

THE ENTHALPY-ENTROPY RELATIONSHIP IN ORGANIC REACTIONS*

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The previously developed statistical treatment of the isokinetic relationship was applied to 100 reaction series involving kinetics as well as equilibria; the variable factor was mostly substituent or solvent. An approximately valid linear enthalpy-entropy relationship was found in 78 cases, which include also the series with constant enthalpy or constant entropy; in 14 cases the validity of the relationship remained undecided. The isokinetic relationship is thus a common phenomenon in series of related reactions, it is not restricted to some special conditions, in particular not to reactions in solution. Nevertheless, it seems to be fulfilled more precisely if the reactions in the series are closely related, as for instance in a Hammett series.

The isokinetic temperature β may acquire all possible values, positive or negative, only those near to the experimental temperature are rare and have been actually proven in but several cases. Theories requiring β to have some particular values are thus clearly disproved. In particular many values of β claimed in the literature, which are virtually identical with the experimental temperature, are artifacts of an incorrect statistical treatment.

The linear relationship between activation (reaction) enthalpy and activation (reaction) entropy in a series of related reactions,

$$\Delta H = h_0 + \beta \Delta S, \quad (1)$$

is called isokinetic relationship (IKR) and is of fundamental importance in structure-reactivity correlations¹⁻³, thermodynamics of pure compounds⁴ and of solutions⁵, catalysis⁶, and biochemistry⁷. The apparently simple equation (1) imposes statistical problems we dealt with in the previous communications⁸⁻¹⁰. The heart of the matter is the *a priori* dependence of the two correlated quantities, ΔH and ΔS , as far as they have been obtained from the same set of data, *viz.* from temperature dependence of rate (equilibrium) constants.** In this case there is a general and un-

* Part V in the series Statistics of the Enthalpy-Entropy Relationship; Parts I-IV: see ref.⁸⁻¹¹.

** All the considerations of this paper relate to this experimental approach; in addition it is assumed that the Arrhenius law holds exactly. Another possibility consists in determining ΔH^0 calorimetrically; it was analyzed in Part III of this series¹¹.

objectionable statistical model which may be represented as a family of Arrhenius lines in the coordinates T^{-1} , $\log k$; equation (1) is then equivalent to the constraint of a common point of intersection (β^{-1} , y_0). This condition reads:

$$\log k_{ij} = y_0 + b_i(T_j^{-1} - \beta^{-1}). \quad (2)$$

Finding the least-squares values of β^{-1} , y_0 and of the slopes b_i is a non-trivial problem, which was solved exactly in a special case⁸ and numerically in the general case⁹. Still more important and more difficult is the decision whether the IKR is valid or not.

These questions were dealt with in some detail in preceding communications⁸⁻¹⁰ while in the present paper the developed mathematical treatment is applied to a set of hundred organic reactions. Previous treatments neglected the dependence of correlated quantities, hence the results obtained are of no significance; this concerns in particular the values of the constant β – the isokinetic temperature. In fact, the IKR is a unique example in the history of science that – due to an improper statistical model – a great many results were accumulated disagreeing completely with the original experimental facts³. The material presented in this paper represents the first available assembly of valid data and firstly offers the possibility to test experimentally some previous theories concerning the generality^{5,12-16} of IKR, its occurrence in relation to the extrathermodynamic relationships^{17,18}, possible values of the isokinetic temperature^{5,12,18-20}, *etc.*

RESULTS

The reactions series investigated are listed in Table I. The data were taken mostly from recent literature, the selection was made with respect to the experimental accuracy, number of reactions, variance of reactivity, number of measurements at different temperatures, and temperature interval. Several reactions were also included which did not comply with some of these criteria but were interesting from another point of view (special conditions, unusual value of β , theoretically important reaction). Attention was also paid to reaction series already discussed in the literature. In but few cases some entries were excluded from the set, the reasons are indicated in notes to Table I.

The data were processed using two programs. In the „special case”, entries for each temperature and each reaction are available, *i.e.* with l reactions and m temperatures there are on the whole $N = lm$ entries. The calculation of all the constants is based on the algebraical solution of the normal equations⁸; there is always a single solution and the values obtained are exact. In the “general case” there are l reactions, m_i entries in each, or the whole $N = \sum m_i$ entries. The value of β is determined by successive approximation⁹; once this is known, all other constants are obtained unambiguously, but β itself is often rather uncertain. Cases with two solutions are mathematically possible but cannot occur among real examples. In practice there is no difference between the results of the two programs and in Table I they were not distinguished. All the experimental values in a given series have been given the same weight for the reasons outlined previously⁹. As to the possible use of weighted data, see ref.⁹; another refinement using a non-linear dependence of $\log k$ on T^{-1} was dealt with in ref.¹⁰.

