups is also assessed. The discussion includes proton transfer and displacements on heteroatoms. Hydrogen bonds and trihalide ions are presented as examples of reactions with negative activation energy, or "frozen transition states," existing when L strain is exceptionally low. Deviations from simple kinetic-thermodynamic relationships, such as the Brønsted equation, are stressed. The E2C mechanism is critically discussed.

One of the most common devices in chemistry is the transition state picture in which dotted bonds are used to represent normal ones that are in a state of either formation or dissolution. The dots are meant to express our ignorance of the structures of transition states as compared to stable molecules but are frequently taken to mean much more than that, in particular a state intermediate in properties between reactant and product. However, in opposition to this simple picture, for many reactions, is the disparity between the kinetic and thermodynamic products and, most significantly, the need for activation energy.

It is possible, by means of the Linnett electronic theory,[1,2] to replace many dotted-bond structures with better defined, yet simple, ones with unique properties that are not derived immediately from reactants or products. One such property is L strain,[3,4] a type of angle strain not yet recognized in conventional molecular representations, but clearly derived form Linnett's double–quartet theory. L strain must nevertheless be latent in conventional theory also, since the Linnett theory is based upon the same underlying quantum mechanical postulates. In contrast with an ordinary bent bond, an L-strained bond suffers from lack of coincidence of the two spin sets about one or more atoms, which weakens the bond in the same way that bending does, namely by forcing the bonding electrons away from their optimum positions. L-Strained bonds are not bent, however. This topic is fully discussed in papers I and II of this series. The policy will be continued here of limiting the discussion to first row elements for the most part.

A prominent example of a dotted-bond transition state is that for the SN2 reaction, depicted universally

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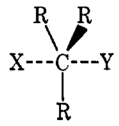
(1) J. W. Linnett, *J. Amer. Chem. Soc.*, **83**, 2643 (1961).

(2) J. W. Linnett, "The Electronic Structure of Molecules," Methuen and Co. Ltd., London, 1964.

(3) R. A. Firestone, *Tetrahedron Lett.*, 971 (1968).

(4) R. A. Firestone, *J. Org. Chem.*, **34**, 2621 (1969).

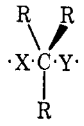


1

as **1**. Associated with this structure are two problems which are often ignored. One is the requirement for activation energy[5] in the exothermic direction, if the formation of the new bond is synchronous with the dissolution of the old. The other is the question of how many electrons are in the outer shell of the carbon atom; although its capacity is at most eight, the sum of the electrons in the three C–R bonds and those in both sets of dots is ten. In the case of a displacement on hydrogen, four electrons are associated with a shell that can hold only two.

These problems have occasionally been brought into the open. Grunwald says that "the intermediate states never conform to the Lewis rule of the octet" for displacement reactions on a saturated carbon atom.[6] Coulson identifies the two dotted bonds as "localized electron-pair bonds,"[7] invoking $d_\sigma p_\sigma$ hybridization at the central carbon atom, a theory endorsed by Gillespie[8] and Dewar[9] as well. Streitwieser,[10] however, places only two of the dotted electrons in a bonding MO, and the other two in a nonbonding one. Ingold's description[11] seems similar.

For related reactions, Linnett has proposed transition states of definite structure in place of the dotted bonds.[12] When his principles are applied to **1**, the structure **2** is

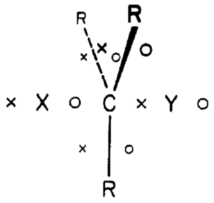


2

obtained. It is meant to represent the midpoint of the reaction coordinate, which may be a transition state or else a metastable intermediate flanked by two less symmetrical transition states. While there are cases to be discussed subsequently in which true intermediates exist, for ordinary SN2 displacements at saturated carbon it is safe to say that, if **2** lies in a potential well, it must be a very shallow one, and consequently **2** will be taken as a transition state in this paper.

It is apparent at once that promotion of electrons to d orbitals is unnecessary and that the Lewis octet rule[13] may be retained intact, provided that the habit of pairing electrons whenever possible—and it is no more than a habit—be abandoned.[14] If promotion is denied, then the octet rule prohibits the involvement of the odd electrons on X and Y.

The number of bonding electrons is constant throughout the transformation, raising the question of why activation energy is required in the exothermic direction.[5] One obvious answer is that a one-electron bond is not necessarily one-half as strong as a two-electron bond. There is, however, another more subtle source of an activation requirement which lies in the three nonreacting C–R bonds. Their bond energies in **2** are lower than they are in either XCR_3 or YCR_3 owing to L strain[3,4] by an amount which is probably more than half the activation energy for many SN2 reactions, exclusive of solvation and ion-pairing effects. The participation in the reaction of bonds that have hitherto been considered to be merely bystanders is not apparent in either the dotted-bond formula **1** or the condensed Linnett structure **2**. However, the full involvement of all the carbon atom's valence electrons at the transition state is brought to light in the double quartet representation of the transition state, **3**.[15] Each C–R bond suffers



3

from 40° of L strain. The published L-strain curve,[4] which though crude is serviceable, assigns 3.6 kcal/mol to a C–C bond L strained by this amount. The estimate for a C–H bond, augmented by the ratio of their bond energies,[16] is 4.3 kcal/mol. Thus, for SN2 displacements on methyl about 13 kcal/mol of L strain in the three C–H bonds is anticipated. From this must be deducted 4 kcal/mol for the fourth electron pair around carbon,[17] which is well correlated in the transition state but was closely paired in the starting molecule (a correlation correction has already been made[4] for the electrons in the L-strained bonds). The net energy demand from this source, then, is about 9 kcal/mol when R = H.

How does this number compare with activation energies in the literature? For proper comparison, reactions must be chosen in which solvation factors are at a minimum, and which are symmetrical along the reaction coordinate in order that the transition state occur at the point of maximum L strain, *i.e.*, midway. Experimental figures in acetone are 15.8 kcal/mol for Br–Br exchange on methyl[18] and 13.5 for I–I exchange.[19] For $CH_3Br + I^-$ in acetone, the activation energy is 15.1 kcal/mol,[20] and the data in that paper allow an estimate of *ca.* 12 to be made for I–I exchange; desolvation of the anion was reckoned an insignificant factor in the activation energy. For $CH_3Br + Cl^-$, E_a's are 17.9 kcal/mol

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(5) In his classic paper on the quantum mechanical interpretation of the process of activation, in *Z. Electrochem.*, **35**, 552 (1929), F. London states "In general . . . . a vanishingly small activation energy is expected for reactions of the type $XY + Z \rightarrow X + YZ$."

(6) E. Grunwald, *Progr. Phys. Org. Chem.*, **3**, 350 (1965).

(7) C. A. Coulson, *Nature*, **221**, 1106 (1969).

(8) R. J. Gillespie, *J. Chem. Soc.*, 1002 (1952).

(9) M. J. S. Dewar, *ibid.*, 2885 (1953).

(10) A. Streitwieser, Jr., *Chem. Rev.*, **56**, 571 (1956); see especially p 577.

(11) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, p 424.

(12) See ref 2, pp 74–75, 103.

(13) G. N. Lewis, *J. Amer. Chem. Soc.*, **38**, 762 (1916).

(14) It is indeed a general feature of the Linnett theory that structures with odd-electron bonds are often advantageous, even when reasonable even-electron counterparts are available.

(15) Heretofore there has been perhaps no essential difference between the description offered by Streitwieser, Ingold, and others, and that outlined here. It is in the complete Linnett array **3** and its consequences that the real novelty lies.

(16) T. L. Cottrell, "The Strengths of Chemical Bonds," 2nd ed, Butterworths, London, 1958.

(17) See ref 2, pp 66 and 91.

(18) P. B. D. de la Mare, *J. Chem. Soc.*, 3180 (1955).

