β-Bromo Acids. III. Heterolytic Fragmentation[1]

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Abstract: The kinetics of solvolysis of four cyclic β-bromo acids, *trans*-2-bromocyclopentanecarboxylic acid, *cis*-2-bromocyclopentanecarboxylic acid, *trans*-2-bromocyclohexanecarboxylic acid, and *cis*-2-bromocyclohexanecarboxylic acid, have been examined in order to provide insight into the effects of conformation on the heterolytic fragmentation reaction (debrominative decarboxylation). Comparison of the behavior of the two trans acids with that of *trans*-10-bromodecalin-9-carboxylic acid strongly suggests that the latter compound provides a clear case of *synchronous* heterolytic fragmentation in the saturated β-halo acid series. The comparatively facile isolation of a *stable* fused-ring β-lactone, *cis*-cyclopentanecarbo-2-lactone, from the solvolysis of *trans*-2-bromocyclopentanecarboxylic acid raises the question as to whether β-lactones are indeed intermediates in the usual solvolytic process. The available evidence suggests that unless there is comparable concomitant fragmentation no actual β-lactone is formed.

Although the dehalogenative decarboxylation of β-halo acids is one of the oldest recognized reactions of such compounds[4] and has been investigated extensively in the senior author's laboratory[5-11] and elsewhere,[12-22] the precise nature of the reaction has not emerged in its entirety for any save β-halo-α,β-unsaturated acids,[21] which constitute a special case because of the rigid geometry involving the halogen, the carboxyl carbon atom, and carbons 2 and 3. This isolated case has been shown by Grob[21] to fit nicely into the general pattern of heterolytic fragmentations, which he has studied very extensively. The purpose of the present study is to reexamine the fragmentation of saturated β-halo acids (dehalogenative decarboxylation) to see if in any instance the reaction conforms completely to Grob's requirements for synchronous heterolytic fragmentation.

Early work in the senior author's laboratory[9] appeared to confirm implicit and explicit arguments that β-halo acid fragmentation was essentially a trans elimination, but at the same time[6-8] cis fragmentations were encountered, being explained by anchimeric involvement of migrating aryl groups, *i.e.*, the fragmentation proceeds from an ionic (dipolar) intermediate. The concept of a two-step fragmentation involving an intermediate dipolar ion appeared to be well established by the behavior of *erythro*-dibromocinnamate ion[17-19] which can experience both a stereospecific trans elimination in nonpolar media and an apparently thermodynamically controlled elimination in polar media (*e.g.*, water). The former process might be likened to the concerted E2 reaction and the latter to the E1-SN1 reaction. But most of the evidence[22-28] favors stereospecific trans fragmentation.

Any β-halo acid which can assume a conformation appropriate for trans fragmentation simultaneously becomes susceptible to β lactonization,[9] and indeed there would seem to be experimental evidence to support the transient formation of such lactones from β-halo acids: one body of such data deduces the transient existence of β-lactones on the stereochemical grounds that the observed Walden inversions involve first-order kinetics, *and* more significant, the reacting species are such that the structure prohibits direct nucleophilic displacement of the halogen by an external nucleophile;[5-8,10,11] and the other body of data involves a careful correlation of kinetics with optical activity studies[15,16] and the isolation of ~6.5% of a β-lactone.[29] Such lactonization presumably is a concerted process (SNi) and competes with trans fragmentation much as an SN2 reaction competes with a concurrent E2 reaction. There is no evidence for β lactonization as a competitor for cis fragmentations of structurally rigid systems; and indeed, one would not expect facile cyclization to a four-membered ring by a dipolar ion in competition with thermodynamically more favorable processes, *e.g.*, deprotonation.

At this point in time, then, we appear to have two limiting mechanisms for heterolytic fragmentation: a

