Organic and Biological Chemistry

Asymmetric Induction. A Model for Additions to Carbonyls Directly Bonded to Asymmetric Carbons

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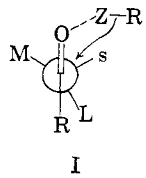
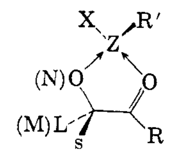
Abstract: This manuscript describes a simple empirical model on the basis of which semiquantitative predictions of product stereospecificity, resulting from chemical additions to carbonyl groups directly bonded to asymmetric carbon atoms, are feasible. The model is based on the following assumptions. (a) Little bond breaking and making marks the diastereomeric transition states. The arrangement of the three groups of the asymmetric carbon atom with respect to the carbonyl is thus as in aldehydes and ketones, *i.e.*, one group eclipsing the carbonyl. (b) The two low-energy diastereomeric transition states that control product stereospecificity have the smallest group of the asymmetric carbon atom closest to the incoming bulky group. (c) The diastereomeric ratio is then evaluated from the relative magnitudes of the carbonyl-eclipsed group interactions. With correspondence between calculated and experimentally determined product diastereomeric ratios being fairly good, several difficulties encountered with previous models are adequately rationalized.

The major diastereomer resulting from chemical additions to carbonyl groups directly bonded to asymmetric carbon atoms can be generally predicted as a consequence of the investigations and correlations of Cram and his co-workers.[2] To this end three empirical models may be used:[2] the open chain (I),[3] the rigid (II),[4] and the dipolar (III).[5] In the open-chain model (s, small, M, medium; L, large), which applies to cases where the groups attached to the asymmetric carbon are alkyls or aryls, approach from the side of the small group s is favored over approach from the side of the medium group M. Product stereospecificity therefore depends on the relative magnitudes of R′ ↔ s and R′ ↔ M steric interactions. When one of the three groups is oxygen or nitrogen, model II is applicable. Approach from the side of the small group s is again favored. Failure of model II to predict correctly the resultant major diastereomer in additions to α-chloro ketones has led to the dipolar model III.



I



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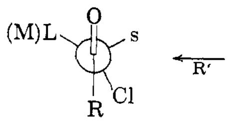
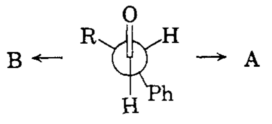


III

Aside from occasional failures[2,6] of the rigid model II to correctly predict the major diastereomer, several aspects associated with the success and failure of these models are puzzling.

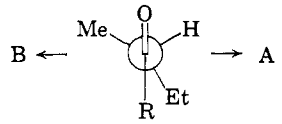
1. The diastereomeric product ratio A/B (IV) decreases with R varying from methyl to isopropyl, as if the effective size of isopropyl were smaller than that of methyl.



IV

R	A/B
Me[3,7]	2–4/1
Et[8]	2.5/1
i-Pr[9]	1, 1.3, 1.9/1

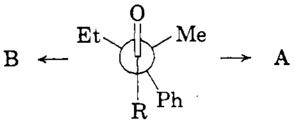
2. When the third group on the asymmetric carbon is ethyl instead of phenyl (V), the diastereomeric product ratio A/B decreases[7] to the point where the model does not predict the major diastereomer.



V

R	A/B
H	1.5/1
Me	0.94, 1.04/1

3. Whereas methyl and ethyl behave as if of equal effective size in IV—and substantially bulkier than hydrogen—methyl competes as effectively against ethyl (VI) as does hydrogen.



VI

R	A/B
H[10]	2/1
Me[11]	2.3/1
Et[11]	4/1
Ph[10]	2.2/1

4. The frequently very high diastereomeric product ratios obtained in reactions where the rigid model II applies contrast sharply with the modest ratios observed in analogous reactions where the open-chain model I applies. The following cogently illustrates

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[1] Fellow of the Alfred P. Sloan Foundation.

[2] D. J. Cram and D. R. Wilson, *J. Am. Chem. Soc.*, **85**, 1245 (1963), and previous references.

[3] D. J. Cram and F. A. Abd Elhafez, *ibid.*, **74**, 5828 (1952).

[4] D. J. Cram and K. R. Kopecky, *ibid.*, **81**, 2748 (1959).

