

to being mounted on a glass fiber, which in turn was transferred to a Nicolet R3m/V four-circle diffractometer (Mo K α , $\lambda = 0.71073 \text{ \AA}$), graphite monochromator). Unit cell parameters were determined from 15 well-centered reflections ($15^\circ < 2\theta < 22^\circ$); $a = b = 21.847(4) \text{ \AA}$, $c = 22.530(6) \text{ \AA}$, $V = 10780(5) \text{ \AA}^3$, and $Z = 16$. Axial photographs and a limited search through an octant of reciprocal space revealed systematic absences and symmetry consistent with the tetragonal space group $I4_1/a$ (No. 88). One octane of data ($+h, +k, +l$) was collected in the 2θ - θ scan mode with 2θ ranging from 3.0 to 45.0° . Scan speeds varied from 2.0 to $29.3^\circ/\text{min}$. A total of 7771 reflections were measured and corrected for Lorentz and polarization effects, but not for absorption. The minimum and maximum drift corrections (based on a set of three standards measured for every 37 reflections) were 0.9073 and 1.0065, respectively. Data processing yielded 3549 unique reflections, of which 1717 had $F > 4\sigma(F)$ with $R(\text{int}) = 0.0275$ for the averaging of equivalent reflections.

The structure was successfully solved by a combination of direct methods (XS:TREF) and Fourier techniques in the tetragonal space group $I4_1/a$ (No. 88), and refined by full-matrix least-squares. The non-hydrogen atoms were refined with anisotropic temperature parameters, hydrogen atoms were allowed to ride on their respective carbons [$C-H = 0.96 \text{ \AA}$, $U(H) = 0.08$], and a weighting scheme based on $\sigma(F)$ was employed. The coordinates of the amine and hydroxy H atoms H(1) and H(30) were free to vary. The final residuals were $R(F) = 0.0809$ and $R_w(F) = 0.0781$ with a value of 1.50 for the goodness of fit. The largest and mean $|\text{shift}/\text{esd}|$ in the final cycle were 0.001 and 0.000, and the minimum and maximum excursions in the final difference map were -0.43 and $0.53 \text{ e}/\text{\AA}^3$, respectively.⁹

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Registry No. 5, 135257-61-3; (Z)-6, 6313-26-4; (E)-7, 10496-80-7; 8, 135257-62-4; 9, 123209-01-8; 10, 91301-41-6; 11, 131266-01-8; 12, 72708-78-2; 13, 5860-38-8; 14, 135257-63-5; 15, 123271-58-9; 16, 72708-71-5; *cis*-17, 135257-64-6; 18, 135257-65-7; 19, 135257-66-8; 20, 135257-68-0; 21, 23340-29-6; 22, 98186-09-5; 23, 135257-69-1; 24, 135257-70-4; 25, 123209-00-7; (\pm)-26, 135257-71-5; PTAD, 15988-11-1; PhCO, 3469-17-8; PhCOCH₂Ph, 451-40-1; MeOCOCH₂COOMe, 108-59-8; PhCOCH₂COPh, 120-46-7; Meldrum's acid, 2033-24-1; dime-done, 126-81-8.

Supplementary Material Available: X-ray data for 14, 17, 20, and 26, figures listing the atomic numbering scheme, and tables for each compound, including (1) X-ray structure determination summary, (2) atomic positional parameters, (3) bond distances, (4) bond angles, (5) anisotropic temperature factors, and (6) hydrogen positional parameters (46 pages). Ordering information is given on any current masthead page.

Rate-Equilibrium Correlations for the Aldol Condensation: An Analysis in Terms of Marcus Theory

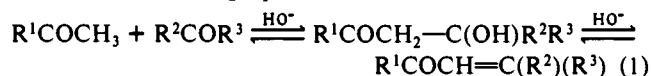
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Contribution from the Department of Chemistry, University of Western Ontario, London, Ontario, Canada N6A 5B7. Received November 13, 1990. Revised Manuscript Received May 28, 1991

Abstract: Both the addition and elimination steps of the intermolecular aldol condensation show approximate agreement with Marcus theory. The calculations are performed for reaction of an encounter complex of enolate and a carbonyl acceptor to give the alkoxide anion of the adduct for the addition reaction and of the enolate anion of the adduct to give the encounter complex of enone and hydroxide ion for the elimination reaction. The intrinsic barriers for these reactions are 13.89 ± 0.80 kcal/mol for the addition reaction and 14.13 ± 0.49 kcal/mol for the elimination reaction. Estimated equilibrium constants are used to predict rate constants for some simple aldol reactions. Large effects of polar substituents on the rates of aldol condensations can be predicted.

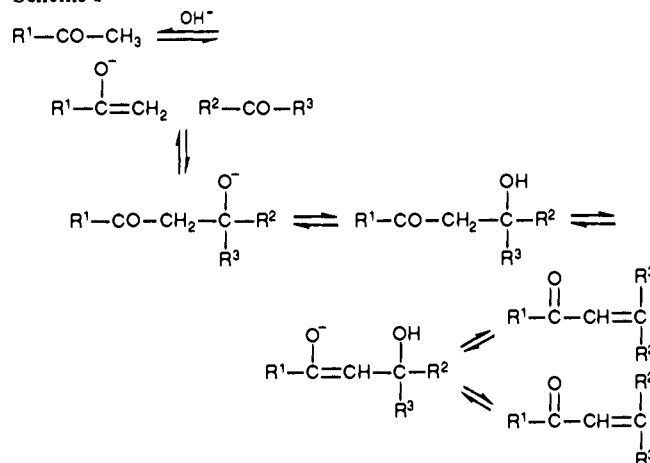
Introduction

The aldol condensation is an extremely important synthetic reaction, as witnessed by the entire volume of *Organic Reactions* required to review it.¹ There has been no method for making even semiquantitative predictions for the rates of the individual steps. Some years ago, we reported² equilibrium constants for a set of simple aldol condensations, eq 1, and demonstrated several methods for estimating equilibrium constants for these reactions.



We³⁻⁹ and others¹⁰⁻³² have carried out detailed analyses of the

Scheme I



kinetics of a series of simple aldol condensations, which now provide a solid basis for developing methods for predicting rates.