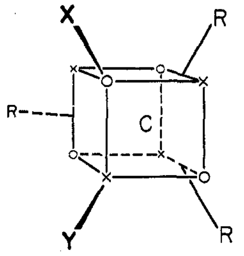
(19) E. R. Swart and L. J. LeRoux, *ibid.*, 406 (1957).

(20) Farhat-Aziz and E. A. Moelwyn-Hughes, *ibid.*, 1523 (1961).

in DMF[21] and 15.7 in acetone.[22] It is likely that these numbers are all on the high side of hypothetical solvation-free values, since the existence of residual external effects even in typical dipolar aprotic solvents is indicated by the report that activation energies for SN2 reactions can be lowered still further by changing from DMSO, DMF, and the like to the newest supersolvent, hexamethylphosphoramide.[23]

It is apparent, therefore, that L strain in the three nonreacting bonds contributes significantly to the energy requirements of the SN2 transition state at saturated carbon.[24]

Walden Inversion.—The requirement for inversion during each act of displacement is an old and apparently rigid rule. We account for it by comparing the transition state for inversion, **3**, with that for retention, **4**.



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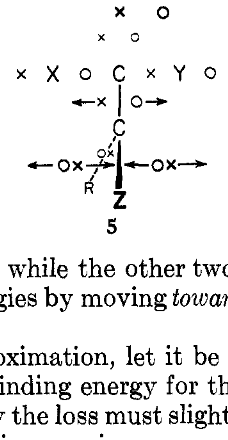
Both L strain and the intrusion of unwanted electrons on the valence shells of X and Y are minimized in the cubical array. Nevertheless, L strain in the three C–R bonds in **4** has risen to 70.5°. Thus the activation energy for retention will be greater than that for inversion by *ca.* 11 kcal/mol for R = H,[4] or 16 kcal/mol[25] for R = CH_3.[26] Retention then competes very unfavorably with inversion, although it is not altogether forbidden and should indeed be detectable under the proper circumstances.

Secondary L Strain.—In transition state **3**, L strain is higher when R is hydrogen than when it is carbon because C–H bonds are stronger than C–C bonds.[16] However, when R is saturated carbon there are three other bonds attached which must also suffer from L strain. Secondary L strain is expected to be less important than primary because spin sets are not completely rigid. Nevertheless, it is sufficient to increase the activation energy by about 1–2 kcal/mol for each R group in **3** that is changed from hydrogen to methyl. The best data on this topic are in the recent report of Cook and Parker[21] on the reaction of alkyl bromides with Cl^- in DMF where these activation energies are given: Me, 17.9 kcal/mol; Et, 19.2; *i*-Pr, 20.9; *tert*-Bu, 21.2. A similar series is reported by Ingold's group[27] for isotopic bromide exchange in acetone: Me, 15.8 kcal/mol; Et, 17.5; *i*-Pr, 19.7; *tert*-Bu, 21.8.[28]

If, as we propose, tertiary and higher orders of L strain are negligible, then the effect of substituting methyl for hydrogen in an ethyl group undergoing SN2 displacement should depend on where it is put. At the 1 carbon, an extra methyl changes ethyl into isopropyl and increases secondary L strain, as seen above, but at the 2 carbon the change is to *n*-propyl and does not increase secondary L strain. Thus, *n*-propyl halides should exhibit activation energies similar to ethyl, as indeed they do. In the first reaction series above, the figures for ethyl and *n*-propyl are 19.2 and 19.8 kcal/mol,[21] respectively, and in the second, 17.5 and 17.5.[18] Even isobutyl, which though still primary is beginning to suffer from steric hindrance, stands even with or slightly higher than *n*-propyl and well below isopropyl, with activation energies of 19.7[21] and 18.9[18] kcal/mol for the two cited reactions, compared to 20.9[21] and 19.7[18] for isopropyl.

Turning from activation energies to rates, we find that the general pattern is Me > Et > *n*-Pr and all other *n*-alkyl > *i*-Pr and all other secondary alkyl > *tert*-Bu and all other tertiary alkyl.[29]

***α*-Halo Ketones and Allylic Halides.**—Secondary L strain can be reduced if a carbon atom attached to the reaction center is unsaturated. This comes about in the following way. Creating L strain at one bond of a saturated carbon atom affects all the other six bonding electrons in an adverse way because they were already in optimum bonding positions beforehand, *i.e.*, on their respective internuclear lines. In contrast, the four bonding electrons about olefinic carbon that form the double bond are far off the internuclear line, and secondary L strain at this bond, if applied in the proper direction as in **5**, moves only two electrons into inferior bonding positions, while the other two actually increase their binding energies by moving *toward* the internuclear line.



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To a first approximation, let it be assumed that the gain and loss in binding energy for these four electrons are equal (actually the loss must slightly exceed the gain because the L-strain curve is concave upward),[4] with the result that two-thirds of the secondary L strain normally present at saturated carbon is absent; the last third still affects the other single bond. Cancellation of even more than two-thirds might be anticipated because secondary L strain will tend to concentrate at the point of least resistance, the double bond. For 40° primary L strain, the magnitude of secondary L strain at saturated carbon has been crudely estimated at 1–2

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(21) D. Cook and A. J. Parker, *J. Chem. Soc., B*, 142 (1968).

(22) E. D. Hughes, C. K. Ingold, and J. D. H. Mackie, *J. Chem. Soc.*, 3173 (1955).

(23) J-J. Delpuech, *Tetrahedron Lett.*, 2111 (1965).

(24) The structure **3** (X, Y, and R = H) is consonant with the calculated electron distribution and bond populations in CH_5^-: T. Yonezawa, H. Nakatsuji, and H. Kato, *J. Amer. Chem. Soc.*, **90**, 1239 (1968).

(25) The figure of 14 kcal/mol for R = CH_3 given in ref 4 was based on an estimated ~1 kcal/mol of secondary L strain per methyl, which is herein revised to 1–2 kcal/mol, *vide infra*.

(26) According to a recent calculation for CH_5^- by the PNDO–SCF method, inversion is preferred to retention by 14.9 kcal/mol: N. L. Allinger, J. C. Tai, and F. T. Wu, *J. Amer. Chem. Soc.*, **92**, 579 (1970).

(27) P. B. D. de la Mare, L. Fowden, E. D. Hughes, C. K. Ingold, and J. D. H. Mackie, *J. Chem. Soc.*, 3169 (1955).

(28) Ingold has reviewed a large body of his group's work in *Quart. Rev., Chem. Soc.*, **11**, 1 (1957), concluding, as we do, that the stepwise increments in activation energy in the series of alkyl groups arise from properties within the carbon skeleton and not from variations in the entering or leaving halogens. Cook and Parker[21] add that most of the polar and steric effects of alkyl substituents are accounted for by the activation energy, not by the log B term. Of course, their analyses take cognizance of factors other than L strain.

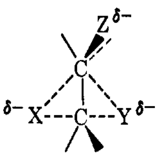
(29) See ref 11, pp 431–436.

kcal/mol more than the difference in primary L strain between C–C and C–H (*vide supra*), or *ca.* 2.2 kcal/mol. Two-thirds of this is 1.5 kcal/mol, worth about one order of magnitude in rate at ordinary temperatures. Rate increases are thus predicted of tenfold or more for allylic halides *vis-à-vis* their saturated counterparts. The observed increases are about a 100-fold.[30] Clearly, secondary L strain is a quantitatively reasonable phenomenon.

When Z in **5** is oxygen instead of CR_2, rate accelerations are much greater, reaching as high as 10^5 compared to saturated carbon.[31,32] This comes about because the other four electrons around Z are bonding when $Z = CR_2$ but nonbonding when Z = oxygen. In either case these electrons are closely paired in the ground state, and when $Z = CR_2$ they tend to remain so in the transition state. However, when Z is O the four nonbonding electrons are free to spread in the transition state, giving rise to a reduction in interelectronic repulsion which could be as great as 4 kcal/mol per electron pair.[17] At maximum, the corresponding rate factor expected for α-halo carbonyl compounds beyond that for allylic halides is 10^5–10^6.