Table I
Validity (V) of the Isokinetic Relationship in Selected Reaction Series

Reaction	Variable ^a ΔT^b	I N	Standard deviations ($\cdot 10^3$)		β K	ψ α^c	V
			s_0 (s_{00})	s_R s_T			
			Equilibria				
1. pK 's of benzoic acids ^{22,d}	HS	9	3	356	-40 ^e	0.079	+
	15 ^d	36	(2)	5		0.10	
2. pK 's of anilines ²³	S	22	7	1 310	-938	0.018	+
	20	110	(7)	112		>0.25	
3. pK 's of 3,5-disubstited anilines ²⁴	HS	6	7	1 527	-961	0.012	+
	45-50	64	(3)	210		<0.005	
4. pK 's of nitroanilines ²⁵	S	12	89	3 356	-1 740	0.090	+
	65	60	(96)	274		>0.25	
5. pK 's of N-anisylidene anilines ²⁶	HS	6	34	757	91	0.076	+
	35	24	(23)	270		0.1	
6. pK 's of N-benzylidene-4-methoxyanilines ²⁶	HS	6	36	1 275	-39 ^e	0.062	+
	35	24	(39)	263		>0.25	
7. pK 's of hydrogen bonded phenols ²⁷	ST	7	20	1 001	-331	0.050	+
	20-25	43	(14)	160		0.05	
8. pK 's of pyridines ^{28,29}	S	11	33	2 640	3 670 ^g	0.046	+
	40-67	63	(18)	195		<0.005	
9. pK 's of dinitromethanes ³⁰	ST	15	25	1 121	-261	0.060	+
	28	30	f	149		f	
10. pK 's of cyanoacetic acids ³¹	ST	4	27	69	259	0.38	-
	40	36	(7)	76		<0.005	
11. $\text{OH}^- +$ triarylcarbonium cations ³²	HS	6	36	676	803 ^g	0.10	+
	30	24	(25)	211		0.25	
12. $\text{CH}_2\text{O} +$ dinitromethanes ^{33,h}	S	9	31	556	491	0.10	+
	40	36	(35)	174		>0.25	
13. $\text{CH}_2\text{O} +$ dinitromethanes ^{33,h}	S	14	61	1 661	1 880 ^g	0.10	+
	40	56	(32)	213		<0.005	
14. trinitrobenzene complexes of sulphoxides ^{34,i}	ST, SO	5	43	131	404 ^g	0.30	-
	20	15	(8)	64		<0.005	
15. trinitrobenzene complexes of sulphoxides ^{34,i}	ST, SO	6	87	1 051	238	0.19	?
	20	18	(92)	187		>0.25	
16. H bonds of H_2O with amides ³⁵	ST	10	38	140	243	0.28	-
	30	40	(36)	128		>0.25	

TABLE I (continued)

Reaction	Variable ^a ΔT^b	<i>l</i> <i>N</i>	Standard deviations ($\cdot 10^3$)		β K	ψ α^c	<i>V</i>
			<i>s</i> ₀ (<i>s</i> ₀₀)	<i>s</i> _R <i>s</i> _T			
Kinetics							
17. ionization of H-bonded phenols ²⁷	ST	7	32	1 201	-234 ^e	0.093	+
	20-25	43	(23)	101		0.05	
18. recombination of H-bonded phenols ²⁷	ST	7	31	277	5 250 ^g	0.12	+
	20-25	43	(29)	256		>0.25	
19. ionization of dinitromethanes ³⁰	ST	15	71	860	-1 280 ^g	0.082	+
	28	30	<i>f</i>	867		<i>f</i>	
20. recombination of dinitromethanes ³⁰	ST	15	64	448	17 ^e	0.11	?
	28	30	<i>f</i>	722		<i>f</i>	
21. recombination of triarylmethyl cations ^{36,j}	HS	5	14	76	335	0.062	+
	65	50	(7)	674		<0.005	
22. recombination of triarylmethyl cations ^{36,j}	HS	13	24	304	399	0.071	+
	30	91	(5)	372		<0.005	
23. recombination of triarylmethyl cations ^{36,k} (<i>ortho</i> substituted)	S	6	89	421	436	0.14	-
	65	42	(15)	940		<0.005	
24. recombination of triarylmethyl cat. (antipyrene series) ^{37,38,l}	HS	12	19	491	1 170 ^g	0.049	+
	19-30	50	(13)	324		0.025	
25. recombination of triarylmethyl cat. (antipyrene series) ^{39,l}	HS	12	21	478	852 ^g	0.053	+
	19-28	48	(15)	328		0.05	
26. recombination of triarylmethyl cations (bisantipyrene series) ^{40,m}	HS	14	29	1 080	-20 ^e	0.063	+
	15-20	56	(14)	198		<0.005	
27. recombination of triarylmethyl cations (bisantipyrene series) ^{40,m}	HS	10	14	325	220	0.056	+
	15-20	39	(14)	187		>0.25	
28. H ⁺ transfer from nitromethane ⁴¹	ST	19	39	822	636	0.058	+
	20-30	61	(24)	553		0.01	
29. benzoic acids + diphenyldiazomethane ⁴²	HS	18	38	956	-1 546 ^g	0.075	+
	20	54	(22)	270		0.01	
30. benzoic acid + substituted diphenyldiazomethanes ^{42,43}	HS	8	22	1 018	-444 ^g	0.039	+
	20	24	(27)	315		>0.25	
31. benzoic acids + substituted diphenyldiazomethanes ^{42,43}	HS	33	36	1 312	-4 500 ^g	0.058	+
	20	99	(29)	292		0.10	
32. arylcyclopropanecarboxylic acids + diphenyldiazomethane ⁴⁴	HS	8	16	288	-1 920 ^g	0.067	+
	15-20	33	(11)	192		0.10	

TABLE I (continued)