[5] J. W. Cornforth, R. H. Cornforth, and K. K. Mathews, *J. Chem. Soc.*, 112 (1959).

[6] J. H. Stocker, P. Sidisunthorn, B. M. Benjamin, and C. J. Collins, *J. Am. Chem. Soc.*, **82**, 3913 (1960).

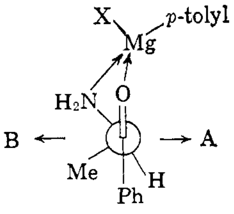
[7] Y. Gault and H. Felkin, *Bull. Soc. Chim. France*, 1342 (1960).

[8] D. J. Cram, F. A. Abd Elhafez, and H. Weingarten, *J. Am. Chem. Soc.*, **75**, 2293 (1953).

[9] D. J. Cram and F. A. Abd Elhafez, *ibid.*, **76**, 22 (1954).

[10] D. J. Cram and J. Allinger, *ibid.*, **76**, 4516 (1954).

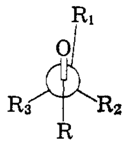
[11] D. J. Cram and J. D. Knight, *ibid.*, **74**, 5835 (1952).



VII

this point. The diastereomeric product ratio[12] A/B in VII is 50. If this ratio is indicative of the relative effective sizes of hydrogen and methyl, at least as large a ratio should have been found in reactions where the open-chain model applies (IV).

5. Although their empirical nature has been stressed, the models have been considered to embody the rationale of their success. For example, the success of I may be justified on the grounds that the metal alkyls or hydrides "probably coordinate with the carbonyl group of the starting material as well as with a mole of ether. The oxygen, therefore, becomes effectively the bulkiest group in the molecule and tends to orient itself between the two least bulky groups attached to the adjacent asymmetric carbon atom."[3] The applicability of model III has been rationalized[5] on the grounds that the depicted conformation III, where polarization of the carbonyl group is easiest as a result of the C=O and C–Cl dipoles being antiparallel, is the most reactive. The accumulation of recent evidence[13] that the stable conformations about sp^2–sp^3 carbon–carbon bonds have a single bond eclipsing the double bond, as in VIII, appears to be—at least superficially—in conflict with these rationalizations and makes the success of models I and III the more intriguing.[14]

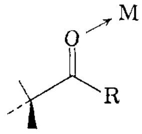


VIII

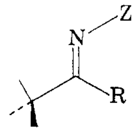
This manuscript represents an effort to explain these difficulties in terms of a simple empirical model, on the basis of which semiquantitative predictions about diastereomeric product ratios might be made.

Grignard additions[15] to and hydride reductions[16] of carbonyl groups have E_a and $\Delta S^{\ddagger}$ values between 8 and 15 kcal/mole and −20 to −40 eu, respectively. As rotational barriers about the relevant sp^2–sp^3 carbon–carbon bonds should be much lower, the Curtin–Hammett principle[17] requires that the diastereomeric product ratio depend solely on the free-energy difference, $G_A^{\ddagger} - G_B^{\ddagger}$, between the two diastereomeric transition states. Successful prediction of product stereospecificity, therefore, requires knowledge of the structures of the pertinent diastereomeric transition states.

With respect to the reaction coordinate, two extreme situations, with a broad spectrum in between, are conceivable: reactant-like transition states marked by little bond breaking and making, and product-like transition states marked by extensive bond breaking and making. From product stereospecificity the terms "steric approach control" and "product development control" have been introduced.[18] The rapidity and exothermicity of the reactions in question, as well as the experimental product stereospecificities, lead to the first assumption on which the proposed model will be based. *Little bond breaking and making has occurred at the transition states. Consequently, the arrangement of the groups of the asymmetric carbon atom with respect to the carbonyl group is similar to that about* sp^2*–*sp^3 *carbon–carbon bonds (VIII).* Although the species in question is the complexed rather than the free carbonyl, expecting the stable conformations to be other than those depicted in IX is unwarranted. In somewhat analogous systems, X (Z = alkyl, OR, NR_2), the stable conformations are as pictured.[19]