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(2) Work done at The University of Connecticut.
(3) Work done at The University of Michigan.
(4) A. Schmitt, *Ann.*, **127**, 319 (1863).
(5) W. R. Vaughan and K. M. Milton, *J. Amer. Chem. Soc.*, **74**, 5623 (1952).
(6) W. R. Vaughan, M. V. Andersen, Jr., and R. Q. Little, Jr., *ibid.*, **76**, 4130 (1954).
(7) W. R. Vaughan and R. Q. Little, Jr., *ibid.*, **76**, 2952 (1954).
(8) W. R. Vaughan and R. Q. Little, Jr., *ibid.*, **76**, 4130 (1954).
(9) W. R. Vaughan and R. L. Craven, *ibid.*, **77**, 4629 (1955).
(10) W. R. Vaughan and A. C. Schoenthaler, *ibid.*, **79**, 5777 (1957).
(11) W. R. Vaughan and A. C. Schoenthaler, *ibid.*, **80**, 1956 (1958).
(12) E. Erlenmeyer, *Ber.*, **13**, 303 (1880).
(13) P. Pfeiffer, *Z. Phys. Chem.*, **48**, 40 (1904).
(14) H. Johannson and S. M. Hagman, *Ber.*, **55**, 647 (1932).
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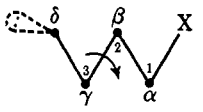
(16) A. R. Olson and J. L. Hyde, *ibid.*, **63**, 2459 (1941).
(17) E. Grovenstein and D. E. Lee, *ibid.*, **75**, 2639 (1953).
(18) S. J. Cristol and W. P. Norris, *ibid.*, **75**, 632 (1953).
(19) S. J. Cristol and W. P. Norris, *ibid.*, **75**, 2645 (1953).
(20) E. R. Trumbull, R. T. Finn, K. M. Ibne-Rasa, and C. K. Sauers, *J. Org. Chem.*, **27**, 2339 (1962).
(21) C. A. Grob, J. Csapilla, and G. Cseh, *Helv. Chim. Acta*, **47**, 1590 (1964).
(22) A. T. Dann, A. Howard, and W. Davies, *J. Chem. Soc.*, 605 (1928).
(23) W. G. Young, R. T. Dillon, and H. J. Lucas, *J. Amer. Chem. Soc.* **51**, 2528 (1929).
(24) G. B. Bachman, *ibid.*, **55**, 4279 (1933).
(25) J. K. Farrell and G. B. Bachman, *ibid.*, **57**, 1281 (1935).
(26) H. J. Lucas and A. N. Prater, *ibid.*, **59**, 1682 (1937).
(27) W. Davies, B. M. Holmes, and J. E. Kefford, *J. Chem. Soc.*, 357 (1939).
(28) E. A. Braude and J. A. Coles, *ibid.*, 2078 (1951).
(29) H. Johannson, *Ber.*, **48**, 1256 (1915).

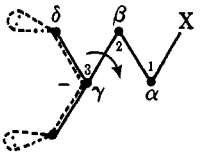
concerted trans process, apparently with a more or less successfully competitive β lactonization; and an ionization process leading to a zwitterion which then decomposes according to the relative thermodynamic requirements of the various pathways open to it. Superficially it would seem that Grob's suggestion[30] that dehalogenative decarboxylation may be considered a specific example of the general "fragmentation reaction"[31] is confirmed.

According to Grob's picture a fragmentable system may most simply be pictured as



with X being a "leaving group," δ being an atom with a lone pair of electrons, and α, β, and γ being intervening atoms. Systematic investigation of γ-amino halides and arenesulfonates has unequivocally supported the concept of two limiting processes: (A) a *synchronous* fragmentation, and (B) a stepwise solvolysis in which fragmentation of the resultant cation is but one of two or more competing reactions.[32] In the general case A, when all bonds involved (including the δ-electron pair) lie in one plane, or in two planes intersecting in the $\beta\gamma$ bond (*i.e.*, rotation about this bond does not inhibit the synchronous process), synchronous heterolytic fragmentation will occur. Furthermore it will be the *only* reaction, and release of X should be greatly accelerated over that observed for normal solvolysis ("frangomeric effect"[32]). And in the general case B, release of X will approximate the normal solvolytic rate, and the extent of fragmentation becomes a function of stereoelectronic factors in the resultant carbonium ion, which may still promote extensive fragmentation. If a β-bromo acid fragments according to the Grob mechanism, the following crucial and experimentally observable facts must obtain: (1) release of bromide ion must be greatly (*e.g.*, 10^5) accelerated over that for a reference β-bromo acid which cannot fragment (for whatever reason); and (2) no products other than olefin, bromide, and carbon dioxide should appear (*i.e.*, no β-lactone α,β-unsaturated, rearranged product).

The above picture for a fragmentable system applied to a β-halo acid must be modified to include a second δ atom, the second oxygen of the *carboxylate* group.



From this picture it is clear that the completely copolar conformation is stereochemically ideal for β lactonization, but that any other conformation involving rotation about the $\beta\gamma$ bond will impede lactonization while not materially affecting fragmentation. It should also be clear that *any* rotation about the $\alpha\beta$ bond will seriously impair the operation of both synchronous fragmentation and β lactonization.

