Solvolysis in Carboxamides. VII.[1] Carboxamide Solvolysis of *threo*-2-Aryl-1-methylpropyl Brosylates. Reactivity-Selectivity Relationships as a Mechanistic Probe

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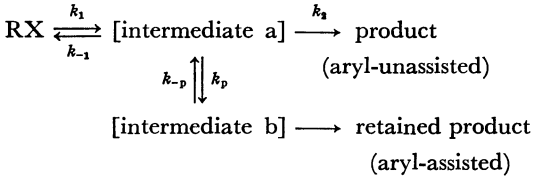
Solvolysis of a series of *threo*-2-aryl-1-methylpropyl brosylates (*p*-MeO, *p*-Me, H, *p*-Cl, *m*-Cl, *m*-CF_3, and *p*-NO_2; **1a**—**g**) has been carried out in four carboxamides, *N*-methylformamide (NMF), *N*-methylacetamide (NMA), *N*,*N*-dimethylformamide (DMF), and *N*,*N*-dimethylacetamide (DMA), as solvent. Fractions of k_s and Fk_Δ pathway were determined on the basis of the upward drift from the Hammett plot of the rate constant (k_t); the extra acceleration by *p*-MeO and *p*-Me substituents was assigned to the Fk_Δ fraction. The Fk_Δ/k_t values were not in agreement with the amount of retained products (*threo*-acetate and *threo*-alcohol) obtained in NMA and DMA solvolysis of **1a**—**c**, although they should be in line with each other on the basis of the bridged-ion theory. The C(2)-deuterated phenyl derivative (**1c**-2-*d*) was solvolyzed in NMF, NMA, and DMF to give retained carboxylates (acetate or formate). However, the isotope scrambling at C(2) and C(1) of the carboxylates is incomplete, indicating that a symmetrical ion, such as a phenyl-bridged ion, can not be the intermediate of the carboxamide solvolysis. A good correlation of log k_t for substrates (**1a**—**g**) with log (% *threo*-acetate/% *erythro*-acetate) or with log (% *threo*-acetate/% olefinic products) was found for solvent systems such as NMA, DMA, and acetic acid, indicating that the reactions of all substituted substrates can be explained by intervention of a common intermediate [R^+X^-], a classical tight ion-pair from which the final products are derived. Such reactivity-selectivity relationship also holds between log k_t's of **1c** in a series of carboxamide and logarithms of *threo*-*erythro* ratio in acetate or formate. Through-space interaction between a face of aryl ring and carbenium ion center in the transition state is considered as a possible cause for the anomalous acceleration by the activating aryl groups.

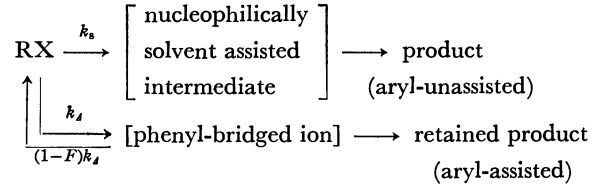
Although a phenyl-bridged ion has been postulated as an intermediate in acetolysis of diastereomeric 2-aryl-1-methylpropyl tosylates accounting for remarkably high stereospecificity of the substitution,[2] the rate enhancement expected in such participation phenomena is not significant in this system.[3] This apparent discrepancy between rate and product stereochemistry has long been a subject of dispute.[4–16]

Brown and Kim[7a] carried out acetolysis of a series of ring substituted *threo*-1-methyl-2-phenylpropyl brosylates and found that this system displays excellent rate-(retained)product correlation. They pointed out that the nature of the k_s pathway in the acetolysis can be recongnized as S_N1 mechanism, and proposed the following mechanism (Scheme 1)[7a] in which the reaction proceeds *via* a tight ion-pair followed by k_p and k_2 processes, denoting aryl-assisted and aryl-unassisted pathways, respectively.



Scheme 1.