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Table I. Rate and Equilibrium Constants for Proton-Transfer Reactions of the Carbon Acids Discussed in this Paper^a

compd	pK _a ^b	k _{OH} ^c (M ⁻¹ s ⁻¹)	k _{H₂O} ^d (s ⁻¹)
CH ₃ CHO	16.73 ^e	1.17 ^f	628
CH ₃ COCH ₃	19.16 ^g	0.173 ^h	25006
CH ₃ COPh	18.24 ⁱ	0.244 ^j	4240

^a In aqueous solution at 25 °C. ^b K_a = [enolate][H⁺]/[keto tautomer], corrected for covalent hydration in the case of acetaldehyde. ^c Rate of hydroxide-catalyzed enolate formation. ^d Rate of protonation of the enolate by water; calculated from K_a and k_{OH}. ^e Reference 36. ^f Reference 36. ^g Reference 37. ^h Reference 73. ⁱ Reference 74. ^j Reference 38.

Table II. Oxygen pK_a Values for Aldol Adducts Discussed in this Paper^a

compound	pK _a ^b	log k _{OH} ^c	log k _{H₂O} ^d
(HCOCH ₂)CH ₂ OH	14.92	7.97	8.89
(HCOCH ₂)CH(CH ₃)OH	15.56	7.59	9.15
(HCOCH ₂)CH(Ph)OH	14.57	8.17	8.74
(HCOCH ₂)C(CH ₃) ₂ OH	16.21	7.19	9.40
(HCOCH ₂)C(CH ₃)(Ph)OH	15.22	7.79	9.01
(CH ₃ COCH ₂)CH ₂ OH	14.92	7.97	8.89
(CH ₃ COCH ₂)CH(CH ₃)OH	15.56	7.59	9.15
(CH ₃ COCH ₂)CH(Ph)OH	14.57	8.17	8.74
(CH ₃ COCH ₂)C(CH ₃) ₂ OH	16.21	7.19	9.40
(CH ₃ COCH ₂)C(CH ₃)(Ph)OH	15.22	7.79	9.01
(PhCOCH ₂)CH ₂ OH	14.54	8.19	8.73
(PhCOCH ₂)CH(CH ₃)OH	15.22	7.79	9.01
(PhCOCH ₂)CH(Ph)OH	14.23	8.37	8.59
(PhCOCH ₂)C(CH ₃) ₂ OH	15.87	7.40	9.27
(PhCOCH ₂)C(CH ₃)(Ph)OH	14.88	7.99	8.87

^a All in aqueous solution at 25 °C. ^b Calculated from the linear free energy relationship for pK_a of a trisubstituted carbinol in terms of the σ* values of the three substituents.^{44,45} σ* values used were as follows (all taken from ref 78): CH₃, 0.0; H, 0.49; Ph, 0.75; HCOCH₂, 0.62; CH₃COCH₂, 0.62; PhCOCH₂, 0.88 (estimated from σ* for PhCO, 2.2, with the fall-off factor of 0.4 recommended by Perrin et al.⁷⁸). ^c Calculated from the Eigen⁴⁶ model of preliminary formation of a hydrogen-bonded complex, followed by the actual proton-transfer step. Equilibrium constants for hydrogen-bonded complex formation were estimated according to the method of Stahl and Jencks,⁷⁵ and rate constants for the actual proton transfer were calculated from the Marcus³⁹ equation with an intrinsic barrier of 5 kcal/mol.⁴⁷ The rate constants for the overall proton-transfer processes were calculated with a steady-state solution to the Eigen model. ^d Rate constant for the re-protonation of the aldol anion by water, calculated from the Eigen⁴⁶ model.

In order to discuss the rate and equilibrium constants of the microscopic rate-determining step for aldol additions, i.e. the attack

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Table III. Rate and Equilibrium Constants for the Aldol Addition Step. Rate and Equilibrium Constants for Intramolecular Aldol Reactions^a

	carbonyl electrophiles			
	CH ₂ O	CH ₃ CHO	PhCHO	CH ₃ COCH ₃
σ*(R ²)	0.49	0.49	0.49	0.00
σ*(R ³)	0.49	0.00	0.75	0.00
(a) CH ₃ CHO as Carbon Nucleophile				
log K _{overall}	7.78 ^d	2.60 ^d	0.59 ^f	-0.40 ^d
log k _{obsd}	3.61 ^{c,d}	0.67 ^e	0.12 ^f	-1.37 ^d
log K _{micro} ^g	9.59	3.77	2.75	0.12
log k _{micro} ^h	6.34	3.40	2.85	1.36
log K ₂ ⁱ	11.36	5.54	4.52	1.89
log k ₂ ^j	8.11	5.17	4.62	3.13
b ^k	9.51	10.20	10.30	10.58
G ^l	12.99	13.93	14.08	14.48
(b) CH ₃ COCH ₃ as Carbon Nucleophile				
log K _{overall}	6.67 ^b	1.59 ^b	1.07 ^m	-1.41 ^b
log k _{obsd}	1.01 ^r	-1.88 ⁿ	-0.78 ^m	-1.74 ^o
log K _{micro} ^g	10.91	5.19	5.66	1.54
log k _{micro} ^h	6.17 ^r	3.28	4.38	3.42
log K ₂ ⁱ	12.68	6.96	7.43	3.31
log k ₂ ^j	7.97 ^r	5.05	6.15	5.19
b ^k		10.94	10.01	9.18
G ^l		14.94	13.67	12.54
(c) PhCOCH ₃ as Carbon Nucleophile				
log K _{overall}	5.74 ^b	0.65 ^b	0.63 ^p	-2.60 ^q
log k _{obsd}	1.39 ^r	-0.89 ^r	-0.08 ^p	-3.48 ^q
log K _{micro} ^g	9.40	3.67	4.64	-0.23
log k _{micro} ^h	5.63 ^r	3.35 ^r	4.16	0.76
log K ₂ ⁱ	11.17	5.44	6.41	1.54
log k ₂ ^j	7.44 ^r	5.16 ^r	5.93	2.53
b ^k			9.80	11.02
G ^l			13.39	15.05
av b	10.17 ± 0.58			
av G	13.89 ± 0.80			