Before one can determine whether frangomeric acceleration of solvolysis is being observed, one must have a suitable reference rate. In Grob's γ-amino halides and arenesulfonates this is a simple requirement, since the related alkyl halide or arenesulfonate can be used, there being no significant inductive effect differences between the amine and the carbon analog. But in a β-halo acylate ion the intrusion of the negative pole clearly accelerates the solvolytic rate even when neither fragmentation nor lactonization is possible.[33] However, one may take two such β-bromo acids as reference compounds: (e)-2-bromobicyclo[3.2.1]octane-1-carboxylic acid (**1**), and (a)-2-bromobicyclo[3.2.1]octane-1-carboxylic acid (**2**), which together provide a range of rates for purely inductively and/or electrostatically assisted β-bromo acylate solvolysis (Table I).

Table I. Solvolyses of Bromo Acids in Water

Compound	T, °C	$k \times 10^5$ sec^{-1}	E_a, kcal	$\Delta S^{\pm}$, eu	% fragmentation
1	62[a]	4.76			0
2	62[a]	55.6			0
α-Bromopropionate	25[b]	0.042	30.3	11	0
-caproate	25[b]	0.055	29.8	10	0
β-Bromopropionate	25[b]	0.35	29.3	13	0
-butyrate	62[c]	404			
	25[d]	1.82	28.8	14	15
-α-Methylbutyrate	25[e]	18.8			66
-α-Ethylbutyrate	25[e]	27.3			63
-caproate	62[c]	670			
	25[b]	3.5	27.7	12	?
γ-Bromovalerate	25[b]	550	22.8	11	0
δ-Bromovalerate	25[f]	13			0
ε-Bromocaproate	25[b]	0.17	25.8	−2	0
ξ-Bromoenanthate	25[b]	0.043	22.8	−13	0

[a] Reference 21. [b] H. W. Heine, E. Becker, and J. F. Lane, *J. Amer. Chem. Soc.*, **75**, 4514 (1953). [c] Calculated from Arrhenius equation. [d] Reference 13. [e] Reference 12. [f] N. Isenberg, M. Topper, and I. B. Shorb, *Chemist-Analyst*, **53**, 41 (1964).

A careful study of the data in Tables I and II will reveal that with but one exception all β-bromo acids solvolyze at rates considerably in excess of those exhibited of **1** and **2**. Thus one is tempted to ascribe the acceleration to either frangomeric effect or to concerted β-lactonization (anchimeric effect), or to both.

The compounds selected for this investigation constitute two pairs of cis–trans isomers: *trans*-2-bromocyclopentanecarboxylic acid (**3**), *cis*-2-bromocyclopentanecarboxylic acid (**4**), *trans*-2-bromocyclohexanecarboxylic acid (**5**), and *cis*-2-bromocyclohexanecarboxylic acid (**6**). It is the latter which shows but little rate enhancement over **2**. Acid **5** constitutes a system which by conformational "flip" can provide an ideal stereoelectronic situation for synchronous fragmentation, which is clearly unavailable to **3**; but **3** surprisingly

(30) (a) C. A. Grob, *Experientia*, **13**, 126 (1957); (b) "Kekule Symposium on Theoretical Organic Chemistry," Butterworths, London, 1959, p 114 ff.

(31) The senior author wishes to acknowledge the hospitality and encouragement afforded him during a sabbatical leave (1959) at the Institut für Organische Chemie, Basel, when much of the present work was conceived as a result of frequent and stimulating discussions with Professor Grob.

(32) C. A. Grob, *Bull. Soc. Chim. Fr.*, 1360 (1960).

(33) W. R. Vaughan, R. Caple, J. Csapilla, and P. Scheiner, *J. Amer. Chem. Soc.*, **87**, 2204 (1965).

Table II. Solvolyses of Cyclic β-Bromo Acids in Water

Compd	T, °C	$k \times 10^5$ sec^{-1}: Bromide method	$k \times 10^5$ sec^{-1}: Carbon dioxide method	E_a, kcal	$\Delta S^{\pm}$, eu
3	62.0	4580[a]			
	40.1	326	338	24.3	5.6
	30.0	88.5			
	25.0	45.1[a]			
4	62.0	151[a]			
	50.3	34.0			
	40.1	8.56		26.8	6.3
	30.0	2.04	2.10		
	25.0	0.968[a]			
5	62.0	914[a]			
	50.3	163			
	40.1	35.3		31.0	23
	30.0	6.73			
	25.0	2.84[a]			
6	62.0	54.3[a]			
	50.3	13.3			
	40.1	3.67		25.4	0.17
	30.0	0.94[a]	0.84		
	25.0	0.465[a]			

[a] Calculated from Arrhenius equation.

solvolyzes faster than **5** in spite of very favorable activation entropy in **5**.