Reaction	Variable ^a ΔT^b	<i>l</i> <i>N</i>	Standard deviations ($\cdot 10^3$)		β K	ψ α^c	<i>V</i>
			<i>s</i> ₀ (<i>s</i> ₀₀)	<i>s</i> _R <i>s</i> _T			
33. diarylcyclopropanecarb. acids + diphenyldiazomethane ⁴⁵	HS	6	16	554	-2 610 ^g	0.049	+
	10-20	23	(17)	185		>0.25	
34. hydrolysis of ethyl benzoate ⁴⁶	SO	7	26	478	573	0.060	+
	25-45	38	(5)	405		<0.005	
35. hydrolysis of dinitrophenyl benzoates ⁴⁷	HS	11	56	1 037	-424 ^e	0.094	+
	5-15	31	(72)	341		>0.25	
36. hydrolysis of dinitrophenyl thiobenzoates ⁴⁸	HS	10	64	624	174 ^c	0.10	+
	20	30	(57)	623		>0.25	
37. hydrolysis of aryl benzoates ⁴⁹	HS	9	22	699	1 280 ^g	0.044	+
	35	36	(22)	367		>0.25	
38. hydrolysis of alkyl benzoates ⁴⁹	ST	8	27	1 045	-28 800 ^g	0.044	±
	35	32	(17)	367		0.05	
39. hydrolysis of alkyl benzoates ⁵⁰	ST	11	51	1 013	923 ^g	0.12	+
	15	44	(57)	184		>0.25	
40. hydrolysis of alkyl benzoates ⁵¹	ST	9	39	658	32 ^e	0.059	+
	35	18	<i>f</i>	648		<i>f</i>	
41. hydrolysis of benzoic anhydrides ⁵²	HS	9	19	1 187	849	0.026	+
	16-33	19	<i>f</i>	459		<i>f</i>	
42. hydrolysis of cyclic anhydrides ⁵³	ST	19	11	533	864	0.037	±
	10	57	(6)	150		<0.005	
43. esterification of thiobenzoic acids ⁵⁴	HS	8	38	231	229	0.15	+
	20	24	(25)	279		0.25	
44. solvolysis of isopropyl benzenesulphonate ⁵⁵	SO	17	18	1 883	-133	0.018	+
	10-48	59	(10)	553		0.005	
45. methanolysis of arenesulphonates ⁵⁶	HS	8	6	535	-2 600 ^g	0.012	+
	20	24	(0.3)	468		<0.005	
46. methanolysis of arenesulphonates ^{56,57}	ST	34	22	957	-142 ^e	0.034	+
	20	102	(2)	444		<0.005	
47. solvolysis of allyl benzenesulphonates ⁵⁶	SO	6	24	362	229	0.060	+
	20	18	(0.2)	453		<0.005	
48. solvolysis of tosylates ⁵⁸	ST	9	2	989	1 590	0.0036	+
	10-20	52	(1.4)	367		0.025	
49. hydrolysis of benzhydryl bromides ⁵⁹	HS	14	36	1 462	1 860 ^g	0.045	-
	10-35	62	(37)	419		>0.25	

TABLE I (continued)

Reaction	Variable ^a ΔT^b	<i>l</i> <i>N</i>	Standard deviations (. 10 ³)		β K	ψ α^c	<i>V</i>
			<i>s</i> ₀	<i>s</i> _R			
			(<i>s</i> ₀₀)	<i>s</i> _T			
50. hydrolysis of diazoacetophenones ⁶⁰	HS	13	25	517	-140 ^e	0.054	+
	15-20	63	(18)	424		0.05	
51. hydrolysis of dinitropropylanilines ⁶¹	HS	14	5	857	629	0.008	+
	20	70	(4)	384		0.025	
52. hydrolysis of vinyl ethers ⁶²	ST	57	40	539	-5 400 ^g	0.10	+
	15	228	(27)	282		<0.005	
53. pyrolysis of nitroethyl benzoates ⁶³	HS	6	23	162	462	0.11	+
	20-40	30	(24)	250		<0.25	
54. pyrolysis of diarylethyl acetates ⁶⁴	HS	11	15	233	1 610 ^g	0.044	+
	47-50	44	(12)	519		0.25	
55. pyrolysis of 1-aryl-3-butenols ⁶⁵	S	9	18	46	815 ^e	0.18	?
	17-34	35	(16)	219		>0.25	
56. pyrolysis of 3-aryl-3-butenols ⁶⁶	HS	7	18	115	11 ^e	0.11	+
	23-29	27	(21)	220		>0.25	
57. decarboxylation of picolinic acid ⁶⁷	SO	13	33	245	520	0.14	+
	4-19	44	(23)	223		0.10	
58. decomposition of formic acid ⁶⁸	C	6	47	240	693	0.14	+
	50-110	32	(43)	480		0.25	
59. pentafluorobenzene + nucleophiles ⁶⁹	ST	4	340	1 683	220	0.18	-
	200	20	(2)	2 142		<0.005	
60. hexafluorobenzene + piperidine ⁷⁰	SO	12	70	823	-75 ^e	0.13	-
	30-60	49	(34)	363		<0.005	
61. halogenonaphthalenes + piperidine ⁷¹	ST	6	25	3 173	-659	0.036	+
	15-20	26	(20)	153		0.25	
62. chloropyrimidines + piperidine ⁷²	S	13	19	1 325	1 940 ^g	0.034	+
	20	39	(13)	229		0.10	
63. bromonitrotriazole + amines ⁷³	ST	6	21	311	233	0.084	+
	15	22	(10)	203		<0.005	
64. chloronitrotriazole + methylamine ⁷³	SO	8	28	214	565 ^e	0.12	-
	15	24	(5)	236		<0.005	
65. hydrolysis of chloroacridines ⁷⁴	S	13	52	694	518	0.094	+
	10-40	40	(33)	438		0.05	
66. bromo ketones + pyridine ⁷⁵	S	7	26	1 043	-699	0.040	+
	30	21	(30)	401		>0.25	