^a In aqueous solution at 25 °C. All rate and equilibrium constants were calculated in terms of free carbonyl compounds; i.e., all are corrected for covalent hydration. ^b Reference 2. ^c Calculated from data in ref 31. ^d Reference 5. ^e Reference 3. ^f Reference 7. ^g Calculated from K_{overall}, pK_a of the adduct (Table II), and pK_a of the nucleophile (Table I). ^h Calculated from k_{obsd} and the pK_a of the nucleophile (Table I). ⁱ Equilibrium constant for reaction within the encounter complex. ^j Rate constant for reaction within the encounter complex. ^k Intrinsic barrier expressed in log rate constant units. ^l Intrinsic barrier expressed in kilocalories/mole. ^m Reference 8. ⁿ Calculated with k_{retroaldol}⁴ and K_{overall}. ^o Calculated with k_{retroaldol}¹⁶ and K_{overall}.^{2,17} ^p Reference 6. ^q Reference 9. ^r Estimated from the average intrinsic barrier, as described in the text.

of an enolate upon a carbonyl, we require pK_a values for the compound acting as the carbon nucleophile. Fortunately these are now available.³³⁻³⁸ We now wish to report an analysis of this reaction in terms of Marcus theory,³⁹⁻⁴¹ which permits the prediction of the rates of the carbon-carbon bond-forming step and the elimination step, for the particular case of hydroxide-catalyzed reactions in aqueous solution.

Results

Rate and equilibrium constants are now available for a set of nine aldol condensations.^{2-9,16-18,24,31} These data, for the overall observable reactions, must be corrected for pre- and postequilibria

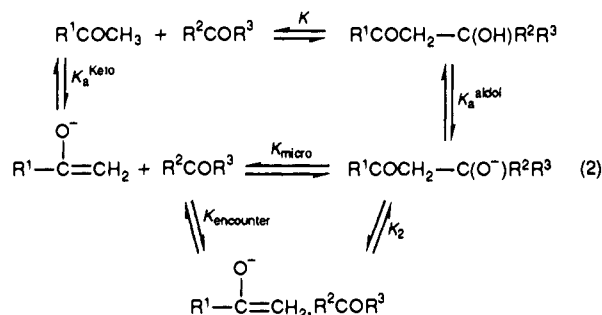
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to allow the microscopic rate and equilibrium constants for the process of interest to be extracted. The detailed analysis for the aldol condensation is carried out in terms of the generally accepted reaction mechanism⁴² shown in Scheme I.

The first step is hydroxide-catalyzed enolate formation; although this can be rate-limiting at high concentrations of carbonyl compounds with reactive acceptors such as acetaldehyde,⁴³ it is normally a fast preequilibrium. Good pK_a values are now available³⁶⁻³⁸ and are summarized in Table I, which also includes the rate constants for the proton-transfer reactions.

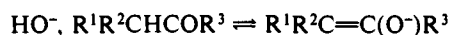
The third step is a proton transfer between alkoxide and hydroxide, which should be a very fast, diffusion-controlled process. The pK_a values are not known but can be estimated on the assumption that aldols behave as normal alcohols, with the acyl group acting only as an electron-withdrawing substituent, by using the linear free energy relationship that we have previously employed.^{44,45} The relevant calculations are summarized in Table II. For the sake of completeness we have also estimated rate constants for the proton-transfer reactions using the Eigen three-step model⁴⁶ for the proton-transfer process and an intrinsic barrier for the microscopic proton transfer of 5 kcal/mol.⁴⁷ As would have been expected, our analysis will show that protonation is invariably fast with respect to C-C bond cleavage for the initial alkoxide.

The rate and equilibrium constants for the second step can now be calculated from the data in Tables I and II and the apparent rate and equilibrium constants summarized in Table III, which also contains the microscopic rate and equilibrium constants for the second step. The calculations in Table III make use of the thermodynamic cycles in eq 2.



We have used work terms, i.e. equilibrium constants for $K_{encounter}$, estimated from the work of Hine,⁴⁸ assuming no stabilizing interactions between the two components, and two reactive positions, one on either side of the acceptor carbonyl.

Now we turn to the elimination phase of the aldol condensation. To begin the analysis, we need to estimate pK_a values for the aldols as carbon acids, i.e. for the process leading to the enolate that can expel hydroxide. We start by evaluating the intrinsic barrier to enolate formation for the process



using the latest data for rate and equilibrium constants.⁴⁹ We assume that the proton transfer involves proton abstraction by hydroxide in contact with the proton to be abstracted. In such an encounter complex, the hydroxide has necessarily lost one solvating water with negligible hydrogen bonding in return. We

have estimated⁵⁰ the energetic cost of this partial desolvation as 7.13 kcal/mol from the difference in pK_a between water and DMSO,⁵¹ which we assume to reflect the cost of losing three hydrogen bonds to the anion. This analysis leads to $b = 7.83$.

We then estimate the pK_a^K for the three parent aldols, $CHOCH_2CH_2OH$, $CH_3COCH_2CH_2OH$, and $PhCOCH_2CH_2OH$. We start with $CH_3COCH_2CH_2OH$. For $CH_3COCH_2CH_3$, $pK_a^E = 7.51$.⁴⁹ The pK_a^E is assumed to be the same as for cyclohexanone, for which the value is 11.70.⁴⁹ This assumes that incorporation into a six-membered ring makes no change in pK_a^E and that the effect of a remote alkyl group is negligible. Both assumptions appear reasonable. This gives us $pK_a^K = 19.21$ for $CH_3COC-H_2CH_3$. From the known rate of hydroxide-catalyzed enolate formation^{52,53} and the Marcus correlation we can estimate $pK_a^K = 20.07$, in good agreement. From the rate of hydroxide-catalyzed enolate formation for $CH_3COCH_2CH_2OCH_3$ (assumed to be the same as for $CH_3COCH_2CH_2OH$) and the Marcus correlation we obtain $pK_a^K = 16.64$ for $CH_3COCH_2CH_2OH$. This gives us a measure of the effect of a β -OH on the carbon acidity of a carbonyl compound, or $19.21 - 16.64 = 2.57$.