The very high reactivity of α-halo carbonyl compounds cannot be ascribed to the electronegativity of the carbonyl group, because electronegative substituents powerfully diminish the rates of SN2 reactions. For example, toward iodide ion in acetone, the purely inductively[33] withdrawing α-CF_3 group reduces the reactivity of alkyl halides and tosylates[32] by a factor of about 10^4; α-halo sulfoxides and sulfones have low SN2 reactivity;[32,34] and, in general, β substitution in alkyl halides by electronegative groups exerts a rate-retarding effect.[35]

Current theory is divided as to the origin of the rate enhancements[30,32,36,37] by α-phenyl, α-vinyl, and α-carbonyl. The most widely accepted representation, **6**, is



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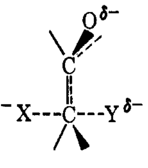
certainly a poor one since it predicts that the reactivities of benzyl halides will be increased markedly by electron-withdrawing substituents in the phenyl ring and diminished by electron-releasing ones, contrary to experiment.[38] Thus, in displacements on para-substituted benzyl halides by oxygen, sulfur, nitrogen, and halide nucleophiles, both nitro and methoxy, as well as other less powerful groups, impose a rate effect compared to hydrogen that ranges from weakly positive to nil.

A modification of **6**, in which no direct bonding exists between the incoming nucleophile and the carbonyl carbon, but in which the reacting orbital of the α carbon overlaps with the C=O π bond, is represented by **7**. In addition to sharing the drawback of **6** mentioned above, **7** clashes with other observations as well. If it were valid, one would expect a parallel to exist between the ability of a substituent S to facilitate SN2 displacement of X in SCH_2X and the addition of base to olefins $CH_2{=}CHS$. However, for the first reaction reactivity decreases in the order S = COR > CN > COOR > alkyl > SO_2R,[32] while for the second, S = COR > SO_2R > CN > COOR[39] (> alkyl).



7

It is significant that the accelerating effect of α-phenyl over α-*n*-butyl (300 times) in SN2 displacement on saturated carbon disappears almost entirely (1.9 times) in displacement on divalent sulfur[40] where secondary L strain is negligible.[41]

The geometrical requirements of the α-halo ketone effect depicted in **5** have been found to be precisely in accord with experiment. The nucleophile is required to approach along a line perpendicular to the >C=O plane.[36]

α **Heteroatoms.**—The reactivity of substrates RCH_2X (relative to CH_3X) is reduced by the effects of secondary L strain when R is saturated alkyl. If now R is changed into an atom bearing unshared electrons, secondary L strain diminishes, disappearing entirely if the unshared electrons number four or more. However, four other factors must be taken into account in addition to secondary L strain: (a) bond energy, (b) electronegativity, (c) electron correlation, and (d) steric hindrance.

(a) L strain has been taken[4] as proportional to the energy[16] of the C–R bond. For 40°, L strain varies with R in the following way (in kcal/mol): C, 3.6; H, 4.3; O, 3.7; N, 3.3; F, 4.6–5.0;[16,45] Cl, 3.5; Br, 3.0; S, 2.8.

(b) Since electron withdrawal at the reaction site inhibits SN2 reactions, the effect from this source of varying R in **3** should be to diminish reactivity in the order H; C, S; Br; N, Cl; O; F.[46]

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(30) See ref 10, p 585.

(31) J. B. Conant, W. R. Kirner, and R. E. Hussey, *J. Amer. Chem. Soc.*, **47**, 488 (1925).

(32) F. G. Bordwell and W. T. Brannen, Jr., *ibid.*, **86**, 4645 (1964).

(33) (a) S. Andreades, *ibid.*, **86**, 2003 (1964); (b) S. F. Campbell, R. Stephens, and J. C. Tatlow, *Chem. Commun.*, 134 (1965); (c) A. Streitwieser, Jr., A. P. Marchand, and A. H. Pudjaatmaka, *J. Amer. Chem. Soc.*, **89**, 693 (1967); (d) D. Holtz, A. Streitwieser, Jr., and R. G. Jesaitis, *Tetrahedron Lett.*, 4529 (1969).

(34) R. L. Loeppky and D. C. K. Chang, *ibid.*, 5415 (1968).

(35) See ref 10, p 589.

(36) P. D. Bartlett and E. N. Trachtenberg, *J. Amer. Chem. Soc.*, **80**, 5808 (1958).

(37) "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, pp 103–106.

(38) (a) See ref 10, p 591; (b) R. F. Hudson and G. Klopman, *J. Chem. Soc.*, 1062 (1962); (c) E. P. Grimsrud and J. W. Taylor, *J. Amer. Chem. Soc.*, **92**, 739 (1970).

(39) R. N. Ring, G. C. Tesoro, and D. R. Moore, *J. Org. Chem.*, **32**, 1091 (1967).

(40) W. A. Pryor, "Mechanisms of Sulfur Reactions," McGraw-Hill, New York, N. Y., 1962, p 63.

(41) The admissibility of divalent sulfur to the discussion is questionable in view of its low-lying d orbitals, for which no analogy exists in **3**. There is, however, evidence that divalent sulfur does not utilize its d orbitals when undergoing SN2 reactions.[42,43] Pryor[44] has criticized one of Fava's arguments but the others still stand, namely (1) the weak effect of *p*-NO_2 on the rate of nucleophilic attack on ArSX,[42] and (2) the Brønsted β for entering (0.25) and leaving (−0.97) groups in the reaction $ArOSCPh_3$ + $Ar'O^-$.[43]

(42) E. Ciuffarin and A. Fava, *Progr. Phys. Org. Chem.*, **6**, 81 (1968).

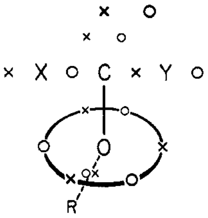
(43) L. Senatore, E. Ciuffarin, and A. Fava, *J. Amer. Chem. Soc.*, **92**, 3035 (1970).

(44) W. A. Pryor and K. Smith, *ibid.*, **92**, 2731 (1970).

(45) L. N. Ferguson, "The Modern Structural Theory of Organic Chemistry," Prentice-Hall, Englewoods Cliffs, N. J., 1963, p 48.

(46) (a) See ref 45, p 179; (b) L. Pauling, "The Chemical Bond," Cornell University Press, Ithaca, N. Y., 1967, p 64.

(c) Unusual effects are predicted here. If the atom R has *two* unshared electrons, their correlation will of course improve as L strain is imparted to the C–R bond, a favorable circumstance; however, the presence of the other two bonds to R will tend to keep both spin sets about R in coincidence, resulting in secondary L strain, though much reduced compared to R = CH_3. If R has *six* unshared electrons, they will already be well correlated in the ground state and will stand neither to gain by way of electron correlation, nor to lose by way of secondary L strain, in the transition state. If R has *four* unshared electrons, they must be closely paired, *i.e.*, poorly correlated, in the ground state, because the two bonds compel both spin sets to coincide. In this instance, however, the imposition of L strain on the C–R bond in the transition state results in no secondary L strain, owing to the ability of both spin sets about R to pivot in a circle around the axis of the other single bond to R. In the example **8**, R = OCH_3. There is further advantage in that spreading of the unshared pairs in **8** lowers the energy relative to the ground state. As much as 4.7 kcal/mol of stabilization is potentially available to the transition state from this source, based on the sin θ relationship proposed in paper II of this series.[4]



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(d) The most common heteroatoms from which steric hindrance is to be expected are the halogens except fluorine, increasing in the order Cl, Br, I. The type of hindrance is that encountered in neopentyl systems.