A partial explanation for this apparent anomaly is to be found in the conformational situation involving **5** and **6**. Nmr spectra of these two compounds[33] make it clear that **5** is to all intents rigidly the diequatorial conformer while **6** is only somewhat less rigidly the conformer with axial bromine. As anions in polar solvents both compounds may be expected to have the carboxylate groups even more extensively equatorial, though potentially always able to become axial with appropriate input of energy and loss of solvating molecules.

An approximate equilibrium constant for the conformational interconversion in **6** may be obtained

$$Br_{axial} \rightleftharpoons Br_{equatorial}$$

from the effective solvolytic rate constants for the reference compounds **1** and **2** by using equation[34]

$$K = \frac{k_a - k_{meas}}{k_{meas} - k_e} \sim 10^{-2} \; (T = 62°)$$

where $k_a = k_2$ (Table I), $k_e = k_1$ (Table I), and $k_{meas} = k_6$ (Table II). The value obtained is consistent with the nmr data and probably represents a limiting value. From this it is not unreasonable to infer a value for the interconversion in **5**:

$$Br_{equatorial} \rightleftharpoons Br_{axial} \quad (K \sim 10^{-2}, T = 62°)$$

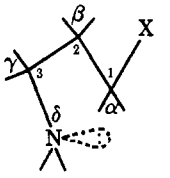
This is equivalent to a mole fraction (N_a) $\sim 10^{-2}$ for axial bromine. Such fragmentation as occurs in either **6** or **5** presumably proceeds from the conformer with axial carboxylate, and it is possible to approximate the rate of solvolysis for the diaxial conformer of **5** from the equation[35]

$$k_{meas} = k_e N_e + k_a N_a \quad (k_a \sim 1 \text{ sec}^{-1}, T = 62°)$$

(34) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw Hill, New York, N. Y., 1962, p 235.

(35) S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, 77, 5562 (1955).

k_a is to be calculated, $k_e = k_1$ (Table I), $k_{meas} = k_5$ (Table II), and N_a is estimated above. With reference to the measured rate of solvolysis of **5**, this estimated value for solvolysis of the diaxial conformer takes into account the ~3 kcal/mol free energy needed to convert the much more stable diequatorial conformer into the diaxial conformer (or into a conformation approaching it). This estimated rate represents an 10^3-fold acceleration over purely inductively and/or electrostatically assisted axial bromide solvolysis (**1**) (or an $\sim 10^4$-fold acceleration over purely inductively and/or electrostatically assisted equatorial bromine solvolysis (**2**)). These values *begin* to approach the substantial accelerations expected for synchronous fragmentation, and they are well in excess of the value for **3** as should be expected from the respective conformations. Thus we have solvolysis accelerations ranging from almost negligible (**6**) up to values between 10^3 and 10^4 (diaxial **5**), between which are all of the other β-bromo acids for which kinetic data are available (Tables I, II), excepting, of course, the reference compounds themselves (**1** and **2**). But *in no case* is fragmentation the *only* reaction, nor does there exist in the literature of saturated β-halo acids any one which solvolyzes only with fragmentation. Even from the diaxial conformation of **5** we observe but 60% fragmentation in water solution and 68% fragmentation in 80% ethanol (Table III). To be sure, one may argue that the 38% *trans*-hydroxy acid was formed *via* a β-lactone, whose formation occurred in a concerted manner along with concerted fragmentation (60%). But such appreciable competition in the synchronous fragmentation is disallowed by Grob's specification of unusual rate acceleration *and* product uniqueness. Thus it must be pointed out that the system



which could readily afford an azetidine (with rate enhancement of X^- release analogous to that for β lactonization) *completely fails* to do so when it is wholly copolanar.[30,32] An obvious inference is that none of the fragmentations reported involve Grob's completely synchronous fragmentation mechanism, although the reaction kinetics of diaxial **5** suggest that it has been approached.