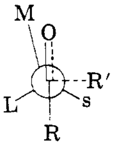


IX

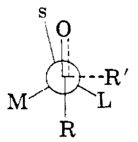


X

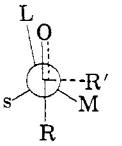
On the basis of the first assumption, the most stable diastereomeric transition states are qualitatively predictable. Consider the three transition states, XI,[20] XI′, and XI″, that lead to one diastereomer, A. Of the three, XI, the one where the incoming bulky group R′ is closest to the smallest group, s, should be the most stable. Its advantage over XI′ is evident by inspection, as the R ↔ s and R′ ↔ s should be favored over R ↔ M and R′ ↔ L, respectively. Even the M ↔ O interaction in XI is less severe than the s ↔ O in XI′. For example, when s is hydrogen and M is methyl, the M ↔ O is favored by about 800 cal/mole.[13] The advantage of XI over XI″ is less obvious, as the R ↔ M interaction in XI″ should be energetically better than the R ↔ L in XI. XI, however, is favored by the interactions involving the bulky group R′ and by M ↔ O over L ↔ O. With respect to the latter interaction, when M is methyl and L is phenyl, M ↔ O is favored by about 600 cal/mole.[13] From similar arguments XII should be the most stable of the three transition states, XII, XII′ and XII″, leading to the



XI



XI′



XI″

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[12] B. M. Benjamin, H. J. Schaeffer, and C. J. Collins, *J. Am. Chem. Soc.*, **79**, 6160 (1957).

[13] G. J. Karabatsos and N. Hsi, *ibid.*, **87**, 2864 (1965), and references cited therein.

[14] Aliphatic ketones and α-haloacetaldehydes also exist in conformation VIII (from unpublished results of G. J. Karabatsos, N. Hsi, and D. Fenoglio).

[15] N. M. Bikales and E. I. Becker, *Can. J. Chem.*, **41**, 1329 (1963); M. Anteunis, *J. Org. Chem.*, **26**, 4214 (1961).

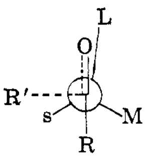
[16] H. C. Brown and K. Ichikawa, *J. Am. Chem. Soc.*, **84**, 373 (1962); W. N. Moulton, R. E. Van Atta, and R. R. Rush, *J. Org. Chem.*, **26**, 290 (1961).

[17] D. Y. Curtin, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **15**, 111 (1954). See also E. L. Eliel, "Stereochemistry of Organic Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Chapter 6, pp 151–156.

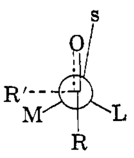
[18] W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).

[19] G. J. Karabatsos, N. Hsi, and K. L. Krumel, *Tetrahedron*, in press.

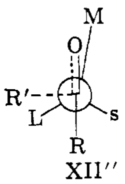
[20] The open-chain model pictured on the first page of ref 2 closely resembles XI. Its dihedral angle differs from that of XI by about 30°.



XII



XII′



XII″

other diastereomer, B. The second assumption, therefore, may now be formulated as follows. *The diastereomeric transition states that control product stereospecificity have the smallest group, s, closest to the incoming bulky group R′ (XI and XII).*

Qualitative prediction of the diastereomeric ratio A/B requires now evaluation of the relative stabilities of XI and XII. When the groups s, M, and L are alkyls or aryls, this evaluation must be primarily based on the relative importance of three corresponding interactions: R′ ↔ M, R ↔ L, and M ↔ O in XI, and correspondingly R′ ↔ L, R ↔ M, and L ↔ O in XII. Of these, the first favors XI and the second XII. Whereas the extent to which these two interactions counteract each other is unpredictable and variant, the third interaction, M ↔ O *vs.* L ↔ O, is evaluable. For example, when M is methyl and L is phenyl, M ↔ O is favored over L ↔ O by about 600 cal/mole;[13] when M is methyl and L is ethyl, M ↔ O is favored by about 100 cal/mole. On the basis of this interaction, therefore, the greater stability of XI over XII would lead to A/B ratios that are greater than unity.