Bearing these considerations in mind, let us consider reactivities in heteroatom-substituted methyl halides RCH_2X. When X = Br, and R is the series of halogens, the relative reactivities toward iodide ion in acetone are F, 0.79, Cl, 0.13, Br, 0.041, and I, 0.059, where ethyl bromide is set at 1.0.[47] Since methyl halides react about 10–100 times faster than ethyl halides in polar aprotic solvents,[21,30] fluorine is seen to be mildly deactivating at the reaction site, compared to hydrogen. This is expected because the two elements differ little in electron correlation change at the transition state and in steric requirements, while fluorine exceeds hydrogen in electronegativity and also slightly in primary L strain. The diminution in reactivity with the other halogens is, of course, no surprise in view of their bulk.

The most important divalent α heteroatoms are oxygen and sulfur. Compared to hydrogen, they both create less primary L strain, but they exceed hydrogen in electronegativity; using fluorine as a gauge for these two factors, reactivity comparable to hydrogen would be anticipated. Secondary L strain, as with the halogens, is still absent. Sterically, groups such as methoxy and thiomethoxy both exceed hydrogen but are comparable to alkyl. However, the electron correlation factor, discussed above, is especially large and favorable for divalent elements.[48] On balance, rate accelerations relative to hydrogen, and large ones relative to alkyl, are expected. In confirmation, the following series of relative rates can be constructed: R = alkyl, 1; methoxy, 900; thiophenoxy, 540; acetoxy, 270; benzyloxy, 59.[32,47]

With nitrogen, a trivalent α heteroatom, secondary L strain will appear, but probably little. Primary L strain will also be less than for either O or C, owing to differences in bond strength,[16] and steric effects will be about the same. There is a gain in electron correlation at the transition state, though less than with O. On the other hand, N is inferior to O in electronegativity.[46] Overall, anticipated rates with α-amino groups are greater than with F or alkyl, but less than with O. We are not aware of any quantitative experimental data on this point, although α-halamines are known to be exceptionally reactive to nucleophiles.[49]

In contrast to the theory just outlined, the "neighboring orbital overlap" theory of α-heteroatom effects[47] suffers from the fact that neighboring O and S activate S_N2 displacements much more than do neighboring F and Cl. One would have expected it the other way around, since the halogens have a greater number of neighboring orbitals. A more recent assessment[50] asserts that there is no good explanation in current theory.

Displacement at Atoms Other than Carbon.—The simplest way to do away with L strain in the nonreacting bonds of **3** is to do away with the nonreacting bonds themselves. Reactions at heteroatoms are therefore expected to be more facile than at saturated carbon, which as a rule they are.

The high reactivity to nucleophiles of halogen molecules, hypochlorites, and chloramines are among the oldest known chemical facts. Hypochlorites are reactive at both heteroatoms.[51] Peroxy bonds are very easily attacked by nucleophiles.[52] The enormous disparity in reactivity at oxygen *vs.* carbon, with matching entering and leaving groups, has been emphasized.[53] Divalent sulfur, too, is subject to very facile S_N2 displacement with a large variety of nucleophiles and leaving groups.[41]

The cases cited so far have a flaw with regard to the L-strain theory, which is that the bonds broken during the reaction are all relatively weak ones, since heteroatoms generally form weaker bonds to each other than they do to carbon.[16] Of course, the bonds being formed are usually weak ones also, but it might be said that the simultaneous making and breaking of bonds must somehow be faster with weak bonds than with strong ones. However, this cannot be so, because the fastest S_N2 reactions of all are those in which the strongest bonds are involved. Proton transfer is an extremely rapid process despite the fact that hydrogen forms stronger bonds to all typical nucleophiles *and* leaving groups than carbon or any of the above-mentioned heteroatoms do.[16] Thus, the strengths of the bonds being made and broken

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(47) See ref 10. p 598.

(48) More favorable for oxygen than for sulfur because the comparatively large valence shell of the second-row element accommodates some spreading of the unshared pairs even in the ground state.

(49) H. Gross and E. Höft, *Angew. Chem., Int. Ed. Engl.*, **6**, 335 (1967).

(50) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, p 284.

(51) C. Walling and M. J. Mintz, *J. Org. Chem.*, **32**, 1286 (1967).

(52) K. M. Ibne-Rasa and J. O. Edwards, *J. Amer. Chem. Soc.*, **84**, 763 (1962), and references cited therein.

(53) E. J. Behrman and J. O. Edwards, *Progr. Phys. Org. Chem.*, **4**, 93 (1967); see specifically p 117.

is not an overriding factor in symmetrical displacements. What hydrogen does have in common with the other heteroatoms is that it suffers from no L strain in the transition state. This topic will come up again in later sections of this paper.

Entering and Leaving Groups.—In the transition state **3**, L strain is not limited to the carbon atom at the center. Both X and Y, the entering and leaving groups, are also subject to its influence, accounting for a wide range of phenomena.

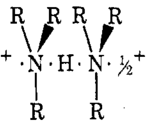
From what has been said before, it is clear that heteroatoms must be better than saturated carbon in either role, and the more nonbonded electrons, the better. For displacements at CH_3, one would ideally like to compare activation energies in series such as $(CH_3)_3N$ + $(CH_3)_4N^+$, $(CH_3)_2O$ + $(CH_3)_3O^+$, CH_3F + $(CH_3)_2F^+$ and $(CH_3)_3C^-$ + $(CH_3)_4C$, $(CH_3)_2N^-$ + $(CH_3)_3N$, CH_3O^- + $(CH_3)_2O$, F^- + CH_3F, all in some dipolar aprotic solvent. Although exact data are not yet available, some comparisons may be made. In the first series, it may safely be said that the first two members are in the expected order, since oxonium cations are known to be extremely reactive alkylating agents to (among others) ethers,[54] while ammonium cations are comparatively stable to nucleophilic attack. The substrates $R_2\overset{+}{N}PR'_3$ have much less susceptibility to nucleophilic attack on R than the corresponding oxygen analogs $RO\overset{+}{P}R'_3$.[55,56] Even the neutral halogens in alkyl halides are better leaving groups than positive nitrogen in ammonium cations,[57] despite the vastly greater electronegativity of the latter moiety. The further prediction that dimethylfluoronium cation, when prepared, will be a methylating agent of fantastic reactivity, even to methyl fluoride, is not a startling one in view of the already facile substitution in the neutral methyl halides as a class.[58]

As for the second series, little can be said at present except that the last two items are probably in the correct order; the severe conditions required for dealkylation of phenyl ethers with alkoxide anions, *ca.* 200°,[59] may be contrasted with the relatively mild 25° that is not uncommon for halide–halide exchange.[20,21] Note that the known vulnerability of SN2 reactions to electron withdrawal at the central carbon atom[32,34,35] would lead to reversal of both the above series if it were the dominant factor.

When displacement on hydrogen is considered, heteroatoms are again expected to be favored over carbon as both entering and leaving groups, and this has long been known to be the case. Proton transfer between atoms with unshared electrons is much faster than between atoms with no unshared electrons,[60] and reprotonation of ambident anions kinetically favors heteroatoms over carbon even when carbon protonation is thermodynamically favored, *e.g.*, $EtNO_2^-$[61] and CHN_2^-.[62] The situation is nicely summarized by Ingold's rule that the less stable tautomer is always most quickly formed.[63] Usually this means that heteroatom protonation is kinetically favored over carbon, and it is significant that the rule holds even when both competing anionic sites are carbon, as in cyclopentylidene malonate anion,[63] when only the kinetically favored site is substituted with groups (COOEt) of exceptionally low secondary L-strain susceptibility, but that the rule fails in another all-carbon system, cumene anion,[64] where the two sites are less unequal in this respect.