TABLE I (continued)

Reaction	Variable ^a ΔT^b	<i>l</i> <i>N</i>	Standard deviations (. 10 ³)		β K	ψ α^c	<i>V</i>
			<i>s</i> ₀	<i>s</i> _R			
			(<i>s</i> ₀₀)	<i>s</i> _T			
67. bromo esters + pyridine or aniline ⁷⁶	ST	20	19	765	-45 ^e	0.034	+
	30	60	(19)	414		>0.25	
68. bromo carbonyl compounds + pyridine or aniline ^{75,76}	ST	34	23	989	-261	0.036	+
	30	102	(21)	416		0.25	
69. phenacyl bromide + anilines ⁷⁷	S	15	15	542	545	0.053	+
	10	45	(20)	151		>0.25	
70. chloroacetanilides + dimethylaniline ⁷⁸	HS	10	42	106	468	0.19	?
	42	30	(56)	458		>0.25	
71. isothiocyanates + butylamine ⁷⁹	HS	5	47	564	5 ^e	0.17	?
	10	15	(38)	134		0.25	
72. isoselenocyanates + butyl- amine ⁷⁹	HS	5	30	587	105 ^e	0.10	+
	15	20	(30)	152		>0.25	
73. isothiocyanates + mercaptopropionic acid ⁷⁹	ST	9	52	601	372	0.16	?
	10	27	(49)	176		>0.25	
74. isothiocyanates + cysteine ⁸⁰	ST	5	83	629	389	0.19	?
	10-35	25	(71)	304		0.10	
75. methylation of thioamides ⁸¹	HS	7	18	263	-257 ^e	0.069	+
	15	21	(17)	255		>0.25	
76. methylation of sulphur compounds ^{81,82}	ST	23	13	563	-618 ^g	0.036	+
	15	69	(12)	245		>0.25	
77. sulphenamides + mercaptobenzothiazole ⁸³	ST	6	8	302	490	0.034	+
	50	24	(8)	198		>0.25	
78. fluorenones + sodium borohydride ⁸⁴	S	10	41	644	-186 ^e	0.084	+
	20-35	34	(46)	362		>0.25	
79. dimethylaminobenzaldehyde + thiazolidines ⁸⁵	ST	7	36	1 144	-139 ^e	0.040	+
	50	21	(32)	695		0.25	
80. benzylglyoxylic acids + rhodanine ⁸⁶	ST	9	37	295	116 ^e	0.10	+
	30	27	(18)	424		0.025	
81. ethyl cyanoacetate + chalkones ^{87,n}	HS	10	41	512	-333 ^e	0.12	+
	20	50	(41)	255		>0.25	
82. ethyl cyanoacetate + chalkones ^{87,n}	HS	13	41	740	-619 ^e	0.11	+
	20	65	(40)	199		>0.25	
83. dinitromethanes + methyl acrylate ⁸⁸	ST	20	44	587	95 ^e	0.075	+
	15-40	77	(38)	588		0.25	

TABLE I (continued)

Reaction	Variable ^a ΔT^b	<i>l</i> <i>N</i>	Standard deviations (. 10 ³)		β K	ψ α^c	<i>V</i>
			<i>s</i> ₀	<i>s</i> _R			
			(<i>s</i> ₀₀)	<i>s</i> _T			
84. dinitromethanes + methyl vinyl ketone ⁸⁹	HS	11	13	145	141 ^e	0.044	+
	45	44	(12)	592		>0.25	
85. dimerisation of cyclopentadiene ⁹⁰	p	5	21	592	162	0.032	+
	20-40	16	(20)	699		>0.25	
86. diazonium salts + R-acid ^{91,o}	S	8	175	1 112	69 ^e	0.10	+
	50	48	(125)	636		0.05	
87. diazonium salts + R-acid ^{91,o}	S	5	104	1 214	-345 ^e	0.12	?
	50	30	(106)	601		>0.25	
88. diazonium salts + R-acid ^{91,o}	S	3	168	994	232 ^e	0.20	?
	50	18	(150)	691		>0.25	
89. diazonium salts + Brønner acid ⁹²	HS	11	17	1 461	1 020	0.031	+
	15-25	43	(5)	214		<0.005	
90. cyclization of benzilic anilides ⁹³	HS	12	32	24	286 ^e	0.40	-
	10	24	<i>f</i>	251		<i>f</i>	
91. cyclization of dimethylbenzilic anilides ⁹³	HS	10	88	310	605	0.24	?
	16	30	(110)	426		>0.25	
92. hydrogen exchange in toluenes ⁹⁴	ST	12	68	1 723	-268	0.063	+
	15-40	36	(21)	681		<0.005	
93. hydrogen exchange in N-methylpyridines ⁹⁵	ST	7	34	1 246	195	0.040	+
	30-80	22	(25)	584		>0.25	
94. bromination of cyclohexanones ⁹⁶	S	11	66	159	-1 030 ^g	0.20	?
	35	44	(76)	715		>0.25	
95. Lossen rearrangement of dihydroxamic acids ^{97,p}	ST	26	15	627	-499 ^g	0.028	+
	8-20	53	<i>f</i>	440		<i>j</i>	
Biochemical Processes							
96. hydrolysis of acetyltryptophan ethyl ester ⁹⁸	pH	10	34	325	457 ^g	0.080	+
	30-45	56	(27)	359		0.10	
97. denaturation of haemoglobins ⁹⁹	ST	7	184	1 023	552 ^g	0.21	?
	24-28	14	<i>f</i>	698		<i>f</i>	
98. denaturation of lobster haemoglobin ¹⁰⁰	pH	3	55	766	701 ^e	0.085	+
	6-8	12	(59)	544		>0.25	