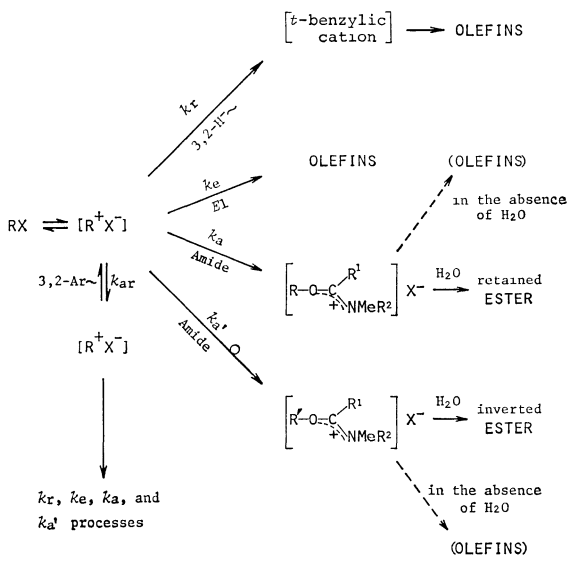
Schleyer and his collaborators[6] suggested that solvolysis of all primary and most of secondary β-arylalkyl systems proceeds through discrete aryl-assisted (k_Δ) and/or aryl-unassisted, *i.e.*, nucleophilically solvent-assisted (k_s), pathways (dual mechanism, Scheme 2).[6h] They considered the rate enhancement due to activated phenyl groups to result from the incursion of the k_Δ process with a phenyl-bridged ion, and the substrate containing a deactivated phenyl group to be a good model for the anchimerically unassisted route (k_s). They showed that the values of Fk_Δ/k_t determined independently from the rate data and product stereochemistry (rate-product correlation) are in agreement with each other for several β-arylalkyl solvolyses.[4]



Scheme 2.

In our effort to scrutinize the nature of carboxamide solvolysis of secondary substrates,[1,17–20] it was found that solvolysis of *threo*-1-methyl-2-phenylpropyl brosylate (**1c**)[20] and that of its *p*-methoxyphenyl derivative (**1a**)[1] in *N*,*N*-dimethylacetamide (DMA) are represented respectively by 100% k_s and 83% k_Δ (17% k_s) solvolysis in the k_Δ-k_s dissection method.[6] However, on the basis of the lack of rate-product correlation, and from an examination of deuterium distribution in the reaction products or unchanged starting brosylates and the nature of the olefinic products, it was disclosed that the solvolysis of these 1-methyl-2-phenylpropyl systems proceeds without intervention of a phenyl-bridged ion but a classical tight ion-pair intermediate, subsequent processes such as *E*1 reaction, phenyl- or hydride-shift, and solvent capture occurring competitively (Scheme 3).[1,20]

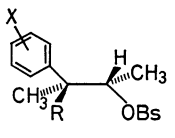
In order to obtain further information on such mechanism, we extended the investigation to a series of ring substituted *threo*-1-methyl-2-phenylpropyl brosylates (**1a**—**g**) and other carboxamide solvents such as



Scheme 3.

N-methylformamide (NMF), *N*-methylacetamide (NMA), and *N,N*-dimethylformamide (DMF).

The present paper describes the results of the examinations of the Hammett correlation for the solvolysis of **1a**—**g** in NMF, NMA, and DMF as solvent, the product distribution in NMA and DMA solvolyses, deuterium distribution in the products for NMF, NMA, and DMF solvolyses of C(2)-deuterated parent phenyl derivative (**1c**-2-*d*), and the reactivity-selectivity relationships. The mechanistic implications of the results, especially in the light of classical solvolysis mechanism, are also discussed.