Similarly, aliphatic nitro compounds and β diketones (CH acids) have Brønsted catalytic constants $^1/_{20}$th those of phenols (OH acids) of comparable acidities,[65] which means that there is a kinetic factor favoring oxygen over carbon as a leaving group which is not fully accounted for by the thermodynamic differences in acidity. As a general rule, rates of proton transfer follow the expected order O > N > C,[66] and amines, when protonated, transfer hydrogen at exceptionally low rates,[67] showing that their special status as heteroatoms is lost when their complement of L-strain-reducing unshared electrons is depleted.

Yet another example of the imposition of a kinetic factor by L strain upon an otherwise thermodynamically controlled situation is provided by the reaction $R_3\overset{+}{N}H + R_3N$.[68] Two types of proton transfer can be distinguished, one through intervening water and the other directly from one nitrogen atom to another. In the first type, where both partners are solvated all around at all times, the rate response to changing R's from hydrogen to methyl one at a time is small, fitting the relative basicities of the various amines. However, in the second type the transition state may be written as **9**. Solvation effects are reduced in magnitude, and secondary L strain increases progressively as R's are changed from hydrogen to methyl. This is expressed in the rates for the second type of process, which fall rapidly as secondary L strain increases, and which now do *not* reflect the relative basicities. Thus basicity, a



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[54] (a) S. Kabuss, *Angew. Chem., Int. Ed. Engl.*, **5**, 675 (1966); (b) K. Dimroth and P. Heinrich, *ibid.*, **5**, 676 (1966).

[55] R. F. Hudson, "Structure and Mechanism in Organo-Phosphorus Chemistry," Academic Press, London, 1965, pp 136–137.

[56] In keeping with this concept, decomposition of tetraalkylammonium salts with bases typically requires comparatively severe conditions, with substitution even then usually outdone by the well-known Hofmann elimination, while decomposition of $(CH_3)_4N^+$ with strong bases such as NH_2^- and OH^- often occurs by an ylide mechanism rather than SN2: W. K. Musker, *J. Org. Chem.*, **32**, 3189 (1967); *J. Amer. Chem. Soc.*, **86**, 960 (1964).

[57] See ref 11, p 339.

[58] Dialkyl chloronium and bromonium ions have recently been prepared. They are more reactive than Meerwein oxonium salts and alkylate *inter alia* nitriles, ethers, carbonyl compounds, and nitro compounds: G. A. Olah and J. R. DeMember, *J. Amer. Chem. Soc.*, **92**, 2562 (1970); P. E. Peterson, P. R. Clifford, and F. J. Slama, *ibid.*, **92**, 2840 (1970).

[59] S. M. Shein and A. D. Khmelinskaya, *J. Org. Chem. USSR*, **4**, 2084 (1968).

[60] J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962, p 112.

[61] R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p 33.

[62] G. W. Cowell and A. Ledwith, *Quart. Rev., Chem. Soc.*, **24**, 119 (1970).

[63] See ref 11, p 565.

[64] G. A. Russell, *J. Amer. Chem. Soc.*, **81**, 2017 (1959).

[65] See ref 50, p 113.

[66] See ref 61, p 122.

[67] (a) A. I. Brodskii and L. V. Sulima, *Dokl. Akad. Nauk SSSR*, **74**, 513 (1950); *Chem. Abstr.*, **45**, 424*a* (1951). (b) L. Kaplan and K. E. Wilzbach, *J. Amer. Chem. Soc.*, **76**, 2593 (1954). (c) C. G. Swain, J. T. McKnight, M. M. Labes, and V. P. Kreiter, *ibid.*, **76**, 4243 (1954); C. G. Swain and M. M. Labes, *ibid.*, **79**, 1084 (1957); C. G. Swain, J. T. McKnight, and V. P. Kreiter, *ibid.*, **79**, 1088 (1957).

[68] E. Grunwald and A. Y. Ku, *ibid.*, **90**, 29 (1968).

thermodynamic and solvent-related phenomenon, dominates the picture when solvation is complete throughout the reaction but gives way to L strain, a kinetic phenomenon, when the transition state excludes solvent molecules.

It is, in fact, a general rule that good Brønsted linear relationships are observed, even for oxygen acids alone, only for acids of closely related structure, and these limitations on the simple kinetic–thermodynamic parallelism are even more severe for carbon acids.[69] A "geometric factor" has been uncovered which contributes to the activation energies for carbon but not for oxygen acids;[70] this factor is here identified as L strain.

In an earlier discussion of deviations from the Brønsted relation,[71] it was pointed out that these deviations could be expressed as variations in the shape of the Morse curve describing proton loss from the acid, with greater steepness of the potential well on the dissociation side identified with lowered rate toward a standard base. The L-strain theory accounts for the shapes of these curves in a natural way.

The kinetics of proton exchange at saturated carbon are also governed by L-strain considerations. The relative rates of exchange at C–H in *N*-alkylanilines with butyllithium, and in alkylbenzenes with both lithium and cesium cyclohexylamide in cyclohexylamine, with potassium *tert*-butoxide in DMSO, and with KND_2 in ND_3, all diminish similarly with increasing alkyl substitution, providing the series methyl, 1.0, methylene, 0.1–0.5, methine, 0.01–0.1.[72] In unactivated aliphatic hydrocarbons, the same general pattern of kinetic C–H acidity is observed: methane > methyl > methylene > methine.[73] Exchange rates in the series HCH_3, HCH_2CH_3, $HCHAlk_2$ fall in the relative order 2300, 34, *ca.* 0.6,[74] corresponding to a stepwise increase in activation energy at 50° of about 2.7 kcal/mol for each hydrogen replaced by alkyl. This figure for secondary L strain in the *leaving* group is quite similar to that assigned earlier, about 1.5 kcal/mol, for secondary L strain at the *seat* of substitution in the halide–halide exchange series.

All these data fit the sequence anticipated by the L-strain theory, since secondary L strain increases as alkyl groups replace hydrogen. It is interesting that hydrogen itself, a Brønsted acid that is free from L strain, displays much greater kinetic acidity than saturated hydrocarbons.[73]

While it is conceded that these rate differences might be said to reflect the as yet unknown thermodynamic acidities[75] rather than any important kinetic phenomenon, the next example is not subject to this qualification. In the series CH_3NO_2, $MeCH_2NO_2$, Me_2CHNO_2, thermodynamic acidity *increases* toward the right, with pK_a's of 10.2, 8.5, and 7.7, respectively,[76] as one would anticipate for the effect of substitution on the double bond in the anions $R_2C{=}NO_2^-$, but the rate of proton abstraction *diminishes* toward the right in the ratio 113:18:1.[77] Thus the existence of a kinetic effect on alkyl substitution cannot be doubted. This cannot be simply steric because proton abstraction is virtually insensitive to steric hindrance.[78]

The foregoing phenomenon is not limited to nitro compounds. The rate of base-catalyzed ionization at the α carbon of esters in ethanol[79] and in liquid ammonia[80] is reduced by successive replacement of the other α hydrogens by alkyl groups. It is likely, however, that the thermodynamic stability of the enolate anions is increased by alkyl substitution, as it is with nitronate anions.[81]

α Effect.—Entering and leaving groups, like the atom that is the seat of substitution, may suffer from not only primary L strain but also secondary L strain at atoms adjacent to those forming or breaking bonds. Consequently, the replacement of carbon adjacent to the nucleophilic center by a heteroatom should enhance nucleophilicity over and above whatever pK_b changes also are effected. This is the well-known α effect[82,83] and is analogous to the α-heteroatom effect presented earlier. In most examples of SN2 displacements, the nucleophilic atom is a heteroatom itself, subject to reduced primary L strain, and therefore almost negligible secondary L strain. As a result, the α effect is expected to be of small magnitude.