TABLE I (continued)

Reaction	Variable ^a ΔT^b	<i>l</i> <i>N</i>	Standard deviations (. 10 ³)		β K	ψ α^c	<i>V</i>
			<i>s</i> ₀	<i>s</i> _R			
			(<i>s</i> ₀₀)	<i>s</i> _T			
99. denaturation of ricin ¹⁰¹	pH	4	264	759	376	0.29	?
	15–33	15	(276)	1 090			
100. denaturation of bovine albumin ¹⁰²	pH	5	94	274	365	0.26	?
	29	20	(97)	464			

^a HS Hammett substituent, S substituent (*i.e.* small variations of structure), ST larger variations of structure in substrate and/or reagent, SO solvent, C catalyst, p pressure; ^b temperature interval; if not unique for all the reactions, limits are given; ^c confidence level at which the IKR would be rejected by comparison of s_0 and s_{00} ; when $\alpha \geq 0.10$ the IKR may be considered to be valid within experimental errors; ^d the temperature interval has been restricted to 15° since the Arrhenius equation is not strictly valid; ^e virtually an isenthalpic series; ^f the kinetics was followed at two temperatures only, hence s_{00} and α are not defined; ^g an approximately isoentropic series; ^h the selection of derivatives into the series 12 and 13 was based on a posteriori arguments; ⁱ in series 14 the complexes in 1,2-dichloroethane were excluded since the data are less precise than the others (see the value of s_{00}); ^j series 21 includes derivatives investigated in a broader interval of temperatures, series 22 all derivatives; ^k substituent 2-SO₃H excluded; ^l the two series 24 and 25 are based on essentially identical data published twice, both are virtually isoentropic but note the difference in the apparent values of β ; ^m series 27 was derived from 26 excluding donor substituents in the *para* position; ⁿ the two series 82 and 83 differ in the position of substituents; ^o dissection of the series 86 into the sets 87 and 88 was suggested in the original literature⁹¹ but it is actually unfounded; ^p one reaction excluded owing to a suspected big error; ^q this value is given erroneously in ref.³.

The calculations were done on the Hewlett-Packard calculator 9820 A. In the input there are values of T (in °C) and $\log k$ (given as k or as $\log k$); if β is to be searched for by approximation, also its initial value and the initial step. In the output one obtains β (in K), y_0 (in log units), and the following standard deviations with the pertinent degrees of freedom: s_{00} from the unconstrained Arrhenius lines; s_0 with the isokinetic constraint (*i.e.* for β as determined); s_x for an arbitrarily assumed value of β , s_∞ — for β in infinity (if the series were isenthalpic), s_S — for $\beta = 0$ (if the series were isoentropic). The calculation of all these quantities and their detailed significance has been described^{8,9}.

For the purpose of the following discussion, the programs were complemented by a simple analysis of variance. The total sum of squares (denoted Z in ref.⁸) is divided into three terms: due to differences in reactivity between individual reactions, *i.e.* “between lines” (denoted⁸ Y), due to temperature changes *i.e.* “due to regression” (denoted⁸ Q/X), and residual (denoted⁸ S_{00}). The standard deviations corresponding to these sums of squares are designated s_R (reactivity), s_T (temperature), and s_{00} , respectively. In the special case they are given by the equations:

$$s_R^2 = \left[\frac{1}{m} \sum_i (\sum_j \log k_{ij})^2 - \frac{1}{ml} (\sum_{ij} \log k_{ij})^2 \right] / m(l-1), \quad (3)$$

$$s_T^2 = \sum_i (\sum_j u_j \log k_{ij})^2 / lm \sum_j u_j^2, \quad (4)$$

where u is the transformed independent coordinate⁸. In the general case the formulae are more complex since the fourth term appears in the sum of squares which is due to different mean temperatures in individual reactions ("due to shifts"). As indicated previously⁹, if the pattern of experimental points were quite irregular, the term isokinetic relationship may even lose its significance. There are, however, no such cases among the reaction series of Table I; mostly the pattern approaches the "special case" with several lacking measurements on the most rapid reactions at highest temperatures, or *vice versa*.

In the output of our programs besides the values of s_R and s_T the ratio $\psi = s_0/(s_R s_T)^{1/2}$ is obtained, evaluating the goodness of fit^{10,21} and the ratio $F = s_0^2/s_{00}^2$, serving for an approximate* F -test (significance level α). In the end the values of ΔH^\ddagger and ΔS^\ddagger , or ΔH^0 and ΔS^0 , respectively, are printed in three sets: unconstrained, with the isokinetic constraint⁸, and with the isoenthalpic constraint⁸ (*i.e.* all the ΔH 's equal).