In order to test the reliability of semiquantitatively predicting diastereomeric product ratios by considering only M ↔ O *vs.* L ↔ O interactions, 30 examples available in literature are listed in Table I. The experimental $G_A^{\ddagger} - G_B^{\ddagger}$ values were calculated from eq 1. The

$$G_A^{\ddagger} - G_B^{\ddagger} = -RT \ln A/B \qquad (1)$$

calculated $G_A^{\ddagger} - G_B^{\ddagger}$ values represent [M ↔ O] − [L ↔ O] interactions.[13] Because the [M ↔ O] − [L ↔ O] values involving phenyl are solvent dependent, those listed for L = phenyl are from ether solvents. The methyl *vs.* cyclohexyl value, entries 22–26, was taken as −300 cal/mole, so as to be 100 cal/mole less negative than the −400 cal/mole of methyl *vs.* isopropyl. On the grounds that [M ↔ O] − [L ↔ O] values for aldehydes and compounds X are similar,[19] their use for the complexed carbonyl is justifiable.

With the exception of entries 29 and 30, for which no good explanation now can be offered, the correspondence between experimental and calculated values must be regarded as surprisingly good, not only because of the experimental uncertainties associated with these values, but also because of the inherent limitations and weaknesses of this as well as any other model designed to quantitatively predict product stereospecificity. The following additional comments further emphasize this point. (a) Judging from the effect that an optically active solvent has on the energies of enantiomeric transition states, $G_A^{\ddagger} - G_{A'}^{\ddagger}$ up to 100 cal/mole,[21] solvation of the two diastereomeric transition states might contribute as much as 50–100 cal/mole to the experimental $G_A^{\ddagger} - G_B^{\ddagger}$ values. (b) The neglected unknown quantity [(R ↔ L) + (R′ ↔ M)] − [(R ↔ M) + (R′ ↔ L)] will depend on R and R′, and the experimental $G_A^{\ddagger} - G_B^{\ddagger}$ values for a given asymmetric carbon will vary. As R′ increases in size the $G_A^{\ddagger} - G_B^{\ddagger}$ values should become more negative. Discarding fortuity as the cause of agreement between experimental and calculated values, this quantity is probably small. (c) The extent of bond breaking and making at the transition states will undoubtedly vary with each reaction. This variation will thus contribute to fluctuations[22] in $G_A^{\ddagger} - G_B^{\ddagger}$. (d) The experimental $G_A^{\ddagger} - G_B^{\ddagger}$ values will be affected by differences in the entropies of the two diastereomeric transition states. Although extensive studies on the variation of diastereomeric product ratio with temperature have not been carried out, the only study[7] on systems to which the present model applies has shown that $G_A^{\ddagger} - G_B^{\ddagger}$

Table I. Experimental and Calculated Free-Energy Differences between the Two Diastereomeric Transition States

		$G_A^{\ddagger} - G_B^{\ddagger}$, cal/mole		
No.	Reaction	Exptl	Ref	Calcd[13]
1	PhMeHC–CHO + MeMgI	−410	3	−600
2	PhMeHC–COMe + $LiAlH_4$	−550	3	−600
3	PhMeHC–COEt + $LiAlH_4$	−410	3	−600
4	PhMeHC–CHO + EtMgI	−650	3	−600
5	PhMeHC–COPh + $LiAlH_4$	−830	3	−600
6	PhMeHC–CHO + PhMgBr	−830	3	−600
7	PhMeHC–CHO + MeMgBr	−460	7	−600
8	PhMeHC–COMe + $LiAlH_4$	−660, −700 (0°) (−70°)	7	−600
9	PhMeHC–C(Me)=$\bar{N}Mg^+X$ + $LiAlH_4$	−400	*a*	−700[c]
10	PhMeHC–C(Me)=$\bar{N}Mg^+X$ + $NH_4^+HCO_2^-$	−420	*a*	−700[c]
11	PhEtHC–CHO + MeMgI	−550	3	−500
12	PhEtHC–COMe + $LiAlH_4$	−650	3	−500
13	PhEtHC–CHO + EtMgBr	−650	8	−500
14	PhEtHC–COEt + $LiAlH_4$	−650	8	−500
15	PhEtMeC–COMe + EtLi	−530	11	−500
16	PhEtMeC–COEt + MeLi	−830	11	−500
17	PhEtMeC–CHO + PhMgBr	−410	10	−500
18	PhEtMeC–COPh + $LiAlH_4$	−470	10	−500
19	Ph-*i*-PrHC–CHO + *i*-PrMgBr	−380	9	−200
20	Ph-*i*-PrHC–CHO + *i*-PrMgBr + $6MgBr_2$	−160	9	−200
21	Ph-*i*-PrHC–CHO + *i*-PrLi (pentane)	0	9	−200
22	C_6H_{11}MeHC–CHO + MeMgI	−380	*b*	−300
23	C_6H_{11}MeHC–CHO + MeLi (pentane)	−220	*b*	−300
24	C_6H_{11}MeHC–CHO + MeLi (ether)	−110	*b*	−300
25	C_6H_{11}MeHC–COMe + $NaBH_4$	−320	*b*	−300
26	C_6H_{11}MeHC–COMe + $LiAlH_4$	−200	*b*	−300
27	EtMeHC–CHO + MeMgBr	−220	7	−100
28	EtMeHC–COMe + $LiAlH_4$	−16, +32, +36 (−70°) (0°) (35°)	7	−100
29	Ph-*i*-PrHC–CO*i*-Pr + $LiAlH_4$	−1380	9	−200
30	C_6H_{11}MeHC–COMe + Al(*i*-PrO)$_3$	+380	*b*	−300