Turning now to $CHOCH_2CH_2OH$, we begin by estimating the pK_a^E for $CHOCH_2CH_3$ as the value for CH_3CHO ⁴⁹ corrected by the difference between the values for CH_3COCH_3 ⁴⁹ and cyclohexanone,⁴⁹ 0.76. In this way we obtain a value of 11.26 for the pK_a^E of $CHOCH_2CH_3$. We estimate the value of pK_a^E by correcting our previous thermochemical estimate of 3.9⁵⁴ by the average difference between thermochemical estimates⁵⁴ and measured values,⁴⁹ namely 1.0, thus obtaining $pK_a^E = 4.9$ for $CHOCH_2CH_3$. Combining these values we obtain $pK_a^K = 16.16$ for $CHOCH_2CH_3$. Assuming the same substituent effect for a β -OH as for $CH_3COCH_2CH_2OH$, we can now estimate $pK_a^K = 13.59$ for $CHOCH_2CH_2OH$.

Finally, for $PhCOCH_2CH_2OH$, we begin with the pK_a^K for $PhCOCH_2CH_3$, 17.56.⁵⁵ Assuming the same substituent effect for a β -OH as for $CH_3COCH_2CH_2OH$, we can now estimate $pK_a^K = 14.99$ for $PhCOCH_2CH_2OH$.

For the various aldols derived from the addition of acetaldehyde to simple carbonyl compounds there seem to be no serious steric interactions, and we have no basis for assuming significant effects on the pK_a of substituents at the β -carbon. We therefore use the same pK_a for all of these compounds.

For the aldols derived from the addition of acetone to simple carbonyl compounds, β -substituents can be expected to introduce crowding into the enolates. We assume that the enolates will be in the *E* configuration to minimize interference with solvation of the oxy anion. There is a distinct preference for a β -alkyl group to be trans to the oxygen even in enol ethers.⁵⁶ The oxygen of an enol ether acts as though it is only slightly smaller than a methyl group,⁵⁶ which suggests that an enolate oxygen would be larger than a methyl group. The magnitudes of these steric effects are taken from the strains observed for 2-pentene, 4-methyl-2-pentene, and 4,4-dimethyl-2-pentene. These in turn are calculated from the differences in the heats of formation of the *E* and *Z* isomers⁵⁷ as follows: 1.02 kcal/mol (0.75 in log *K*) for 2-pentene, 0.96 kcal/mol (0.70 in log *K*) for 4-methyl-2-pentene, and 3.87 kcal/mol (2.83 in log *K*) for 4,4-dimethyl-2-pentene. The difference relative to 2-pentene gives the correction to the carbon pK_a relative to the formaldehyde adduct. The strain correction deduced for the interaction of *cis*-methyl and isopropyl is used for the interaction of methyl and $CH(CH_3)(OH)$ and for methyl and $CH(OH)(Ph)$. The strain correction deduced for the in-

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Table IV. Rate and Equilibrium Constants for Enolate Formation from the Aldols^a

compound	p <i>K_a</i> ^b	log <i>K</i> ^c	log <i>K</i> ₂ ^d	log <i>k</i> ₂ ^e	log <i>k</i> _{corr} ^f	log <i>k</i> _{deprot} ^g	log <i>k</i> _{reprot} ^h
CHOCH ₂ CH ₂ OH	13.67	0.03	7.02	8.08	1.09	1.39	1.06
CHOCH ₂ CH(Me)OH	13.67	0.03	7.02	8.08	1.09	1.39	1.06
CHOCH ₂ CH(Ph)OH	13.67	0.03	7.02	8.08	1.09	1.39	1.06
CHOCH ₂ C(Me) ₂ OH	13.67	0.03	7.02	8.08	1.09	1.39	1.06
MeCOCH ₂ CH ₂ OH	16.64	-2.94	4.05	6.85	-0.14	0.16	2.80
MeCOCH ₂ CH(Me)OH	16.59	-2.89	4.10	6.88	-0.11	-0.19	2.78
MeCOCH ₂ CH(Ph)OH	16.59	-2.89	4.10	6.88	-0.11	-0.19	2.78
MeCOCH ₂ C(Me) ₂ OH	18.72	-5.02	1.97	5.91	-1.08	-0.78	3.94
PhCOCH ₂ CH ₂ OH	14.99	-1.29	5.70	7.55	0.56	0.86	1.85
PhCOCH ₂ CH(Me)OH	15.09	-1.39	5.60	7.51	0.52	0.82	1.91
PhCOCH ₂ CH(Ph)OH	15.09	-1.49	5.50	7.47	0.48	0.78	1.97
PhCOCH ₂ C(Me) ₂ OH	17.34	-3.64	3.35	6.54	-0.45	-0.14	3.20

^aAll in aqueous solution at 25 °C. ^bp*K_a* for enolate formation from the keto tautomer, estimated as described in the text. ^cLogarithm of the equilibrium constant for the reaction of hydroxide with the keto tautomer to give the enolate. ^dLogarithm of the equilibrium constant for the reaction of the encounter complex of the keto tautomer and hydroxide to give the enolate. ^eLogarithm of the rate constant per hydrogen for the reaction of the encounter complex of the keto tautomer and hydroxide to give the enolate, estimated with the Marcus correlation for monocarbonyl compounds with *b* = 7.83, as described in the text. ^fLogarithm of the rate constant per hydrogen for the reaction of hydroxide with the keto tautomer to give the enolate. ^gLogarithm of the rate constant for hydroxide-catalyzed deprotonation of the free carbonyl compound to give the enolate. ^hLogarithm of the rate constant for reprotonation of the enolate by water to give the free carbonyl compound.

Table V. Rate and Equilibrium Constants for the Elimination Step of the Aldol Condensation^a