Acting upon this inference we determined to investigate a conformationally rigid diaxial β-bromo acid. Ideally the bromine should be secondary, and while (a)-3-bromobicyclo[3.2.1]octane-(a)-2-carboxylic acid has been prepared in the senior author's laboratory,[36] it was extremely difficult to prepare free from other isomers. Consequently we examined the possibility of hydrobrominating β,γ-unsaturated acids and eventually selected $\Delta^{4,10}$-octalin-9-carboxylic acid, relying on the (presumed) greater thermodynamic stability of the *trans*-bromo acid to produce a favorable yield of the compound with the desired geometry. A single compound was produced (hydrogen bromide in toluene)

(36) W. R. Vaughan and R. Caple, *ibid.*, **86**, 4928 (1964).

Table III. Product Analyses[a]

Compound in water	% fragmentation, 30°[b]	% fragmentation[c]	% *cis*-hydroxy acid[c]	% *trans*-hydroxy acid[c]	% unsaturated acid[c]	α,β:β,γ unsaturated acid[c]
3	26	36	17.4[d]	10.1[d]	1.5	1.5:1
4	42	46	0	19.4	34.6	7:1
5	45	60	0	38	2	4:1
6	5	13	0	0	87	4:1
7		0	60	20	0	0
In 80% ethanol						
3		29	71	0	0	0
4		47	0	13.3[e]	26.5	3:1
5		68	15	9.9	7.1	4.5:1
6		13	0	0	87	4:1

[a] Under kinetic conditions and at 100° except as noted. [b] Analyses by carbon dioxide evolution (see Experimental Section). [c] Analyses by isolation and glc (see Experimental Section). [d] In addition 35% lactone **7** actually isolated. [e] In addition 13.2% of unidentified product, presumably ethoxy acid(s).

and shown to be a 10-bromodecalin-9-carboxylic acid by examination of its nmr spectrum which completely lacks a signal for a proton attached to a carbon atom bearing bromine. That this is indeed the trans isomer unfortunately has not, to date, proven capable of unequivocal demonstration by synthesis. However, Fisher–Hirschfelder and Dreiding models strongly indicate that the trans isomer is less strained and therefore is the isomer expected under the conditions used for the present preparation. But more significant is its solvolytic behavior in alkaline media: *only* 9,10-octalin is produced, and the rate is incomparably greater than for any known β-bromo acid solvolysis. Consequently there can be little or no doubt that the objective of preparing a structurally rigid trans-diaxial β-bromo acid has been achieved.

All attempts to obtain precise kinetic data for solvolysis of *trans*-10-bromodecalin-9-carboxylic acid either in water or in 80% ethanol were fruitless. The most sophisticated attempts to secure such data involved continuous analysis by infrared measurement of carbon dioxide evolution at temperatures down to −78° (80% ethanol), and solubility problems appeared to interdict measurements at substantially lower pH values. The best information afforded by infrared analysis indicated that the reaction is complete in <10 sec at −78°. Thus if one allows ten half-lives to reach substantial completion (99.9%), one may estimate $k_{-78°} \sim 0.693$ sec^{-1}. And by allowing a rate doubling for each 10° temperature increase, at 62° $k \sim 10^4$ sec^{-1}. This is $\sim 10^7$-fold increase over k_2 (Table I) and $\sim 10^6$-fold over k_5 (or $\sim 10^4$-fold over the rate calculated for fragmentation *only* for diaxial **5** ($k_a \times 0.68$)) (Tables III and IV). Since all runs afforded *only* $\Delta^{9,10}$-octalin with these accelerations, the conformity to Grob's picture is obvious. Thus the decalin acid would appear to be the first example of a saturated β-halo acid which so conforms. To be sure, *some* steric acceleration (as well as from tertiary compared to secondary bromide) is to be expected from the 1,3-diaxial interferences in the decalin acid (four of them as opposed to two in **5**). But it seems unlikely to us that this will account for the magnitude of the observed acceleration, which is based on minimum estimates (both *less* than 10 sec for complete reaction and temperature dependence as only twofold/10°). It must be concluded that previous failures to observe it are directly attributable to the unique problems involved in providing the requisite stereoelectronic conditions for its occurrence.