The values of l , N , s_{00} , s_0 , s_R , s_T , β , ψ , and α are listed in Table I. In previous literature many of these reaction series were treated by statistically incorrect methods. We did not consider it useful to quote the results and to compare with ours; for some examples of such comparison see ref.³.

DISCUSSION

General validity of IKR. The main goal of the present investigation was to ascertain inasmuch the IKR is a general phenomenon. One could simply ask in how many of our hundred reaction series it is fulfilled, but there is no single criterion of validity. Instead, the following two points of view are to be considered:

1) By comparing the standard deviations with (s_0) and without (s_{00}) the isokinetic condition using the F -test* one may decide whether the IKR is fulfilled within the experimental error. The latter is estimated equal to s_{00} since the exact validity of the Arrhenius law in a given temperature interval is assumed. This reasoning works, strictly speaking, with the hypothesis that IKR is valid exactly. The two possible results are that the hypothesis was either disproved on a given significance level, or that the available material is insufficient for its disproving. If the IKR is not an exact law, but only an approximate empirical relationship, it is always possible to disprove it by improving the accuracy of experiments.‡

2) By comparison of the isokinetic standard deviation s_0 with the range of $\log k$ values using the ψ -test²¹, one may test the goodness of fit, *i.e.* decide whether the IKR is a useful empirical relationship in a given reaction series. The range of $\log k$ values depends on two independent factors, reaction and temperature, which are both of the same importance. Hence the quantity

* As indicated previously⁸, the F -test is not strictly applicable since the problem is not linear. However, the examples of this paper contain sufficient number of data to allow its use as an approximation; in addition the results are mostly quite unambiguous, either $\alpha < 0.005$ or $\alpha > 0.25$.

$\psi = s_0/(s_R s_T)^{1/2}$ was suggested¹⁰ for a ψ -test in this case. The whole reasoning assumes that the differences between experimental and calculated values are due only to the imperfection of the empirical relationship, the experimental error being negligible. It is further assumed that the standard deviations have been estimated from a large sample. The result may be that relationship is more or less useful, or even worthless, always within the range covered by the available experimental data. If the experimental error is considerable, the test loses its validity and simulates a worse fit.

Our results indicate that IKR is rather an approximate relationship. This is best seen from Fig. 1: Data of high experimental precision reveal a clear difference between s_0 and s_{00} and prove the limited accuracy of IKR. Only higher values of s_{00} (say

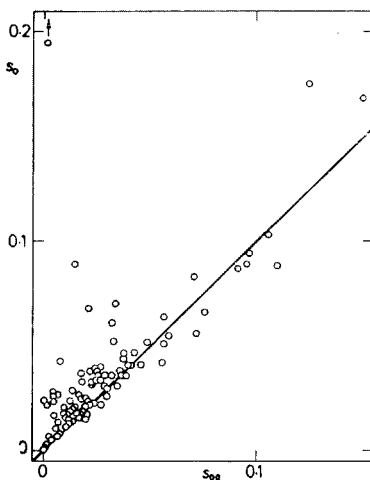


FIG. 1

Comparison of the Accuracy of IKR (standard deviation s_0) with That of the Arrhenius Law (standard deviation s_{00})

The line corresponds to the equality $s_0 = s_{00}$.

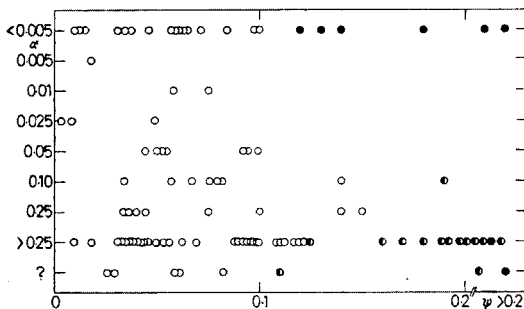


FIG. 2

Distribution of the Statistics ψ and α at the Isokinetic Reaction Series

The goodness of fit increases from right to left, the reliability that IKR holds within experimental error increases from the top to the bottom; ○ IKR valid, ● invalid, ◐ undecided.

greater than 0.04) are paralleled by s_0 of similar magnitude, both can be taken as estimates of the experimental error. (Due to more degrees of freedom s_0 can be even smaller than s_{00} .) Since for an approximate relationship the ψ -test is decisive, we considered IKR to be valid as far as $\psi \leq 0.1$, irrespective of other characteristics (69 reaction series of Table I). This accuracy corresponds to the correlation coefficient of 0.995 in a linear regression and is higher than in most linear free energy relationships. (In reaction series obeying both Hammett equation and IKR, the latter was always fulfilled with a higher accuracy¹⁷.) The remaining sets with $\psi > 0.1$ were evaluated with respect to α and s_0 . Those with $\alpha \leq 0.05$, or with $\psi \geq 0.2$ and simultaneously $s_0 \leq 0.06$ were classified as not obeying the IKR (8 series); for $\alpha \geq 0.10$ and simultaneously both $\psi \leq 0.15$ and $s_0 \leq 0.06$ the IKR is believed to hold (9 series). The remaining cases were classified as undecided (14 series). If the reactions were investigated at two temperatures only, s_{00} and α are not defined; those series were classed with $\alpha \geq 0.10$. These criteria should express the ideas that IKR fulfilled within the (not too large) experimental errors is valid even when ψ is not very favourable, further that too large experimental errors, or an intermediate value of ψ prevent the decision. In order to reach the significant result it is important to have small experimental error, a broad temperature interval, and great differences between individual reactions.