compound	p <i>K_a</i> ^b	log <i>K</i> _{dehyd} ^c	log <i>k</i> ^d	log <i>K</i> _{micro} ^e	log <i>k</i> _{micro} ^f	log <i>K</i> _{conf} ^g	log <i>K</i> ₂ ^h	log <i>k</i> ₂ ⁱ	<i>b</i> ^j	\bar{G}^k
CHOCH ₂ CH ₂ OH	13.67	-0.49 ^l	-1.01 ^l	-0.82	-1.34	0.16	-7.65	-1.17	9.77	13.34
CHOCH ₂ CH(Me)OH	13.67	0.50 ^m	-0.96 ^m	0.17	-1.29	0.00	-6.82	-1.29	10.39	14.19
CHOCH ₂ CH(Ph)OH	13.67	2.89 ⁿ	0.20 ⁿ	2.56	-0.13	0.01	-4.42	-0.12	10.59	14.46
CHOCH ₂ C(Me) ₂ OH	13.67	0.87 ^a	-1.60 ^a	0.54	-1.93	0.85	-5.60	-1.08	10.89	14.88
MeCOCH ₂ CH ₂ OH	16.64	-1.37 ^p	-3.10 ^p	1.27	-0.46	0.08	-5.64	-0.37	10.16	13.87
MeCOCH ₂ CH(Me)OH	16.59	-0.85 ^r	-3.39 ^r	1.74	-0.80	0.17	-5.08	-0.62	10.39	14.19
MeCOCH ₂ CH(Ph)OH	16.59	1.38 ^t	-2.14 ^t	3.97	0.45	0.17	-2.85	0.62	10.34	14.12
MeCOCH ₂ C(Me) ₂ OH	18.72	-1.20 ^u	-5.12 ^u	3.52	-0.40	2.59	-0.88	2.19	9.78	13.36
PhCOCH ₂ CH ₂ OH	14.99	-0.36 ^v	-1.76 ^v	0.63	-0.77	0.45	-5.91	-0.32	9.94	13.57
PhCOCH ₂ CH(Me)OH	15.09	-0.80 ^v	(-2.58) ^x	0.29	(-1.49) ^p		-6.10	(-0.74) ^p		
PhCOCH ₂ CH(Ph)OH	15.19	1.40 ^y	-1.59 ^y	2.59	-0.40	0.71	-3.69	0.32	10.32	14.09
PhCOCH ₂ C(Me) ₂ OH	17.34	-1.01 ^z	-4.51 ^z	2.33	-1.17	3.40	-1.27	2.22	10.28	14.04

av *b* 10.34 ± 0.36

av \bar{G} 14.13 ± 0.49

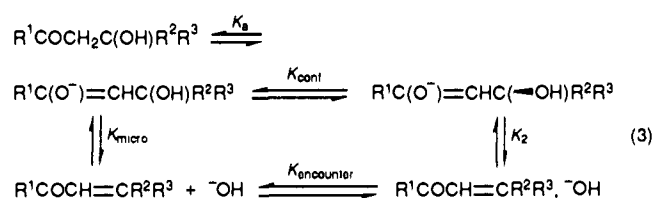
^aAll in aqueous solution at 25 °C; rate and equilibrium constants are expressed in terms of free carbonyl compounds, i.e. corrected for covalent hydration. ^bp*K_a* for enolate formation, estimated as described in the text. ^cEquilibrium constant for dehydration, $R^1COCH_2C(OH)R^2R^3 \rightleftharpoons R^1COCH=CR^2R^3 + H_2O$. The standard state for water is the pure liquid, at unit activity. ^dSecond-order rate constant for dehydration, catalyzed by hydroxide ion. ^eEquilibrium constant for dehydration of the enolate ion, $R^1C(O^-)=CHC(OH)R^2R^3 \rightleftharpoons R^1COCH=CR^2R^3 + HO^-$. ^fRate constant for dehydration of the enolate ion. ^gEquilibrium constant for the change from the minimum energy conformation of the enolate to the conformation with the C-OH bond orthogonal to the plane of the enolate. ^hEquilibrium constant for dehydration of the enolate ion to form an encounter complex of enone and hydroxide, $R^1C(O^-)=CHC(OH)R^2R^3 \rightleftharpoons R^1COCH=CR^2R^3, HO^-$. ⁱRate constant for dehydration of the enolate ion to form an encounter complex of enone and hydroxide. ^jIntrinsic barrier, expressed in units of log (rate constant). ^kIntrinsic barrier, expressed in units of kilocalories/mole. ^lReference 30, as corrected in ref 5. ^mReference 3. ⁿReference 7. ^oReference 5. ^pReferences 2 and 76. ^qCalculated from the equilibrium constant and the rate constant for hydration.¹⁵ ^rReference 2. ^sReference 4. ^tReference 8. ^uReference 77. ^vCalculated from the equilibrium constant and the rate constant for hydration.¹⁵ ^wCalculated from the equilibrium constant and the rate constant for hydration.³² ^xEstimated assuming that the average value of *b* applies to this reaction, as described in the text. ^yReference 6. ^zReference 9.

teraction of *cis*-methyl and *tert*-butyl is used for the interaction of methyl and C(CH₃)₂(OH) and for methyl and C(CH₃)(OH)(Ph).

A similar approach is taken for the aldols derived from the addition of acetophenone to simple carbonyl compounds. From the difference in heats of formation of the *E* and *Z* isomers of 3,3-dimethyl-1-phenyl-1-butene⁵⁸ we derive a strain correction of 7.79 kcal/mol (5.70 in log *K*). This is larger than the methyl-*tert*-butyl strain correction but smaller than the *tert*-butyl-*tert*-butyl strain correction.⁵⁸ It may be larger than the enolate-*tert*-butyl strain, but we have no basis for deciding at this time. No data appear to be available for 1-phenyl-1-butene or 3-methyl-1-phenyl-1-butene, so we use the difference in steric energy between *cis* and *trans* isomers, calculated by MM2⁵⁹ as 4.58 kcal/mol (3.35 in log *K*) for 1-phenyl-1-butene and 4.72 kcal/mol (3.45 in log *K*) for 3-methyl-1-phenyl-1-butene. Mo-

lecular mechanics calculations reproduce the *tert*-butyl-*tert*-butyl and *tert*-butyl-phenyl strains quite reasonably: *t*-Bu-Ph, calculated value 8.91 kcal/mol, experimental⁵⁸ 7.79 kcal/mol; *t*-Bu-*t*-Bu calculated 9.93 kcal/mol, experimental⁵⁸ 10.49 kcal/mol. The difference relative to 1-phenyl-1-butene gives the correction to the carbon p*K_a* relative to the formaldehyde adduct. In this way the values for p*K_a*^K in Table IV were obtained.