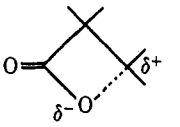
If the decalin acid is accepted as a thus far unique example of wholly synchronous heterolytic fragmentation in saturated β-halo acids, then at the other extreme we have two present examples of the previously recognized dipolar or zwitterion mechanism, **4** and **6**. In the former the zwitterion decomposition favors fragmentation, with deprotonation somewhat less important; and in the latter it is deprotonation which is favored almost to the exclusion of other reactions, fragmentation accounting for but 13% (Table III). Such product distribution has been attributed to thermodynamic control by earlier investigators,[17-19] and Grob[21] has proposed that the composition of fragmentation products (*e.g.*, cis and trans olefins) will be achieved or approached by rotation about the C^2–C^3 bond prior to loss of carbon dioxide. Such potentially free rotation is effectively inhibited in a cyclic system such as **4**, and in one such as **6** it is effectively limited to conformational interconversion. Thus only the cis olefin can be produced, and competition in reaction is limited to fragmentation and deprotonation.

All cases intermediate between the decalin acid and purely zwitterionic examples must partake to a greater or less extent of both mechanisms. Previous examples which show rate enhancement (*e.g.*, the present **3** and **5**), and in particular those in which *only* the less thermodynamically stable olefin is produced, clearly are "concerted." But since apparent β lactonization frequently, if not invariably, is a competitive reaction, it seems reasonable to make a clear distinction between the terms concerted and synchronous in the context of heterolytic fragmentation. The concerted character of β lactonization can scarcely be questioned. But as in any SN2 reaction, the bond-breaking and bond-making processes need not proceed with precise simultaneity. We suggest that the same situation obtains in a nonideally oriented β-halo acid with respect to the "making" of π bonds and the breaking of the C–Hal bond, the latter somewhat preceding the former. Only if the conformational requirements cited above are precisely satisfied (*i.e.*, perfect prealignment of the p orbitals comprising the new π orbitals) will the free energy of activation be sufficiently lowered so that fragmentation supercedes all possible competitors and

is completely concerted, or synchronous. This is readily rationalizable in the ideal conformation in terms of the activation parameters with both decrease in enthalpy and increase in entropy clearly favoring fragmentation over β lactonization. And this at once raises two significant questions: to what extent is β lactonization involved (anchimerically) in any of the solvolyses of β-bromo acids in which the stereochemistry does not disallow it; and where lactonization appears to be a dominant reaction, why is it essentially unaccompanied by fragmentation, *e.g.*, in β-bromo butyrate (Table I)?

Lactonization of any halo acid on solvolysis is effectively a unimolecular process, and one is tempted by the kinetic data for α- to δ-bromo acids in Table I to infer that α- to δ-bromo acids all solvolyze *via* intermediate lactones (effectively constant activation entropies), rate differences being a function of ring strain in the transition states leading to the various sized lactones (*i.e.*, activation energies parallel the strain factors). The inference is strengthened by the change from an activation entropy of $\sim+12$ eu to negative values when unimolecular lactonization becomes improbable, and a higher molecularity (still pseudo first order) is involved in the solvolysis. We suggest, however, that α- and β-bromo acids are pivotal, lactonization being problematical in α-bromo acids and but occasionally demonstrable by actual isolation in β-bromo acids.

Although β-bromobutyrate has been shown to lactonize,[29] albeit in only 6–7% yield under special conditions, the only substantial isolation of a β-lactone under simple solvolytic conditions has been carried out in the improbable case of **3**, which provides a substantial yield of *cis*-cyclopentanecarbo-2-lactone (**7**) on solvolysis (Table III). If such a fused ring β-lactone is stable enough to permit ready isolation, it is not unreasonable to suppose that similar formation and isolation of monocyclic β-lactones should be possible; but this appears not to be the situation, very possibly since there is clearly a much greater entropy increase in opening a monocyclic β-lactone than in opening a fused ring β-lactone such as **7**. The converse is of course true for β lactonizations. One may infer, then, that actual β-lactone formation is the exception rather than the rule. Even though there is considerable circumstantial kinetic evidence for a lactonic intermediate in the most carefully studied case (β-bromobutyrate[15,16]), the very small amount of fragmentation ($\sim$15%), which has a necessarily identical conformational ground state and which is the dominant reaction in two α-alkyl-β-bromo butyrates (Table I), implies that very little lactone is actually formed (*cf.* amount isolated, above). This leaves the special cases cited above[5–8,10,11] and **3**, in all of which extensive fragmentation is also observed. We infer that in such cases where fragmentation is either nonexistent or minimal actual β lactonization will be comparably minimal or nonexistent. This answers the second question posed above: lactonization is *not* a dominant reaction *unless* it is accompanied by comparable fragmentation. And the first question is answered by the obvious corollary that if β lactonization actually occurs, it is anchimerically involved in the solvolytic process by its very (unimolecular) nature. The stereochemical consequences of β-bromobutyrate solvolysis (retention of configuration, pH $\sim$8.5) may be explained without actual lactone formation, as are those for α-bromopropionate solvolysis, *i.e.*, "protection" of the backside of C^β by the proximate carboxylate ion without actual bond formation. The farther from ideality of conformation