1a R=H, X=*p*-MeO
1b R=H, X=*p*-Me
1c R=H, X=H
1c-2-*d* R=D, X=H
1d R=H, X=*p*-Cl
1e R=H, X=*m*-Cl
1f R=H, X=*m*-CF_3
1g R=H. X=*p*-NO_2

Results and Discussion

Unsatisfactory Rate-product Correlation. First-order rate constant (k_t) for the respective carboxamide solvolyses (NMF, NMA, and DMF) of the substrates **1a**—**g** have been determined titrimetrically.[19,20] The results are summarized in Table 1. The Hammett plot for each carboxamide solvolysis, including DMA solvolysis,[1,20] is given in Fig. 1.

A satisfactory linear correlation holds solely for the substrates containing deactivating and, partly, activating phenyl groups with ρ-values, —0.69, —0.64, —0.57,

Table 1. Kinetic data for the solvolysis of *threo*-2-aryl-1-methylpropyl brosylates **1a**—**g** in various carboxamides

Amide	Substituent	$10^5 k_t$/s^{-1}[b]				$\frac{\Delta H^{\ddagger}}{A}$[c]	$\frac{\Delta S^{\ddagger}}{B}$[d]
		25.0 °C[e]	50.0 °C	75.0 °C	100.0 °C		
DMF	*p*-MeO	0.327	6.25	78.1		21.3	−11.7
	p-Me	0.0187		7.64	84.4	24.2	−8.2
	H	0.0138		4.79	49.5	24.1	−11.0
	p-Cl	0.00794		2.81	29.3	24.2	−11.9
	m-Cl	0.00764		2.65	27.4	24.1	−12.2
	m-CF_3	0.00622		2.48	27.1	25.1	−10.7
	p-NO_2	0.00372		1.63	18.5	25.4	−10.4
NMA	*p*-MeO	1.15[f]	25.7	371		23.2	−3.2
	p-Me	0.0575	1.78	33.6		25.7	−1.0
	H	0.0381	1.06	18.1		24.8	−4.7
	p-Cl	0.0205		8.92	101	24.4	−7.1
	m-Cl	0.0192		8.26	93.1	24.4	−7.4
	m-CF_3	0.0170		7.07	78.7	24.3	−8.1
	p-NO_2	0.00875		4.13	48.3	24.8	−7.7
NMF	*p*-MeO	3.27[f] 13.0[g]	72.3	1020		23.1	−1.6
	p-Me	0.246	6.49	107		24.4	−2.2
	H	0.0735	2.17	38.5		25.1	−2.3
	p-Cl	0.0399		16.3	180	24.2	−6.7
	m-Cl	0.0267	0.743	12.8		24.8	−5.3
	m-CF_3	0.0245	0.680	11.7		24.8	−5.5
	p-NO_2	0.0155		6.79		24.4	−7.8
				3.95[h]	29.8[i]		

a) [ROBs]=0.075 mol/dm^3; [C_5H_5N]=0.077 mol/dm^3; [H_2O]=0.003 (for DMF), 0.01 (for NMA), or 0.02 (for NMF) mol/dm^3. b) Mean deviations for k_t's are ±2%. c) At 25.0 °C; A=4.184 kJ/mol. d) At 25.0 °C; B=4.184 J/K mol. e) Extrapolated from data at other temperatures. f) Determined at 25.0 °C. g) Determined at 35.0 °C. h) Determined at 70.0 °C. i) Determined at 90.0 °C.