According to the above classification, IKR is valid in 78 from the cases investigated, invalid in 8 cases, and 14 cases remain undecided (see the last column of Table I). We are aware that the criteria used are arbitrary but they were defined with respect to the actual pattern, as visualized in Fig. 2. Most frequent values of α are the two extremes; the group of reactions not obeying IKR (above right) distinctly separates from the others. The undecided cases are mostly due to a too large experimental error, *i.e.* both large s_{00} and s_0 ; these values are not perceptible in Fig. 2.

We conclude that IKR is common as an approximate but relatively precise relationship in series of related reactions. Note that the definition of IKR according to the above criteria includes even isoenthalpic and isoentropic series, hence the existence of any finite, well-defined isokinetic temperature β is not involved.

Range of validity. All the reaction series of Table I are composed of similar reactions differing only by one variable factor (substitution, solvent, pH, *etc.*). No doubt the similarity is a condition of validity of the IKR, it is, however, very difficult to define how close this similarity must be. The more difficult is to delimit the range of validity as to the other conditions. There is even a shortage of series consisting of less similar but still comparable reactions.

For the time being we can only express our opinion that a small variation of structure, like substituents of the Hammett type, is most suitable for the IKR to hold. In Table I, there are 38 Hammett series; IKR is valid in 35 cases, 3 cases are undecided due to too large experimental errors, or too narrow temperature interval, respectively.

The IKR is, on the whole, better fulfilled than the Hammett equation¹⁷, in most cases much better. The extension of the range of validity outside the limits of the Hammett equation resulted in an impaired fit in the series 23 and 46, compared to 22 and 45, respectively. On the other hand, this effect was not observed in series 76 and 75. Double substitution seems to have no unfavourable effect (series 29, 30, 31, or 32, 33). Sometimes an improved fit was achieved by restriction of the data but the choice was based on *ad hoc* arguments, see series 12 and 13, 14 and 15, 23, 95; in some of these cases there is a suspicion of big errors.

Solvent as the variable factor can apparently give rise to a valid IKR as well, although the observed examples are not numerous. In three cases variation of solvent gave as good results as variation of substituents in otherwise similar reactions (series 64 and 63, 34 and 37, 47 and 46, or 45). Some reactions in the gas phase (53–56, 58) also fit reasonably. For three series of our sets, rates of the forward and reverse reaction as well as equilibria are available (series 7, 17, 18; 9, 19, 20; 11, 21, 22). In all cases IKR is fulfilled most precisely for equilibria; of course, this result need not be valid generally.

We also tried to analyze the eight series in which IKR has been clearly disproved but the reasons are not uniform. In series 10, 14, 23, and 59 a too broad variation of structure may be taken into consideration but there are also other factors as a narrow temperature interval or low values of ΔH . The reaction series 59 is extraordinary due to the temperature interval of 200°C, and cannot be compared with others.

We conclude that the validity range of IKR is not well defined; it seems to be broader than for most extrathermodynamic relationships but is certainly also limited. Some attempts to derive the IKR theoretically are either too general^{2,19} and would ultimately apply to all reaction series, or, on the other hand, they restrict the validity only to special conditions, as condensed phase⁵ or solution^{12,13,16,18,20}. This paper presents new evidence in favour of our earlier conclusions³ that these theories are at variance with the experimental facts.

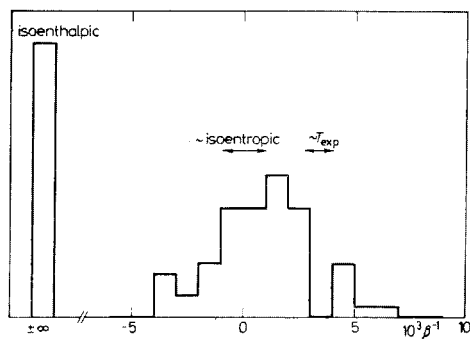


FIG. 3

Histogram of Distribution of the Isokinetic Temperature β (plotted as β^{-1})

The isokinetic temperature. A puzzling corollary of the IKR is the predicted reversal of reactivity at the temperature $T = \beta$. It was the more strange as values of β near to the experimental temperature or even within the experimental interval were often claimed (see³). Hence the question is of importance, which values β can actually acquire.

In Fig. 3 the observed values of β are collected in the form of a histogram, choosing β^{-1} as the independent coordinate. Reaction series where IKR either is invalid, or the experimental error is too large, were excluded. If the isoenthalpic hypothesis, $\beta = 0$, could not be rejected, the reaction series was classed as isoenthalpic, *i.e.* this hypothesis is always preferred as the simplest one. Series with $\beta > 1000$ K, or $\beta < -1000$ K may be approximately considered as isoentropic. Fig. 3 reveals that β either higher than the experimental temperature, or negative (*i.e.* in general $\beta^{-1} < T_{\text{exp}}^{-1}$) are common, the reverse ($\beta < T_{\text{exp}}$) has been observed only on 7 examples. From these two are of relatively low accuracy but the remaining ones give a firm evidence that such values of β occur. We are, however, not able to give some common features of these reaction series. Since in our previous communications^{8,9} no quite convincing example of this remarkable type was encountered, we reproduce such an example in Fig. 4 (reaction series 93).

Blackadder and Hinshelwood¹² distinguished three classes of reaction series: 1) isoentropic, ($\beta^{-1} = 0$), 2) isoenthalpic, ($\beta = 0$), and 3) with compensation, ($\beta > 0$).