one moves (*e.g.*, rotation about the C^1–C^2 bond), the more likely that activation parameters will disfavor fragmentation, but not necessarily β lactonization to the same extent. Thus in **3** we find an acceleration, with real β lactonization competing on nearly equal terms (Table III) with fragmentation. But the C–Br bond-breaking process is clearly not sufficiently in advance of the other processes to afford a free zwitterion, *i.e.*, the one produced from the epimeric **4**. This argues for a concerted but not synchronous fragmentation.

In **5** we also have a concerted process in distinction to the zwitterionic process for the epimeric **6**, the possibility of two individual zwitterions being unlikely if one accepts $\sim10^5$ sec^{-1} for conformational inversion. In the latter compound the rate constant (Tables II and IV) exactly duplicates that for **2** (Table I), which can only involve a zwitterion because of its structural rigidity. That both members of these epimeric pairs cannot involve a zwitterion is evident from the wholly different character of the products, which of course would be the same for each epimer if the same intermediate were involved. Thus we have a zwitterion which cannot fragment (from **1** and **2**), one which fragments slightly (**6**) and one which fragments extensively (**4**), the whole spectrum of postulated behavior with no more than a threefold acceleration for the best fragmenter (**4**) over the fastest nonfragmenter (**1**).

Table IV. Solvolyses of Cyclic β-Bromo Acids in 80% Ethanol

Compd	T, °C	$k \times 10^5$ sec^{-1}	E_a, kcal	$\Delta S^{\neq}$, eu
3	62.0	3470[a]		
	40.1	281	23.7	3.4
	30.0	79.5		
4	62.0	10.2[a]		
	50.3	2.84		
	40.1	0.726	23.9	−7.7
	30.0	0.235		
5	62.0	1030[a]		
	50.3	226		
	40.1	54.6	28.0	14
	30.0	12.7		
6	71.1	6.12[b]		
	62.0	1.93[a]		
	60.0	1.66[b]		
	40.1	0.127[a]	26.8[b]	−2.0[b]
	30.0	0.0302[a]		

[a] Calculated from Arrhenius equation. [b] Reference 21.

Even though there is considerable circumstantial kinetic evidence for a lactonic intermediate in the most carefully studied case (β-bromobutyrate[15,16]), the very small amount of fragmentation ($\sim$15%), which has a necessarily identical conformational ground state and which is the dominant reaction in two α-alkyl-β-bromo butyrates (Table I), implies that very little lactone is actually formed (*cf.* amount isolated, above). This leaves the special cases cited above[5–8,10,11] and **3**, in all of which extensive fragmentation is also observed. We infer that in such cases where fragmentation is either nonexistent or minimal actual β lactonization will be comparably minimal or nonexistent. This answers the second question posed above: lactonization is *not* a dominant reaction *unless* it is accompanied by comparable fragmentation. And the first question is answered by the obvious corollary that if β lactonization actually occurs, it is anchimerically involved in the solvolytic process by its very (unimolecular) nature. The stereochemical consequences

A few words on solvent effects are in order. Two of the examples in Tables II and IV (**4** and **6**) are markedly decelerated by the poorer ionizing solvent, 80% ethanol; **5** is slightly accelerated and **3** is but slightly decelerated. This reinforces the foregoing

Table V. Rate–pH Dependence at 30.1°[a,b]

pH	3		4		5		6	
	$k \times 10^5$ sec^{-1}	% fragmentation	$k \times 10^5$ sec^{-1}	% fragmentation	$k \times 10^5$ sec^{-1}	% fragmentation	$k \times 10^5$ sec^{-1}	% fragmentation
3.52	2.22	23.5			4.32			
3.92	38.4	24.0						
4.35	52.3	23.5			5.42	~40		
5.01	76.8[c]	23.2[c]			7.60			
	62.2[d]	23.0[d]	2.04	40	6.74[d]			
5.35	69.0	25.0			7.69			
5.77	65.2	26.2	2.29	42	8.42	~50		~5
6.78	53.8		2.19	45	7.92		2.02[e]	5
7.55	55.6	26	2.09		6.59		1.80[e]	
8.26	56.8							
	46.1[d]		2.09		9.93			
8.90	53.8		2.00		10.5		0.84[e]	