The rate and equilibrium constants for the fifth step can now be calculated from the apparent rate and equilibrium constants as summarized in Table V. The calculations in Table V make use of the detailed reaction scheme in eq 3. In calculating the



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microscopic rate and equilibrium constants for this process, we need no work term for the starting material, since we have a

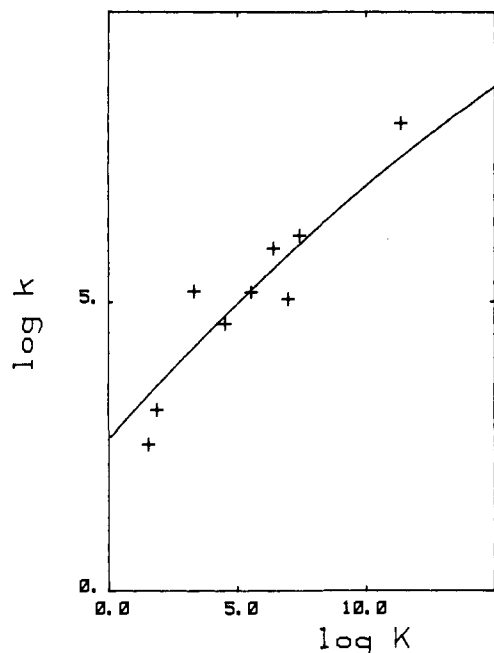


Figure 1. Marcus plot of data for the aldol addition step. The line is calculated with $b = 10.17$.

unimolecular reaction except for any conformational energy cost in going from the most probable conformation to one that has the hydroxyl group properly oriented for elimination. This conformational cost was estimated from MM2⁵⁹ calculations. First the minimum energy structure for the enolate was calculated, and then the C–OH bond was constrained to be perpendicular to the plane of the enolate and the energy was re-minimized. The difference in conformational energy was taken as the conformational cost of attaining the initial state for reaction. These values are included in Table V. The main contribution to the work term for the products comes from the way the hydroxide created in this step is generated in contact with the enone; hence the hydroxide must be missing one solvating water. The energetic cost of partially desolvating a hydroxide ion was estimated as already described. Rate and equilibrium constants incorporating these corrections are included in Table V.

We can now search for rate and equilibrium correlations in terms of Marcus theory.^{39–41} This theory predicts a relationship of the form $\Delta G^\ddagger = \bar{G}(1 + \Delta G^\circ/4\bar{G})^2$, where ΔG^\ddagger and ΔG° refer to reaction within an encounter complex, i.e. to K_2 and k_2 in the above analysis, and \bar{G} is the intrinsic barrier, the activation energy that would be obtained if ΔG° were zero. This equation can be expressed equally well in terms of rate constants, becoming at 25 °C

$$\log k_2 = 12.79 - b[1 - (\log K_2/4b)] \quad (4)$$

$$b = 0.5(0.5 \log K + 12.79 - \log k) \pm ((0.5 \log K + 12.79 - \log k)^2 - (\log K)^2/4)^{1/2}$$

where b is the intrinsic barrier expressed in units of $\log k$.

For the aldol addition step, rate and equilibrium constants are satisfactorily described by Marcus theory, as shown in Figure 1. Intrinsic barriers calculated for each reaction from eq 4 with $\log k_2$ and $\log K_2$ values are included in Table III. All of the reactions for which kinetics data are available are described by an intrinsic barrier of 13.82 ± 0.80 kcal/mol. We have inverted the calculation in order to fill in the gaps in Table III with estimated rate constants for the reactions not yet studied.

Similarly, the rate and equilibrium constants for the elimination step are satisfactorily correlated by Marcus theory, as shown in Figure 2. All of the reactions for which both rate and equilibrium data are available are described by an intrinsic barrier of 14.13 ± 0.49 kcal/mol. We have inverted the calculation in order to fill in the gaps in Table V with estimated rate constants for the reactions not yet studied.

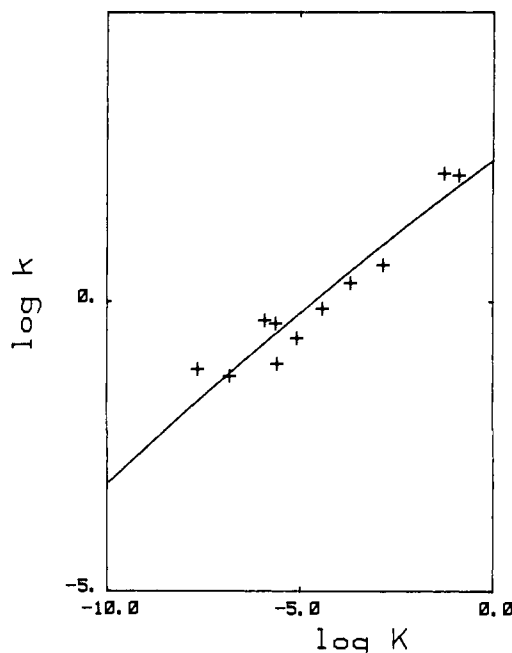


Figure 2. Marcus plot of data for the aldol elimination step. The line is calculated with $b = 10.34$.

Table VI. Equilibrium Constants for Additions to Trifluoroacetophenone^a

nucleophile	$\log K^d$	γ^b
H ₂ O	1.89	-3.58
H ₂ O ₂	1.40	-0.64
HCN	2.88	2.44
HSO ₃ ⁻	3.36	4.02
BuNH ₂	2.00	-0.25
NH ₂ OH	3.17	1.24
NH ₂ NH ₂	3.30	0.81
CH ₃ CHO	(2.54) ^c	0.45
CH ₃ COCH ₃	(2.47) ^c	0.16
CH ₃ COPh	(2.44) ^c	0.05

^a Experimental equilibrium constants from ref 61, most are in 10% acetonitrile–90% water, at 25 °C. ^b γ is a measure of the tendency of a nucleophile to add to a carbonyl compound;⁶⁰ values are from ref 2 and 60. ^c Estimated from the correlation line defined by the other data. ^d $\log K = (2.43 \pm 0.58) + (0.24 \pm 0.10)\gamma$.

There are many aldol condensations where it would be helpful to be able to estimate rates by the Marcus relation if only equilibrium constants could be obtained. This is frequently difficult because of the shortage of thermochemical data for disproportionation calculations and the difficulty of performing direct measurements of equilibrium constants. We wish now to explore in a preliminary fashion an alternative indirect way of estimating equilibrium constants for aldol additions. This makes use of the γ values, first proposed by Sander and Jencks,⁶⁰ to measure the tendency of a nucleophile to add to a carbonyl compound. γ is defined by

$$\gamma = \log (K_{\text{nuc}}/K_{\text{MeNH}_2})_{\text{py-4-CHO}} \quad (5)$$

where K_{nuc} is the equilibrium constant for addition of a nucleophile to pyridine-4-carboxaldehyde.