[a] D. J. Cram and J. E. McCarty, *J. Am. Chem. Soc.*, **76**, 5740 (1954). [b] D. J. Cram and F. D. Green, *ibid.*, **75**, 6005 (1953). [c] These values are from ref 19.

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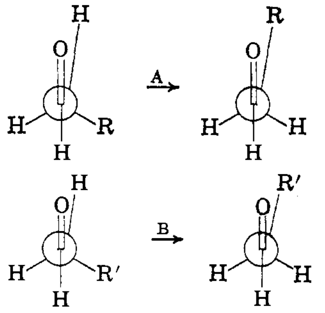
(21) N. Allentoff and G. F. Wright, *J. Org. Chem.*, **22**, 1 (1957).

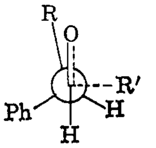
(22) Of interest is the question of whether product stereospecificity in acyclic systems might not be controlled by product stability, even if extensive bond breaking and making marked the transition state. It has been suggested by H. C. Brown and J. Muzzio, *J. Am. Chem. Soc.*, **88**, 2811 (1966), that additions to both monocyclic[18] and simple acyclic ketones are primarily controlled by product stability.

varies by less than 60 cal/mole in the range −70° to +35° (entries 8 and 28 in Table I). (e) The reliability and applicability of the calculated $G_A{}^{\neq} - G_B{}^{\neq}$ values may also be questioned. These values were calculated as follows. Considering sequences A and B,

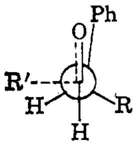


when R is methyl, $\Delta H_A{}^\circ$ is −800 cal/mole;[13] when R′ is isopropyl, $\Delta H_B{}^\circ$ is −400 cal/mole.[13] By using hydrogen as the reference, therefore, O ↔ Me is favored over O ↔ *i*-Pr by 400 cal/mole. The use of $\Delta H_A{}^\circ - \Delta H_B{}^\circ$ instead of $\Delta G_A{}^\circ - \Delta G_B{}^\circ$ values in Table I is justified.[13,19] It should be stressed, however, that (O ↔ R) − (O ↔ R′) might be different, when the groups R and R′ are in the same compound, from what it is when they are indirectly compared to hydrogen.

These criticisms notwithstanding, the usefulness of the model should not be denied. For example, the decrease in ratio A/B observed in IV as R increased from methyl to isopropyl is predictable, as the ratio does not depend on the relative magnitudes of R′ ↔ H and R′ ↔ R interactions, but on R ↔ O (XIII)

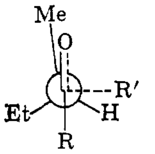


XIII

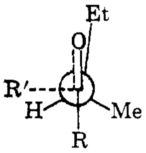


XIV

and Ph ↔ O (XIV). When R is methyl, (R ↔ O) − (Ph ↔ O) is about −600 cal/mole; when isopropyl, it is −200 cal/mole. Similarly, the ratio A/B in V is not controlled by the interactions of R′ with hydrogen and methyl, but by (Me ↔ O) (XV) − (Et ↔ O) (XVI).