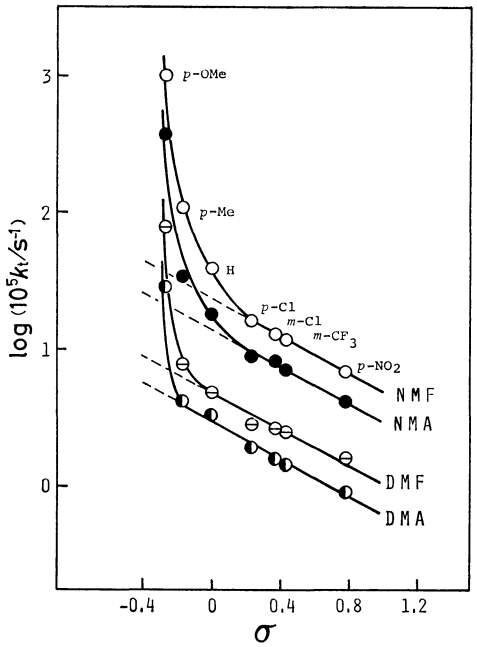


Fig. 1. Plot of log k_t (**1a**—**g**) for the carboxamide solvolysis *vs.* σ at 75 °C; ρ-value and correlation coefficient for DMA, DMF, NMA, and NMF are −0.72 and 0.991, −0.57 and 0.974, −0.64 and 0.986, and −0.69 and 0.999, respectively; for the rate constant in DMA, see Ref. 20.

Table 2. Effect of aryl participation on the rate of solvolysis of *threo*-2-aryl-1-methylpropyl brosylates at 75 °C

Substrate	Amide	Rate const/10^{-5} s^{-1}		$100Fk_\Delta$[c] / k_t
		k_t[a]	k_s[b]	
1a (OCH_3)	DMA[d]	28.8	4.77	83
	DMF	78.1	6.17	92
	NMA	371	19.6	95
	NMF	1020	35.5	97
1b (CH_3)	DMA[d]	4.15	4.15	0
	DMF	7.64	5.43	29
	NMA	33.6	16.9	50
	NMF	107	30.4	72
1c (H)	DMA	3.34	3.34	0
	DMF	4.79	4.79	0
	NMA	18.1	13.2	27
	NMF	38.5	23.2	40

a) Data in Table 1. b) Calculated from the least-squares line (k_s line) in Fig. 1. c) $Fk_\Delta = k_t - k_s$. d) See Ref. 20, Table 1.

and −0.72, respectively, for NMF, NMA, DMF, and DMA solvent. Such linear portions of the Hammett plot give the k_s values for **1a**—**c** by the least-squares treatment, from which the predicted amounts of retained product arising from the so-called k_Δ route was calculated by $100Fk_\Delta/k_t$, where $Fk_\Delta = k_t - k_s$. The results are given in Table 2.

The rate-(retained)product correlation is used as a probe for the dual mechanism concept and the phenyl-bridged ion intervention.[6] However, there are cases in which the agreement between the predicted and observed values is less satisfactory.[4,7] Acetolysis of a series of *threo*-2-aryl-1-methylpropyl brosylates has provided a representative example in which the agreement between the predicted and observed values is excellent.[7a]

Table 3. Comparison of the predicted and observed amounts of retained product arising from the carboxamide solvolysis of *threo*-2-aryl-1-methylpropyl brosylates at 75 °C

Substrate	Amide	Retained product yield/%	
		Predicted	Obsd
1a (OCH_3)	DMA[c]	83	67
	NMA[d]	95	91
1b (CH_3)	DMA[d]	0	16
	NMA[d]	50	43
1c (H)	DMA[e]	0	4
	NMA[d]	27	13

a) See Table 2. b) Amounts of sum of *threo*-acetate and *threo*-alcohol. c) Ref. 1. d) See Table 5. e) Ref. 20.

When the correlation was examined on the NMA and DMA solvolysis (Table 3), the results were far less satisfactory, a gap between predicted and observed values clearly existing. This suggests that a dual mechanism (Scheme 2) can not be applied to the carboxamide solvolysis; the mechanism shown in Scheme 3, postulated for the DMA solvolysis of **1a**[1] or **1c**,[20] is applicable to the NMA solvolysis and the other carboxamide solvolysis in NMF and DMF.

Incomplete Scrambling of Deuterium in the Products of Carboxamide Solvolysis of **1c**-2-d. In order to test whether Scheme 3, which does not need the intervention of the phenyl-bridged ion, can serve as a generalized reaction scheme in carboxamide solvolysis, the deuterium distribution in the products of the NMF, NMA, and DMF solvolysis of **1c**-2-*d* was examined by means of ^{1}H NMR spectroscopic method.[20] The results are summarized in Table 4.