The experimental facts support this conclusion. The α effect is a real phenomenon but quantitatively a minor one and varies from case to case. The widespread attention it has received apparently stems from its hitherto mysterious nature[83,84] rather than from its experimental importance.

Typical examples are the enhanced nucleophilicity of OOH^- relative to OH^- toward *p*-nitrophenyl diethyl phosphate,[85] benzyl bromide,[86] isopropyl methylphosphonofluoridate,[87] tetraethyl pyrophosphate,[88] and benzonitrile,[89] despite the fact that OH^- is by far the stronger base. The α effect also operates in aminol-

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[69] D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 9.

[70] C. D. Ritchie, *J. Amer. Chem. Soc.*, **91**, 6749 (1969).

[71] See ref 61, p 173.

[72] A. Streitwieser, Jr., and J. H. Hammons, *Progr. Phys. Org. Chem.*, **3**, 63 (1965), and references cited therein; (b) A. R. Lepley and W. A. Khan, *Chem. Commun.*, 1198 (1967).

[73] See ref 69, p 21.

[74] Relative exchange rates with cesium cyclohexylamide in cyclohexylamine at 50° are CH_4, 2300; C_2H_6, 34; cyclohexane, 1 (preliminary unpublished data kindly related by Professor A. Streitwieser, Jr.). Rates for $(CH_2)_n$ rings large enough to minimize steric and annular effects are *ca.* 0.6 relative to cyclohexane: A. Streitwieser, Jr., R. A. Caldwell, and W. R. Young, *J. Amer. Chem. Soc.*, **91**, 529 (1969). Steric effects, associated perhaps with accessibility of the cation, are not responsible for these rate differences since even very bulky groups lower the rate for CH_3R but little, the relative rates in the same study being CMe_4, 8, and C_2Me_6, 5.

[75] It is, in fact, likely that the *intrinsic* acidities of C–H bonds follow the sequence methine > methylene > methyl, because in the gas phase the acidities of N–H bonds increase progressively with alkyl substitution: J. I. Brauman and L. K. Blair, *J. Amer. Chem. Soc.*, **91**, 2126 (1969).

[76] D. Turnbull and S. H. Maron, *ibid.*, **65**, 212 (1943).

[77] F. G. Bordwell, W. J. Boyle, Jr., J. A. Hautala, and K. C. Yee, *ibid.*, **91**, 4002 (1969).

[78] H. C. Brown and B. Kanner, *ibid.*, **88**, 986 (1966).

[79] W. G. Brown and K. Eberly, *ibid.*, **62**, 113 (1940).

[80] C. R. Hauser, R. Levine, and R. F. Kibler, *ibid.*, **68**, 26 (1946).

[81] Malonate anions are somewhat unusual, compared with simple esters, in that an α-phenyl slows base-catalyzed protium–deuterium exchange,[79] and also in that ethylmalonic ester may be less acidic than malonic ester: R. G. Pearson, *ibid.*, **71**, 2212 (1949). However, these anomalies clearly stem from steric inhibition of coplanarity in the highly crowded anions and do not detract from the main argument.

[82] J. O. Edwards and R. G. Pearson, *ibid.*, **84**, 16 (1962).

[83] For a thorough recent discussion, see T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *ibid.*, **89**, 2106 (1967).

[84] See ref 55, p 106.

[85] J. Epstein, M. M. Demek, and D. H. Rosenblatt, *J. Org. Chem.*, **21**, 796 (1956).

[86] R. G. Pearson and D. N. Edgington, *J. Amer. Chem. Soc.*, **84**, 4607 (1962).

[87] See ref 55, p 107.

[88] G. Aksnes, *Acta Chem. Scand.*, **14**, 1515 (1960).

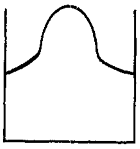
[89] K. B. Wiberg, *J. Amer. Chem. Soc.*, **77**, 2519 (1955).

ysis[90] and base-catalyzed hydrolysis[91] of *p*-nitrophenyl acetate, in displacement on oxygen in AcOOH (where PhNHOH is 6 times more reactive than $PhNH_2$),[52] and in displacement on hydrogen in base-catalyzed reactions; thus ketoxime anions exhibit >20 times positive deviations from the Brønsted catalysis law.[65] This case, like the one cited earlier, illustrates a kinetic factor overriding thermodynamic ones. Many other examples have been given.[83,87]

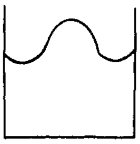
On the other hand, no α effect was seen in the aminolysis of alkyl iodides in water[90] or acetonitrile,[92] or in attack of amines on the acidic α hydrogen of nitroethane.[93] Clearly, there is much concerning the α effect that is not understood.[94]

The data on the α effect presently obtainable suffer from the facts that many of the reactions were run in hydroxylic solvents with their attendant complications; not all of the examples involve SN2 displacement at a saturated atom (although all of those cited are relevant to this discussion); and few, if any, have the transition state at the midpoint of the reaction coordinate. From the standpoint of the L-strain theory, the α effect ought to be maximized when (1) solvation effects are minimized; (2) the reaction is symmetrical; (3) the attacking atom has few nonbonded electrons, *i.e.*, suffers most from primary L strain; and (4) α atoms are compared that differ greatly in the expected degree of secondary L strain they suffer in the transition state. Typical examples might be $Me_3N + CH_3N^+Me_3$ *vs.* $PhONMe_2 + CH_3\overset{+}{N}Me_2OPh$, or $Me_3N + H\overset{+}{N}Me_3$ *vs.* $XNMe_2 + H\overset{+}{N}Me_2X$, where X is methoxy or halogen.

Frozen Transition States. Hydrogen Bonds and Trihalide Ions.—If L strain at atoms X, C, and Y in transition state 2 indeed plays an important role in its properties, then, if we were to gradually change the nature of all the atoms and attached groups in such a way that L strain progressively becomes altogether abolished, we might anticipate a gradual sinking of the reaction coordinate diagram to an ultimate form representing a completely L-strain-free reaction. In cases of the latter type, the transition state, having the same number of bonding electrons but better electron correlation than the reactants, could be lower in energy than they are and thus exist as a stable species. This phenomenon will clearly be most pronounced in SN2 displacements on univalent atoms such as hydrogen and the halogens.[96]



Normal SN2



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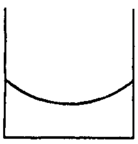

11

Hydrogen bonds and trihalide ions are immediately recognized as examples of such frozen transition states.[97] Their Linnett structures are **12** and **13**, first proposed by Linnett.[98] Trihalide ions **13**, having good electron correlation and no L strain whatever, fit well into category **11**. They are linear[99] and have two half bonds,[100] as expected. Almost all combinations of halogens form X_3^- ions,[99] and the absence of F_3^- from the list is undoubtedly owing to the extremely great reactivity of F_2; F_3^- will presumably be found when a system is devised in which F_2 and free F^- can coexist in solution without attacking the solvent. In least interacting media the order of stability is $Cl_3^- > Br_3^- > I_3^-$,[101] indicating that higher orbitals[102] are not involved in trihalide ion formation.

$$\cdot Y \cdot H \cdot Z \cdot \qquad\qquad :\underset{\cdot\cdot}{\overset{\cdot\cdot}{X}}\cdot\underset{\cdots}{\overset{\cdots}{X}}\cdot\underset{\cdot\cdot}{\overset{\cdot\cdot}{X}}:$$

12 **13**

The cations Hal_3^+ offer an interesting contrast. Having two fewer valence electrons, they may adopt the configuration $:\underset{\cdot\cdot}{\overset{\cdot\cdot}{X}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{X}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{X}}:$, whose Linnett structure has two-electron bonds and an angle of about 109.5°. The species ClF_2^+ fit the overall picture well. Valence force constants in millidynes/Å follow: ClF_2^+, 4.6–4.8,[103] 4.8;[104] ClF_2^-, 2.35;[100] *cf.* ClF, 4.36.[105] Bond angles are as follows: ClF_2^+, 95–110°,[103] 90–120°;[104] ClF_2^-, 180°.[100]