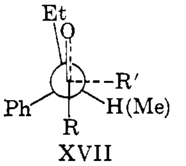


XV

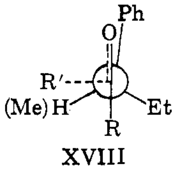


XVI

This difference being about −100 cal/mole, it is not surprising to be confronted with a case where the open-chain model fails to predict the major diastereomer. The puzzling observation that methyl competes against ethyl (VI) as effectively as hydrogen does (IV) is expected by considering XVII and XVIII. In both cases, the diastereomeric ratio is controlled by (Et ↔ O) − (Ph → O).

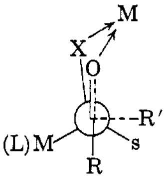


XVII

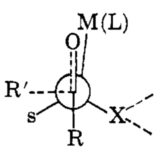


XVIII

Turning attention now to cases where a heteroatom is present at the asymmetric carbon, product stereospecificity will depend not only on the relative merits of X ↔ O (XIX) and M(L) ↔ O (XX) but also on the degree of stability imparted to XIX by pseudo-ring



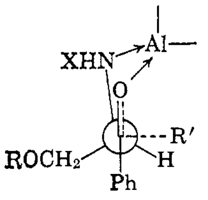
XIX



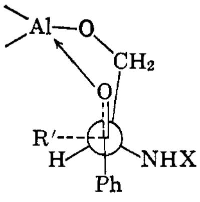
XX

formation. Furthermore, entropy differences will become prominent. It is not surprising, therefore, to find very high diastereomeric product ratios that are strongly susceptible to the polarity and nature of the solvent, to concentration and nature of reagent and added salt, and to the presence of agents capable of complexing with the metal.[23] The over-all high diastereomeric product ratios observed with reactions of this type, as—specifically—VIII, support further the credibility of the assumption that the diastereomeric transition states controlling product stereospecificity are those with the smallest group s closest to the incoming bulky group R′. Cases 15–18 constitute additional experimental support of this assumption.

The explanation advanced to rationalize the observed product stereospecificity in reactions of dehydrochloramphenicols,[24] *i.e.*, XXII is favored over XXI when R is hydrogen, is consonant with the proposed model.



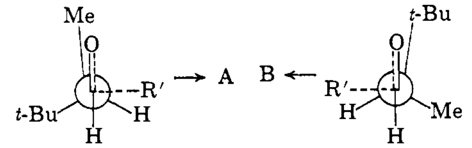
XXI



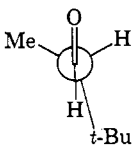
XXII

In the final analysis the usefulness of a model must be measured by its success in correctly predicting new results. The following two predictions might hopefully stimulate experimentation to test the reliability of the proposed model and the plausibility of its underlying assumptions.

From (Me ↔ O) − (*t*-Bu ↔ O) = −1100 cal/mole,[13] the diastereomeric product ration A/B [(XXIII) *vs.* (XXIV)] should be about 7–8. On the basis of the open-chain model XXV, there is no special reason to expect it to be other than 2–4.



XXIII XXIV



XXV

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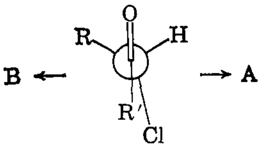
(23) These factors have been clearly and adequately discussed by Cram and Wilson in terms of competiton between the rigid and dipolar models.[2]

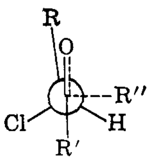
(24) J. Sicher, M. Svoboda, M. Hrdá, J. Rudinger, and F. Šorm, *Collection Czech. Chem. Commun.*, **18**, 487 (1953).

The diastereomeric product ratio A/B in XXVI is about 4/1 ($G_A^{\ddagger} - G_B^{\ddagger} = -800$ cal/mole) when R is methyl or ethyl.[5] On the basis of the dipolar model

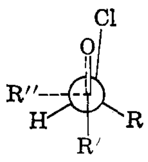


XXVI

XXVI this ratio should increase when R is changed to isopropyl or *t*-butyl. From consideration of XXVII and XXVIII, however, the opposite conclusion is reached. Since XXVII is experimentally favored over XXVIII by 800 cal/mole when R is methyl, it should be favored only by 400 cal/mole when R is isopropyl. The diastereomeric product ratio should therefore decrease from 4/1 to about 2.5/1. Even more striking is the case when R is *t*-butyl, as XXVIII should now be the more stable of the two by about 300 cal/mole. The major diastereomer should thus be B, the diastereomeric product ratio A/B being 0.5/1.