Although the amounts of the retained products, *i.e.*, the sum of *threo*-ester and *threo*-alcohol, increase in the order NMF>NMA>DMF>DMA[20] in accord with the order of increase in the amount of Fk_Δ component (Table 2), the deuterium label is situated more at position C(2) than C(1) in the retained *threo*-1-methyl-2-phenylpropyl acetate or formate. This indicates that a symmetrical intermediate such as a phenyl-bridged ion is ruled out as a precursor of the retained products.

Linear Reactivity-Selectivity Relationship in Carboxamide Solvolysis. The product distribution, rearrangement, and steric course in carboxamide solvolysis can not be explained by means of the k_Δ-k_s rate treatment.[1,20] The linear reactivity-selectivity relationship[21] in the solvolysis of a series of substrates in a series of solvents has been utilized to prove the existence of a common intermediate which produces more than two products.[22] The relationship was examined for a series of the 1-methyl-2-phenylpropyl system (**1a**—**g**) independent of the k_Δ-k_s analysis.[6]

When the log k_t values are plotted against the

Table 4. Isotope distribution in the products for the carboxamide solvolysis of *threo*-1-methyl-2-phenylpropyl-2-*d* brosylate at 75 °C[a]

Product	Yield/% (Composition/%)			
	DMA[c]	DMF	NMA	NMF
Butene:				
(*Z*)-2-Ph-2- (3-H: 3-D)	54.9(82: 18)	43.5(75: 25)	43.0(74: 26)	35.5(70: 30)
(*E*)-2-Ph-2- (3-H: 3-D)	8.6(64: 36)	5.8(57: 43)	5.3(53: 47)	4.9(48: 52)
3-Ph-1- (3-D: 2-D)	6.7(100: ≈0)	7.1(87: 13)	6.2(83: 17)	4.2(80: 20)
2-Ph-1- (3-D,H: 3-H_2)	5.1(100: ≈0)	4.9(100: ≈0)	5.2(100: ≈0)	5.9(100: ≈0)
Ester:[d]				
erythro-1-Me-2-Ph-propyl (2-D: 1-D)	21.0(87: 13)	26.3(82: 19)	22.9(80: 20)	17.3(75: 25)
threo-1-Me-2-Ph-propyl (2-D: 1-D)	3.7(65: 35)	6.6(60: 40)	16.5(55: 45)	23.2(53: 47)
Alcohol:[e]				
erythro-3-Ph-2-butanol	trace	4.1	0.5	3.6
threo-3-Ph-2-butanol	0	1.7	0.4	5.4[f]

a) [**1c**-2-*d*]=0.075 mol/dm³; [C_5H_5N]=0.077 mol/dm³; [H_2O]=0.17 mol/dm³. b) Accuracy for NMR measurement of isotopic content was ≤1%; reproducibility=±3%. c) Ref. 20. d) Acetate for DMA or NMA and formate for DMF or NMF. e) Deuterium distribution not determined unless otherwise noted. f) The ratio 3-D: 2-D=55: 45.

Table 5. Rates and product distributions for the DMA and NMA solvolysis of *threo*-2-aryl-1-methylpropyl brosylates at 75 °C[a]

Substrate	Amide	k_t[b] / 10^{-5} s^{-1}	Product yield/%			
			Olefins	Acetate		Alcohol
				erythro	*threo*	
1a	DMA[c]	28.8	29.7	2.6	60.1	7.6
	NMA	371	8.6	0.3	79.4	11.7[e]
1b	DMA	4.15	72.0	10.4	13.4	4.2
	NMA	33.6	48.3	6.7	35.5	9.5[f]
1c	DMA[d]	3.34	83.2	13.3	2.4	1.1
	NMA	18.1	62.3	18.6	9.8	9.3[g]
1d	DMA	1.90	—	(87.6	12.4)[h]	—
1e	DMA	1.59	—	(89.4	10.6)[h]	—
	NMA	8.26	68.9	28.9	1.1	1.1[i]
1f	DMA	1.44	72.5	25.2	1.5	0.8[i]
	NMA	7.07	70.9	28.5	0.6	trace
1g	DMA	0.916	71.0	28.5	0.5	trace
	NMA	4.13	68.3	31.5	0.2	trace