From the linear correlation of equilibrium constants for addition of nucleophiles to trifluoroacetophenone⁶¹ with γ values for the

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Table VII. Predicted Rate Constants for Reactions with Trifluoroacetophenone^a

compd	pK_a (ketone) ^b	pK_a (aldol) ^c	$\log K^d$	$\log K_{\text{micro}}^e$	$\log K_2^f$	$\log k_2^g$	$\log k_{\text{micro}}^h$	$\log k^i$
CH ₃ CHO	16.73	11.78	2.54	7.49	9.26	6.53	4.76	2.03
CH ₃ COCH ₃	19.16	11.78	2.47	9.85	11.62	7.41	5.64	0.48
CH ₃ COPh	18.24	11.43	2.44	9.25	11.02	7.19	5.42	1.18

^aAll in aqueous solution at 25 °C; rate and equilibrium constants are expressed in terms of free carbonyl compounds, i.e. corrected for covalent hydration. ^bAcid dissociation constant for the carbon nucleophile, Table I. ^cAcid dissociation constant for the adduct, estimated as in Table II. ^dOverall equilibrium constant, expressed in terms of neutral reagents and products. ^eCalculated from $\log K$, the pK_a of the adduct, and the pK_a of the nucleophile. ^fEquilibrium constant for reaction within the encounter complex. ^gRate constant for reaction within the encounter complex. ^hRate constant for reaction of the enolate of the nucleophile to give the anionic adduct. ⁱOverall third-order rate constant for hydroxide-catalyzed aldol condensation.

nucleophiles⁶⁰ and the γ values for acetaldehyde, acetone, and acetophenone as carbon nucleophiles,² we can estimate equilibrium constants for aldol additions to trifluoroacetophenone. These calculations are summarized in Table VI.

From these equilibrium constants we can estimate rate constants for the aldol additions and eliminations. These rate constants are found in Table VII, which summarizes the calculations involved in the estimation procedure.

Discussion

Marcus initially derived his theory relating rate and equilibrium constants for electron-transfer reactions⁶⁷ and later extended it to atom transfers.⁶⁸ Hine⁴⁸ and others^{47,63} showed that data for electrophile–nucleophile combination reactions fit the same pattern. The present paper provides yet further examples of such behavior. Although empirical observation is running well ahead of theoretical justification, it seems that Marcus theory captures a deep and general feature of chemical reactivity, possibly extending to most if not all classes of reactions.

Although the use of Marcus theory has been challenged,⁶² it has also had considerable empirical success for reactions well-removed from the electron-transfer processes for which it was derived.^{39–41,47,48,63} Ritchie's objections⁶² to the use of Marcus theory for electrophile–nucleophile combination reactions are based on the absence of any identity reaction that can be used to define two independent contributions to the intrinsic barrier, as can be done for electron-transfer, atom-transfer, or group-transfer reactions. This is a valid point, but it does not rule out the use of Marcus theory. Even for classes of reactions where there are identity reactions, the fact that to date there is no way to calculate intrinsic barriers a priori means that contributions to the intrinsic barrier derived from identity reactions are purely empirical quantities. As Marcus pointed out,⁶⁸ the intrinsic barrier can be "assumed constant as a conjecture for a reaction series when the substituent is not part of the reaction site". The success of the correlations illustrated by Figures 1 and 2, combined with the success of similar correlations, validates the conjecture and indicates that Ritchie's conclusions⁶² "that attempts to use the Marcus equations for electrophile–nucleophile combination reactions are completely without foundation" are overstated. Nonetheless it must not be forgotten that without definable identity reactions the application of Marcus theory requires the assumption of a constant intrinsic barrier for a set of "similar" reactions, and the validity of this assumption must be confirmed for each such application.

The major problem limiting the use of Marcus theory is that there is relatively little knowledge about the origins of the intrinsic barrier. Although it has been argued that the intrinsic barrier arises largely from solvation,⁴⁷ the observation of intrinsic barriers for gas-phase reactions^{64,65,66} demonstrates that structural reorganization within the reacting molecules also contributes in an important way.

We have shown that Marcus theory correlates rate and equilibrium constants for both steps of the intermolecular aldol condensation for a variety of compounds spanning much of the likely

normal range for these quantities. As we have shown,² acetaldehyde, acetone, and acetophenone have very similar properties as carbon nucleophiles, as measured by the γ values. It is not known how much the equilibrium properties of carbon nucleophiles could be increased by substituent variation, so there may be greater variability to be discovered here. If so, the span of possible rate and equilibrium constants might be expanded. Few carbonyl compounds are more reactive than formaldehyde, and it becomes difficult to study, or even carry out, simple aldol condensations with compounds much less reactive than acetophenone.⁶⁹

All of the available rate–equilibrium data points for the aldol addition step are in accord with an intrinsic barrier of $b = 10.17 \pm 0.58$ ($\bar{G} = 13.89 \pm 0.80$ kcal/mol). The available rate–equilibrium data points for the aldol elimination step are in accord with an intrinsic barrier of $b = 10.34 \pm 0.36$ ($\bar{G} = 14.13 \pm 0.49$ kcal/mol). The existence of these rate–equilibrium correlations means that, provided equilibrium constants can be obtained, it will be possible to make useful estimates of the rate constants for novel aldol reactions. Since experimental measurement of these rate constants is often difficult, this should prove a useful method.

In order to have the elimination occur, there is a stereoelectronic requirement that the C–OH bond be aligned with the p orbital of the π system of the enolate; this requires an unavoidable steric compression when the OH is tertiary.⁵ If we simply used k_2 and K_2 values calculated from observed values by correcting for the pK_a of the aldol and the work term for product complex formation, then the apparent intrinsic barriers were distinctly larger for aldols derived from addition to acetone. MM2⁵⁹ calculations give the strain energies shown in Table V and lead to satisfactory agreement with a single value for the intrinsic barrier.