XXVII



XXVIII

Acknowledgment. The author thanks the National Science Foundation for a Senior Postdoctoral Fellowship, 1965–1966, and the Department of Chemistry, University of California, Berkeley, for its generous hospitality.

Equilibrium Constants and Substituent Effects in the Ionization of Aniline as a Base and the Ion-Pair Dissociation of Anilinium Acetate in Glacial Acetic Acid[1]

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Contribution from the Lecks Chemical Laboratories, Brandeis University, Waltham, Massachusetts 02154. *Received November 16, 1966*

Abstract: This paper shows that in the analysis of substituent effects, it is scientifically fruitful to divide base dissociation into two steps: ionization to form an ion pair, and dissociation of the ion pair into free ions. Equilibrium constants, K_i and K_d, for the separate steps are reported for a series of aromatic amines in acetic acid. For *meta*- and *para*-substituted anilines, substituent effects on K_i are typical of aromatic side-chain reactions: $\delta_R \log K_i$ is proportional to Hammett's σ. Substituent effects on K_d are qualitatively different from those on K_i but resemble those reported by others for K_d of quaternary ammonium salts in aprotic solvents. The relative ion-pair dissociating power of substituents is approximately alkyl or phenyl > methoxy or CH_3OCH_2 > haloalkyl or halogen. This paper also reports values of K_i and K_d for several N,N-dialkylanilines and for pyridine, and compares acetic acid and cyanoacetic acid as proton donors in ionization.

Glacial acetic acid is a good medium for the study of substituent effects on base strength in solution because one can measure separately the equilibrium constants for ionization (eq 1) and dissociation (eq 2).[2–5] In this paper we report measurements of both

$$B + HAc \rightleftharpoons B\cdot HAc \tag{1a}$$

$$B\cdot HAc \rightleftharpoons BH^+\cdot Ac^- \tag{1b}$$

$$K_i = [BH^+\cdot Ac^-]/([B] + [B\cdot HAc]) \tag{1c}$$

$$BH^+\cdot Ac^- \rightleftharpoons BH^+ + Ac^- \tag{2a}$$

$$K_d = [BH^+][Ac^-]/[BH^+\cdot Ac^-] \tag{2b}$$

K_i and K_d for a series of substituted anilines and pyridine. According to eq 1, K_i is a complex quantity since it depends on two equilibria, 1a and 1b. However, because HAc is the solvent, we may assume that the equilibrium in 1a lies far to the right, and K_i is then a close approximation to the equilibrium constant for the elementary proton transfer step, 1b. K_d is simply the equilibrium constant for the dissociation step, 2a.

We find for *meta*- and *para*-substituted anilines that $\log K_i$ varies linearly with the Hammett substituent constant σ,[6] with a correlation coefficient of 0.996. On the other hand, we find that $\log K_d$ is correlated only partially with σ; the correlation coefficient is 0.78. It follows, of course, that substituent effects on K_i are *not* analogous to those on K_d, and that the plot of $\log K_i$ *vs.* $\log K_d$ is *not* a linear free energy relationship.

We also find, from the effect of added cyanoacetic acid on the ionization of substituted anilines in acetic acid, that the relative basicity of acetate ion and cyanoacetate ion is quite close to the ratio of K_B for these carboxylate ions in water.[7]

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(1) This work was supported by the National Science Foundation under Grant GP-3921.

(2) I. M. Kolthoff and S. Bruckenstein, *J. Am. Chem. Soc.*, **78**, 1 (1956).

(3) S. Bruckenstein and I. M. Kolthoff, *ibid.*, **78**, 10 (1956).

(4) S. Bruckenstein and I. M. Kolthoff, *ibid.*, **78**, 2974 (1956).

(5) For a general theoretical discussion, see J. N. Brønsted, *Z. Physik. Chem.*, **A169**, 52 (1934).

(6) (a) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter 7; (b) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).