a) [ROBs]=0.075 mol/dm³; [C_5H_5N]=0.077 mol/dm³; [H_2O]=0.17 for DMA and 0.34 mol/dm³ for NMA. b) See Table 1 for NMA; Ref. 20 for DMA. c) Ref. 1. d) Ref. 20. e) *threo*: *erythro*=99.6: 0.4. f) *threo*: *erythro*=81.4: 18.6. g) *threo*: *erythro*=44.1: 55.9. h) Isomer composition. i) Isomer composition not determined.

logarithms of the ratio (% yield of the retained acetate: % yield of the inverted acetate) or (% yield of the retained acetate: % yield of the olefinic products) for the DMA or NMA solvolysis of a series of *threo*-2-aryl-1-methylpropyl brosylates, a good reactivity-selectivity relationship was found. The results are shown in Figs. 2.1, 2.2 with use of the data in Table 5.

The linear relationships observed between log k_t and log (% *threo*-ROAc/% olefin) suggest that such processes as k_a, k_r, and k_e, (Scheme 3) result from a single intermediate [R^+X^-]. The proposed classical *E*1-S_N1 competition mechanism is substantiated from the carboxamide solvolysis.

An examination of these treatments was also carried out for the log k_t's of the acetolysis of a series of *threo*-2-aryl-1-methylpropyl brosylates using the data of Brown and Kim.[7a] As in the case of the DMA or NMA, solvolysis, excellent linear relationships were observed (Fig. 3), indicating that even for the acetolysis, in which the rate-(retained)product correlation satisfactorily holds the reaction proceeds through a single intermediate, the open ion-pair (Scheme 1).

When the log k_t values of the brosylate **1c** in a series of amide solvents are plotted against the logarithm of the ratio (% yield of the retained ester: % yield of the inverted ester), an excellent linear relationship is observed (Fig. 4, correlation coefficient=0.990). Pertinent data for the test are given in Table 6.

On the basis of this linear relationship, it is deduced that both the retained and inverted esters stem from a

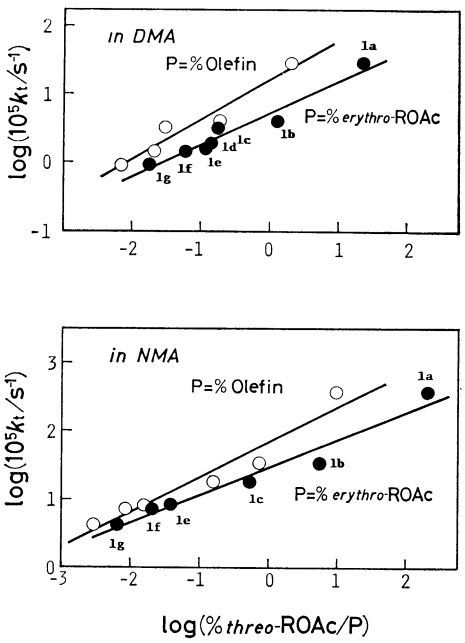


Fig. 2. Linear reactivity-selectivity relationship between log k_t and log (% *threo*-acetate/% *erythro*-acetate) or log (% *threo*-acetate/% olefin) for the DMA (upper) and NMA (bottom) solvolyses of *threo*-2-aryl-1-methylpropyl brosylates at 75 °C; correlation coefficient=0.976 (P=% *erythro*-acetate, DMA), 0.970 (P=% olefin, DMA), 0.981 (P=% *erythro*-acetate, NMA), and 0.969 (P=% olefin, NMA).