Hydrogen-bonded molecules exhibit more structural variety because the groups Y and Z in **12** are frequently not entirely free of L strain. Thus, typical hydrogen bonds have the proton closer to one side than the other, as in **10**,[106] corresponding to resonance between **12** and **14**. However, symmetrical hydrogen bonds of type **11**

$$\cdot Y \cdot H \cdot Z \cdot \longleftrightarrow Y{:}H{:}Z$$

12 **14**

are known, and it is significant that in all cases the groups Y and Z are capable of forming one-electron bonds, as in **12**, without suffering any increase in L strain. Examples are HF_2^-,[107] HCl_2^-[107] (and probably HBr_2^- and HI_2^-),[107] $H(NO_3)_2^-$,[107,108] $H(OCOR)_2^-$ (R = CH_3, CF_3, Ar).[109]

The hydrogen-bond phenomenon, as an aspect of proton transfer, must represent equilibrium basicity as well as L strain. Basicity effects cancel when Y and Z are the same, and in these cases we expect hydrogen bond strengths to diminish in the order Y, Z = F > O > N >

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[90] M. J. Gregory and T. C. Bruice, *J. Amer. Chem. Soc.*, **89**, 4400 (1967).

[91] W. B. Gruhn and M. L. Bender, *ibid.*, **91**, 5883 (1969).

[92] S. Oae, Y. Kadoma, and Y. Kano, *Bull. Chem. Soc. Jap.*, **42**, 1110 (1969).

[93] M. J. Gregory and T. C. Bruice, *J. Amer. Chem. Soc.*, **89**, 2327 (1967).

[94] From a recent study of the α effect in oxazolone reactions with nucleophiles,[95] good evidence was adduced that these nucleophiles acted as biphilic reagents; *i.e.*, that the α heteroatom bore a proton which acted as an acid catalyst in the transition state. The biphilic and L-strain interpretations of the α effect are, however, not necessarily exclusive, since each may apply under different circumstances.

[95] M. Goodman and C. B. Glaser, *J. Org. Chem.*, **35**, 1954 (1970).

[96] The possibility that these diagrams also have shallow dips at the centers is acknowledged (*vide supra*) but plays no part in the discussion.

[97] Frozen transition states are by definition intermediates, and not true transition states. The expression is used because it is uniquely descriptive for our present purpose.

[98] See ref 2, p 118.

[99] K. O. Christe and J. P. Guertin, *Inorg. Chem.*, **4**, 905 (1965), and references cited therein.

[100] K. O. Christe, W. Sawodny, and J. P. Guertin, *ibid.*, **6**, 1159 (1967).

[101] R. Alexander, E. C. F. Ko, and A. J. Parker, *J. Amer. Chem. Soc.*, **89**, 3703 (1967).

[102] R. F. Hudson, *Angew. Chem., Int. Ed. Engl.*, **6**, 749 (1967).

[103] R. J. Gillespie and M. J. Morton, *Inorg. Chem.*, **9**, 616 (1970).

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[106] (a) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman Co., San Francisco, Calif., 1960, p 259; (b) see ref 46b, p 223.

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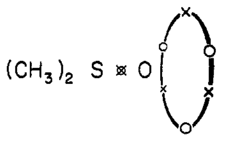
C, since L strain in **12** ↔ **14** increases with the number of groups borne by Y and Z. Although the experimental data must be viewed against a background of solvent effects poorly understood, they clearly are in accord with this expectation.[110] This is also the order of relative rates of proton transfer.[66]

The clash between thermodynamic and kinetic effects, presented earlier, appears here also. It has become increasingly apparent in recent years that hydrogen bonds are subject to a powerful influence which sometimes runs counter to trends in basicity. Dimethyl sulfoxide, though a very weak base, should be a potent hydrogen-bond acceptor, in keeping with the structure **15**. The unshared electrons on the oxygen atom are not closely paired and consequently can accept a hydrogen bond with no increase in L strain. Hexamethylphosphoramide is alike in this respect. Divalent oxygen is less favored because both spin sets are formally coincident.[4] However, doubly bonded oxygen can separate its spin sets more easily than ether oxygen for reasons given earlier (*cf.* α-halo ketones), with amides better than ketones owing to their pronounced resonance. Trivalent nitrogen suffers still more L strain in **12** ↔ **14** than divalent oxygen, offsetting its greater basicity. As with oxygen, ease of accepting hydrogen bonds should increase with multiplicity, countering the concurrent decrease in basicity.



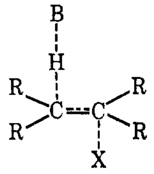
15

Dimethyl sulfoxide, even in the presence of proton donors, profoundly increases the reactivity of bases and nucleophiles,[111] which we ascribe to its role as hydrogen-bond acceptor.[112] In activating piperidine to nucleophilic attack on nitroaromatic substrates by coordinating with NH, DMSO far outstrips dioxane and the much more basic pyridine.[113]

Recent comprehensive studies of hydrogen bonding provide strong confirmation of the L-strain theory. Toward phenylacetylene, hydrogen bond strengths diminish in the sequence HMPA > DMSO > DMF > acetone, ethers > acetonitrile,[114] in accord with the theory but not with their relative basicities. In a comparison of 62 bases toward *p*-fluorophenol,[115] no correlation between basicity and hydrogen bond strength was found. The trends, however, were precisely as predicted above, with DMSO, HMPA, and DMF unusually potent hydrogen bond acceptors for their basicity, and amines unusually weak. Carbonyl compounds and ethers, in that order, were intermediate. In a second paper,[116] a plot for all bases of log K_f (H bond) *vs.* pK_a (H_2O) fit no one line but could be resolved into a series of roughly parallel lines, each representing a family of compounds of the same type in the order just given. Within each family, log K_f was proportional to pK_a, but some factor other than pK_a operated to separate the various classes. We identify this factor as L strain.

The theory of hydrogen bonding and trihalide ions outlined above does away with the problem of hypervalency[102] previously associated with these phenomena. An MO description of the hydrogen bond by McClellan and Pimentel[117] may be equivalent to ours, although it makes no provision for L strain.

The E2C Mechanism.—Related to the problem of basicity *vs.* hydrogen bonding ability is the theory of bimolecular elimination called the E2C mechanism. In the E2 reaction, as in neutralization by a protic acid, a Lewis base forms a new bond to hydrogen, while in the SN2 reaction the new bond is to carbon. Because the logarithms of E2 reaction rates of cyclohexyl tosylate with various bases were related randomly toward their pK_a's, but linearly toward the logarithms of the concurrent SN2 reaction rates of the same substances, it was proposed[118] that E2 transition states be categorized as E2H (**16**) or E2C (**17**), or a combination of the two. Further studies have appeared,[111e,119] as well as opposed views.[120]



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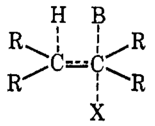

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It had been noted[118] that the poor Brønsted relationship was markedly improved if hydrogen-bonding ability were considered in place of equilibrium basicity. In the light of the discussion above on hydrogen bonding, it becomes clear that the tendency for a base to attack on hydrogen *vs.* carbon ought to be compared with its hydrogen-bonding ability, not its basicity. The latter measures its states before and after complete proton transfer has occurred, but it is the former which relates to the contrast between the ground and transition states. Thus those factors, such as L strain, which cause differences to arise between pK_a and hydrogen bond basicity will also be operative in transition state **16**, making the consideration of unusual forms such as **17** less imperative.

Conclusion

The Linnett electronic theory and its corollary, L strain, account for a wide variety of phenomena

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[110] See ref 106a, pp 212, 224.