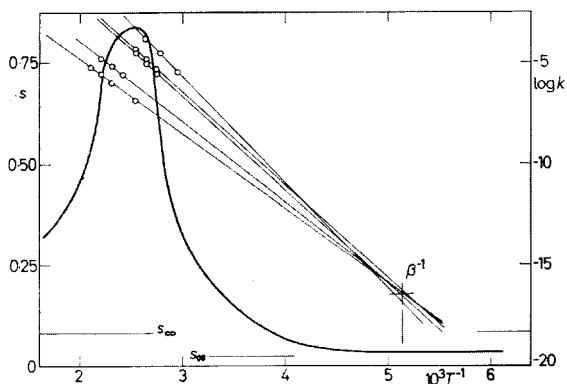


FIG. 4

Isokinetic Relationship for the Isotopic Hydrogen Exchange in N-Methylpyridines⁹⁵, Plotted in the Coordinates T^{-1} , $\log k$

In addition to the Arrhenius lines and their point of intersection, the curve is plotted showing the dependence of the standard deviation on the assumed isokinetic temperature, further the unconstrained standard deviation s_{00} (see⁸).

The case 4) anticomensation ($\beta < 0$) could be detected only by correct statistical methods³. In this paper we have found the following numbers of reaction series belonging to the classes 1.–4. respectively: 21, 22, 29, and 11. The classification has several imperfections: The terms isoentropic and isoenthalpic are not sharply defined; if we denote, *e.g.*, as isoentropic all series where the hypothesis $\beta^{-1} = 0$ cannot be rejected, values of β higher than 1000 K or lower than -1000 K are approximately included. Another weakness is that the class of isoenthalpic series contains all cases not sufficiently studied; if, *e.g.*, the temperature interval is too narrow or the experimental accuracy low, differences in ΔH cannot simply be detected. In some extreme cases of this type neither the isoenthalpic nor the isoentropic hypothesis can be rejected. For these reasons we suggested³ another classification into the series with β higher or lower than the experimental temperature, as indicated above. This classification is unambiguous but, like the original one, it does not offer any straightforward possibility of physical interpretation.

The only values of β lacking in Fig. 3 are those between 250 and 333 K, they correspond to the commonly used experimental temperatures. The possibility of reaching the isokinetic temperature experimentally and of demonstrating the reversal of reactivity has been much discussed. Since most of the claimed values have been shown to be artifacts, resulting from erroneous statistical treatment, the meaning was offered that β is merely an extrapolation without any physical meaning. If it is approached experimentally it could always shift further away^{3,16}. Nevertheless, reaction series do exist where the reversal of reactivity has been observed directly.

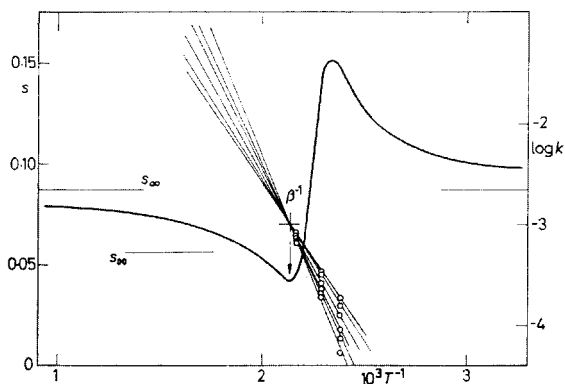


FIG. 5

Isokinetic Relationship for the Reaction of Substituted Chloroacetanilides with Dimethylaniline⁷⁸
 Symbols as in Fig. 4.

Indisputable examples are known from heterogeneous catalysis^{6,68}, in which catalyst is the variable factor. In homogeneous kinetics no quite convincing example is known. The reaction series 21, much discussed in the literature^{36,103}, was really followed at a temperature where the differences in reactivity diminished up to the experimental error. However, at still higher temperatures the Arrhenius law is violated in such a manner that the isokinetic point is approaching from either side with a different slope. There is no explanation of this phenomenon. In addition, the differences in reactivity are very small since the series is structurally very restricted; not even all the Hammett substituents can be included, compare reaction series 22. Of the other reaction series of Table I, the isokinetic point is approaching most closely in series 70, which is visualized in Fig. 5. The figure furnishes a convincing proof of the isokinetic relationship, although the statistic ψ is unfavourable due to large experimental errors and relatively small differences in reactivity. No doubt the isokinetic temperature could be reached but with respect to the preceding example one cannot predict the behaviour above this temperature.

We conclude that the isokinetic temperature is in principle accessible but in homogeneous kinetics this is very seldom actually possible, and if it is, the consequences are not known. In practice the isokinetic relationships cannot invalidate current theories operating with temperature independent concepts (inductive effect, ring strain, etc.). As to the possible values of β , there is good evidence that negative as well as positive and high as well as low values occur. Hence all the theories requiring β to have particular values, or at least in a certain interval, are experimentally disproved. It concerns the opinion that β should be only positive², or lower than the experimental temperature¹⁸, or acquire several characteristic values^{5,16,19}. Particularly wrong is the assumption²⁰ that β is usually close or almost equal to the experimental temperature. At present there is no possibility to predict the value of β , or to interpret it theoretically when it is experimentally determined. In our opinion this numerical value is not of much significance and attention should be focussed merely on the question whether IKR is valid in a given case or not; this has evident consequences for structure-reactivity relationships.

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