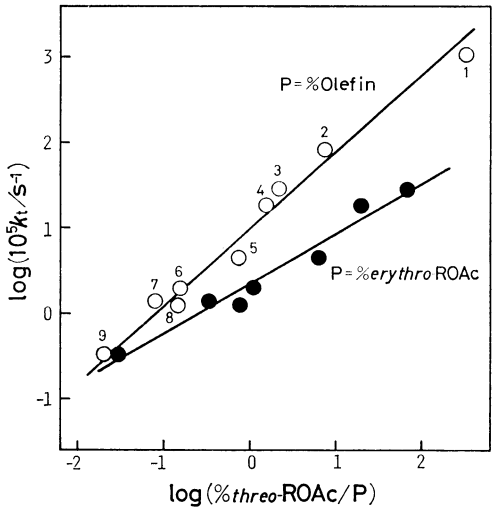


Fig. 3. Linear reactivity-selectivity relationships between log k_t and log (% *threo*-acetate/% *erythro*-acetate) or log (% *threo*-acetate/% olefin) for the acetolysis of *threo*-2-aryl-1-methylpropyl brosylates at 75 °C (data from Ref. 7a); 1=**1a**, 2=**1b**, 3=*m*-MeC_6H_4- derivative, 4=**1c**, 5=**1d**, 6=**1e**, 7=**1f**, 8=*p*-$CF_3C_6H_4$- derivative, and 9=**1g**; correlation coefficient=0.982 (P=% *erythro*-acetate) and 0.991 (P=% olefin).

single solvolytic species, a tight ion-pair intermediate, as shown in Scheme 3. The *threo*-type imidatonium ion (retained), which leads to *threo*-ester by hydrolysis, is formed by the front-side attack of the carboxamide on the tight ion-pair. A front-side solvent capture may

Table 6. Solvolysis rates and retention/inversion ratios for the carboxamide solvolysis of *threo*-1-methyl-2-phenylpropyl brosylate **1c** at 75 °C

Amide	$\frac{k_t}{10^{-5}\,s^{-1}}$ [a]	Yield of *threo* ester[b]	Ratio $\left(\frac{\text{retention}}{\text{inversion}}\right)$
DMA[c]	3.34	2.4%	0.179
DMF[d]	4.79	4.5%	0.251
NMA[e]	18.1	9.8%	0.526
NMF[d]	38.5	19.9%	1.18

a) See Table 1. b) Acetate for DMA or NMA and formate for DMF or NMF. c) Ref. 20. d) The solvolysis was conducted under the same conditions as those described in Ref. 20. e) See Table 5.

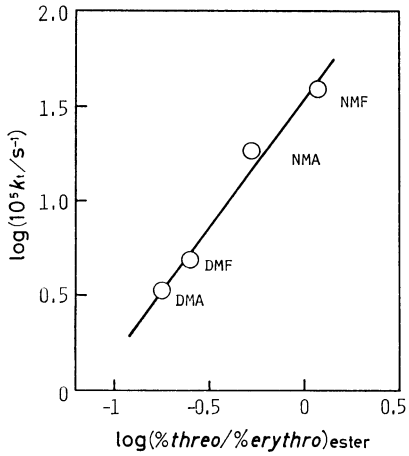


Fig. 4. Linear reactivity-selectivity relationship between log k_t and log (% *threo*-ester/% *erythro*-ester) for the carboxamide solvolysis of **1c** at 75 °C; correlation coefficient=0.990.

have an advantage over a rear-side solvent capture when the rate of 2,1-phenyl migration becomes fast enough to shield the rear-side effectively. Thus, as the selectivity increases on going from DMA solvolysis to NMF solvolysis (Table 6), the extent of deuterium scrambling in the ester products becomes greater (Table 4). This might explain why the DMF solvolysis produces retained ester in a larger amount with more scrambling of the deuterium label than the DMA solvolysis (Table 4). The dual mechanism (Scheme 2) gives no explanation.