[111] (a) E. C. Steiner and J. M. Gilbert, *J. Amer. Chem. Soc.*, **85**, 3054 (1963); (b) C. A. Kingsbury, *J. Org. Chem.*, **29**, 3262 (1964); (c) D. Bethell and A. F. Cockerill, *J. Chem. Soc. B*, 913 (1966); (d) A. F. Cockerill and S. Rottschaefer, *J. Amer. Chem. Soc.*, **89**, 901 (1967); (e) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969); (f) K. Kalliorinne and E. Tommila, *Acta Chem. Scand.*, **23**, 2567 (1969).

[112] The authors of the papers cited are not always in agreement with this point of view.

[113] C. F. Bernasconi, M. Kaufmann, and H. Zollinger, *Helv. Chim. Acta*, **49**, 2563 (1966).

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[115] D. Gurka and R. W. Taft, *J. Amer. Chem. Soc.*, **91**, 4794 (1969).

[116] R. W. Taft, D. Gurka, L. Joris, P. v. R. Schleyer, and J. W. Rakshys, *ibid.*, **91**, 4801 (1969).

[117] See ref 106a, p 236.

[118] A. J. Parker, M. Ruane, G. Biale, and S. Winstein, *Tetrahedron Lett.*, 2113 (1968).

[119] (a) D. J. Lloyd and A. J. Parker, *ibid.*, 5183 (1968); (b) D. Cook, A. J. Parker, and M. Ruane, *ibid.*, 5715 (1968); (c) D. Cook and A. J. Parker, *ibid.*, 4901 (1969); (d) G. Biale, A. J. Parker, S. G. Smith, I. D. R. Stevens, and S. Winstein, *J. Amer. Chem. Soc.*, **92**, 115 (1970).

[120] (a) D. Eck and J. F. Bunnett, *ibid.*, **91**, 3099 (1969); (b) D. J. McLennan and R. J. Wong, *Tetrahedron Lett.*, 881 (1970).

dealing with SN2 reactions on carbon, hydrogen, and heteroatoms. No other valence theory presently makes allowance for L strain although this may come about in the future, since the Linnett theory is complementary to, and not incompatible with, the valence bond and molecular orbital viewpoints. A strong point of the new method is the facility with which it can be applied. Definite structures are easily assigned to molecules and transition states with no need to invoke dotted-bond forms with vague properties. The systematic application of Linnett's theory to other organic reactions will follow in due course.

The $12\alpha,13\beta$-Etiojervane Analog of Testosterone

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The 3-keto-17α-acetoxyetiojervane **1f** was converted *via* the 2,4-dibromide to the unsaturated ketone **5f**; room-temperature formation of the ethylenedioxy ketal **6e** followed by successive saponification, oxidation, and hydride reduction afforded the 17β-hydroxy derivative **6a** ($R' = -CH_2CH_2-$) which was hydrolyzed to the title compound. Attempts to prepare and use the 2,4-dibromide **4b** in the 17β-acetoxy series were unsuccessful. The corresponding 12β-etiojervanes were prepared from jervine by modification and extension of known methods.

The objective of the research described here was to synthesize, starting from hecogenin, simple etiojervane derivatives which would display some of the potent physiological characteristics of the Veratrum alkaloids.[1] The initial group of etiojervanes (12α, 13α)[2] prepared had both a C/D cis ring fusion and a 13α substituent (methyl) in analogy to the Veratrum alkaloids. These derivatives had no noteworthy physiological activity. The serendipitous preparation[3] (by fermentation) of the corresponding 13β-methyldione **5d** (Δ^1), however, led to the syntheses of a series of compounds with good potency as antialdosterone agents.[4]

The primary target of our research was a practicable synthesis of the title compound **5a**. One starting material was the saturated 3-ketone **1b**, obtained by rearrangement of hecogenin and subsequent degradation of the sapogenin side chain.[5] The 2-monobromide **2b** was investigated as a possible intermediate to be used in the introduction of the C-4 double bond. The bromide **2b**, a crystalline compound prepared by direct bromination of the ketone **1b**, had both gross structure (C-2 bromine) and configuration (α-bromine) in analogy to the steroidal bromination product, as suggested by nmr and ORD measurements.[6] A chemical confirmation was obtained by zinc–acetic acid reduction to starting material **1b** and by magnesium oxide dehydrohalogenation to give preponderantly the Δ^1 ketone **3b**. A minor by-product of the latter reaction was the Δ^4 ketone **5b** which was separated and characterized. The monobromide **2f** (17α-acetate) underwent analogous reactions, although neither the 17α-acetate **3f** nor its alcohol **3e** was obtained in a crystalline form.

Dehydrobromination of 2-bromo steroids with lithium chloride in dimethylformamide proceeds vinylogously to yield 45% of the Δ^4 derivative.[7] With the etiojervane monobromide **2f**, the same reagent afforded, rather than an elimination product, a displacement product, the monochloride **2f** ($X = Cl$). The same chloride was produced readily from the monobromide over a wide range of temperatures. Similarly, treatment of the bromide with sodium iodide provided an iodo derivative (**2f**, $X = I$). The position of the chlorine atom in **2f** was not readily determined because of its stability to relatively vigorous dehydrohalogenation conditions; treatment of the compound in boiling collidine for 7 hr effected little change in the starting material. With magnesium oxide in boiling dimethylformamide, the monochloride **2f** slowly yielded mixtures from which the Δ^1 derivative **3f** could be isolated. In contrast, the iodide underwent a facile elimination to give mainly the Δ^1 ketone, thus supporting directly the assigned position of the iodine atom in the iodo ketone **2f** and indirectly the position of the chlorine atom in the chloro ketone **2f**. The configuration of the chlorine atom in **2f** was determined by ORD and nmr measurements.[8]

The behavior of the 2-monobromo-17β-acetate **2b** on treatment with lithium chloride differed markedly from that of the corresponding 17α-acetate, reacting very slowly in this case and producing an intractable chlorine-containing mixture. Under conditions vigorous enough to remove halogen, the product lacked an unsaturated ketone component (ir analysis). Several other reagents also failed to generate an unsaturated ketone from the lithium chloride product. The difference in behavior between the 17α-acetate and the more strained 17β-acetate[9] on treatment with lithium chloride may be attributed either to a long-range effect (transmission of strain through the carbon–carbon bonds) or to a steric effect (produced by the cupping of the D ring toward the β face of the A ring). Molecular models imply the former to be the more important cause.

Direct dibromination of the 3-keto-17α-acetate **1f** led to the 2,4-dibromide **4f** in good yield. Treatment of this compound sequentially with sodium iodide, acid,

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[1] S. M. Kupchan and A. W. By in "The Alkaloids," Vol. X, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1968, Chapter 2.

[2] W. F. Johns and I. Laos, *J. Org. Chem.*, **30**, 123 (1965).

[3] W. F. Johns, *ibid.*, **35**, 3524 (1970).

[4] The physiological activity of the compounds reported will appear in a forthcoming publication.

[5] W. F. Johns, *J. Org. Chem.*, **29**, 2545 (1964).

[6] Professor W. Klyne, Westfield College, University of London, kindly supplied this data and its interpretation.

[7] B. J. Magerlein, *J. Org. Chem.*, **24**, 1564 (1959).

[8] Preparation of 2-iodocholestanone from the 2-bromide has been recorded: G. Rosenkranz, O. Mancera, J. Gatica, and C. Djerassi, *J. Amer. Chem. Soc.*, **72**, 4077 (1950). The displacement by chloride, however, leads to elimination (ref 7). For displacement of halo ketones at other positions, *cf.*, *inter alia*, G. P. Mueller and W. F. Johns, *J. Org. Chem.*, **26**, 2403 (1961).

[9] The 17β derivatives are more strained because of the interaction of the 17β substituents with C-19. See ref 2 for a further discussion of this point.