The Marcus correlations that we have found, and which we suggest can be used to estimate rate constants for aldol condensations, refer to steps 2 and 5 as rate-determining steps. We must consider when proton-transfer processes might become rate-limiting. It is known that at high acetaldehyde concentrations (greater than 0.5 M) the self-condensation of acetaldehyde is first-order in acetaldehyde with deprotonation as the rate-limiting step,^{24,70} and at high formaldehyde concentrations the rate-determining step for the condensation of acetaldehyde with formaldehyde is no longer first-order in formaldehyde.³⁰ The situation with formaldehyde is potentially confusing because the observed reaction rate for a given total hydroxide concentration is lowered both by change in the rate-determining step and by the consumption of hydroxide by deprotonation of formaldehyde hydrate.^{30,70} As a further complexity, formaldehyde hydrate anion could act as a general base catalyzing the condensation.³⁰ In fact, once one has corrected for the decrease in hydroxide concentration resulting from deprotonation of formaldehyde hydrate, the observed rate is linear in formaldehyde concentration up to at least 0.4 M.^{5,31}

One might ask why formaldehyde, which is more reactive than acetaldehyde, shows less tendency for there to be a change in the rate-determining step from carbon–carbon bond formation to proton transfer? Although free formaldehyde is markedly more reactive than free acetaldehyde, only one part in approximately

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2000 of formaldehyde is present in the reactive form, most being present as the unreactive hydrate, while half the acetaldehyde is in the free form. If, from the data in Table III, we calculate the rate constant for enolate reacting with the total aldehyde, the values of $\log k$ are 3.02 for formaldehyde and 3.10 for acetaldehyde. For comparison, the rate constant for reprotonation of acetaldehyde enolate is given as $\log k = 2.80$ (Table I). Thus, we expect formaldehyde to show simple behavior up to slightly higher concentrations than acetaldehyde, even though it is inherently more reactive!

Other condensations with formaldehyde will be expected to be similarly prone to changes in the rate-determining step. Most other carbonyl compounds will be less acidic than acetaldehyde and so will have faster reprotonation rates, but they will also be more powerful nucleophiles and so have faster rates of attack on formaldehyde. For acetophenone the reprotonation is governed by $\log k = 3.60$, while our predicted rate of addition is governed by $\log k_{\text{micro}} = 7.42$ (expressed in terms of free formaldehyde) or $\log k = 4.10$ expressed in terms of total formaldehyde. The situation is clearly similar to that for reaction of acetaldehyde with formaldehyde, and the rate-determining step should change at high concentrations. Similar conclusions result for acetone.

Our predictions for aldol additions to trifluoroacetophenone indicate that the expected rate constants are larger than the corresponding rate constants for acetophenone; for the reaction of acetone with trifluoroacetophenone the observable rate constant is predicted to be $4.5 \text{ M}^{-1} \text{ s}^{-1}$, and the microscopic rate constant for reaction of acetone enolate with trifluoroacetophenone is predicted to be $6.5 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$. By contrast, for the reaction of acetone with acetophenone⁷¹ we find that the observed rate

constant is $3.2 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ and the calculated microscopic rate constant is $47 \text{ M}^{-1} \text{ s}^{-1}$. Thus, the polar substituent has led to a large increase in the rate as well as a large increase in the equilibrium constant. Recently, Thornton et al. have reported studies of the effect of polar substituents on the relative rates of aldol condensations.⁷² For the condensation in diethyl ether of the solvent of the enolate of pinacolone with 1,3-dimethoxyacetone or acetone, they report a relative rate of 3.0×10^4 , favoring the ketone with the electron-withdrawing groups. The closest comparison is with our k_{micro} values, where we found a rate ratio of 1.4×10^4 . Since the σ^* value for CF_3 is 2.61, which is significantly greater than twice the σ^* value for CH_3OCH_2 , i.e. $2 \times 0.66 = 1.32$, this appears anomalous. There is likely to be a solvent effect favoring reaction in ether because the transition state will have less concentrated charge than the initial or final states and so will be selectively favored in the less polar solvent. Both our predictions and Thornton's experimental results agree that there are large rate effects to be obtained from substitution by polar groups near the reaction centers for the aldol condensation.

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Ips0 Substitution of Triarylvinyl Cations by Alkoxide Anions

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Abstract: Photolysis and solvolysis of triaryl bromoethanes **1** in the presence of alkoxide anions in alcohols resulted in significant formation of products derived from ipso substitution by alkoxide anions. Photolysis of 1-aryl-1-bromo-2,2-diphenylethenes **1Aa** and **1Ab** with 10 mol equiv of alkoxide anions gave 1-alkoxy-1-aryl-2,2-diphenylethenes **2A** and 3,3-dialkoxy-6-(2,2-diphenylvinylidene)-1,4-cyclohexadienes **3A** (ipso adducts). However, the photolysis with weak bases such as TEA, pyridine, NaHCO_3 , and K_2CO_3 did not give ipso adducts **3A** but only enol ethers **2A**. Interestingly, photolysis of 2,2-bis(*p*-alkoxyphenyl)-1-bromo-1-phenylethenes **4a** and **4b** with NaOEt in ethanol afforded ipso adducts **6a** and **6b**, respectively, which had a 1,2-aryl-rearranged structure. Furthermore, solvolysis of 1-bromo-1-(*p*-methoxyphenyl)ethenes **1Aa**, **1Ba**, and **1Ca** in ethanol containing 10 mol equiv of NaOEt at 120–130 °C for 1–3 days provided *p*-ethoxyphenyl-substituted enol ethers **2bb**, *p*-ethoxyphenyl-substituted bromoethenes **1b**, and *p*-methoxyphenyl-substituted enol ethers **2ab**, respectively. The major formation of *p*-ethoxyphenyl-substituted compounds (ipso-substituted products) suggests that there is no large difference in ipso substitution between vinyl cations generated by photolysis and solvolysis. On the basis of the results obtained above the factors affecting ipso attack on arylvinyl cations are discussed.

Ips0 substitution at an aromatic ring has been focused on destabilized benzylic cations which bear electron-withdrawing groups on the α carbon.¹ The electron-withdrawing groups increase the electron demand of the cationic center toward the aromatic ring and cause the charge delocalization of the aromatic

ring. Such delocalization is favorable for ipso substitution.

On the other hand, it is impossible, in α -arylvinyl cations, to introduce the electron-withdrawing group onto the α carbon because there are no bonds displaced at the α carbon. Also introduction of electron-withdrawing groups onto the β position does not accelerate the formation of arylvinyl cations² but causes vinylic substitution via addition-elimination mechanism.^{2,3} A strong

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