Possible Origin of the Rate Enhancement. From a kinetic point of view, there is another mechanistic feature for the solvent effect on the carboxamide solvolyses. When the log k_t values for the NMF, NMA, and DMF solvolysis, or the acetolysis[7a] of a series *threo*-2-aryl-1-methylpropyl brosylates **1a**—**g** are plotted against those for the DMA solvolysis,[20] satisfactory linear free-energy relationships are observed (Fig. 5): correlation coefficients are 0.988, 0.997, 0.995, and 0.971, respectively.

If the observed titrimetric rate constant (k_t) is represented by the sum of two independent processes, k_s and Fk_Δ, no such linear correlation would hold. Consequently, the deviation of the points for the

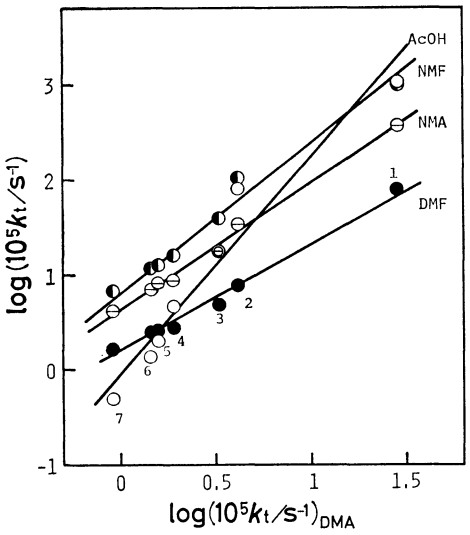
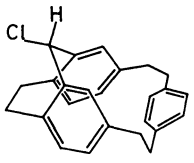


Fig. 5. Linear free-energy relationships between log k_t (DMA) and log k_t (DMF (●), NMA (⊖), NMF (◐), or AcOH (○)) for **1a**—**g** (1=**1a**, 2=**1b**, 3=**1c**, 4=**1d**, 5=**1e**, 6=**1f**, and 7=**1g**) at 75 °C; slope and correlation coefficient are 1.11 and 0.995 (DMF), 1.29 and 0.997 (NMA), 1.47 and 0.988 (NMF), and 2.27 and 0.971 (AcOH); for the rate constants in DMA and AcOH, see Refs. 20 and 7a, respectively.

substrates containing activating phenyl groups in the Hammett plot (Fig. 1) should be attributed to cause other than the intrusion of the Fk_Δ component and of the phenyl-bridged ion.

According to Tabushi *et al.*,[23] the remarkable rate enhancement is observed in the solvolysis of pseudo-axial system of [2.2.2]paracyclophane derivative (**2**) in which the developing carbenium ion center can advantageously interact with the face of benzene ring through space; solvolysis rate of the pseudo-axial substrate was accelerated by a factor of $10^{14.7}$ as compared with corresponding pseudo-equatorial substrate. The same type of interaction, therefore, might be operative between the β-aryl group and the carbenium ion center. The proposal is, however, qualitative. Confirmation of the cause of the deviation in the Hammett plot (Fig. 1) would be achieved by a precise estimation of the intrinsic magnitude of such a transannular interaction between the individual β-aryl group and a p-orbital of the cationic carbon in the transition state.



2

In conclusion, the mechanism which formulates the initial ionization as formation of tight ion-pair (open or classical), followed by a variety of competing processes (k_r, k_e, k_a, k_a', and k_{ar} pathways, Scheme 3), can explain the results of carboxamide solvolysis. This is essentially the same as that proposed by Brown *et al.*[5b] No intervention of a phenyl-bridged ion is necessary for the carboxamide solvolysis.

Experimental

The four carboxamides were purified in the same way as described.[18] The substrates **1a**—**g** and **1c**-2-*d* were the products from the same lot employed in the previous work; product analysis and deuterium distribution analysis were performed in the same manner as reported.[20] Kinetic measurements were carried out following the method described previously.[19]

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