[a] Analyses by carbon dioxide evolution (Warburg) (see Experimental Section). [b] Buffers at $\mu = 0.45$: R. G. Bates, "Determination of pH; Theory and Practice," Wiley, New York, N. Y., 1964. All rates slightly less for $\mu < 0.45$. [c] No rate change with added pyridine: 22.1% fragmentation. [d] Buffer prepared with KBr in place of KCl ([KBr] ~0.2 *M*). [e] These data involve a large (~50%) uncertainty owing to small per cent of CO_2 produced by fragmentation (*cf.* Table III).

mechanism distinctions: **5** is highly concerted as regards fragmentation and **3** is considerably less so, β lactonization (concerted) being the predominant reaction. Compounds **4** and **6** definitely ionize and dissociate to zwitterions. And competition between fragmentation and β lactonization is predictably affected (Table III): where the former is dominant (**5**), it becomes more so; and where it lags behind, it lags farther. Earlier work in the senior author's laboratory[9] has shown that acetone effects still more extensive fragmentation in **5** than does 80% ethanol.

That **5** should fragment both faster and more extensively in less polar media than **3** suggests that conformational equilibrium may be involved, with a lower dielectric constant leading to destabilization of the diequatorial conformer in which the polar substituents are relatively close together as compared to the diaxial conformer. Such effects are not unknown, but there are insufficient data to make a strong case for the possible significance of such an effect here.

The kinetic data pertinent to the previous and following discussions are assembled in Tables I–VI. The data in Table V show little ionic strength and/or common ion effects. It should be pointed out that two fundamentally different techniques have been used: the usual bromide titration (using an automatic halide ion titrator) and carbon dioxide evolution (using either a Warburg apparatus or a more sophisticated means of measuring volume of carbon dioxide as a function of time). The Warburg method is particularly useful for multiple runs and simultaneous measurement of per cent fragmentation.

One generalization for the acids **3–6** is significant: the per cent of fragmentation is essentially independent of pH and of temperature in the ranges investigated in spite of rate dependence on pH for the trans acid, **5**; and the cis acid, **4**, releases carbon dioxide at a rate which is pH independent. This suggests that pH dependence is most closely associated with lactone formation and does not enter into any of the other possible reactions under these conditions. Thus a β-lactone may be presumed to be formed from **5** and to be progressively more rapidly cleaved with rising pH. The deviation from theoretical pH dependence in the case of **3** (Table VI) is suggestive of general acid catalysis in this range, which disappears as the pH increases.

Table VI. pH Deviation (Δ) of Experimental Rate Constants at 30.1° for **3** from Theory[a]

pH[b]	$k_{exptl} \times 10^5$ sec^{-1}	$k_{theor} \times 10^5$ sec^{-1}	$\Delta \times 10^5$
6.5	58	56	+2
6.0	60	55	+5
5.5	66	54	+12
5.0	77	51	+26
4.5	60	42	+17
4.0	41	28	+13
3.5	22	14	+8

[a] $k_{exptl} = k_{theor}K_a/[H_3O^+]/(1 + K_a/[H_3O^+]) = k_{theor}/([H_3O^+]/K_a + 1)$; $k_{theor} = k_1 + k_2$. [b] Buffers at $\mu = 0.45$ (*cf.* Table V, footnote *b*).

There is nothing in the proposed zwitterion hypothesis which necessarily contradicts any of the stereochemical arguments relative to β lactonization. But it must be pointed out that **7** does not obey the rule of exclusive alkyl–oxygen cleavage[15,16,37] in mildly alkaline media. And with the exception of **5**, all solvolyses are retarded in 80% ethanol (Table IV), as would be expected for processes whose rates are ionization–dissociation dependent. The acceleration in the case of **5**, with increase in per cent of fragmentation, suggests that the diaxial conformation is more readily attained in the poorer solvating medium and thus one more nearly approaches the ideal conformation for fragmentation.

In summary, one is led to confirm Grob's assignment of the dehalogenative decarboxylation to the general class of heterolytic fragmentation reactions. Two limiting mechanisms exist: the synchronous process, and a stepwise process involving ionization–dissociation of the β-carbon–bromine bond, distribution among the various possible products from the zwitterion moiety being governed by its stereoelectronic characteristics.

Experimental Section[38–40]

Preparation of β-Bromo Acids. Compounds **1–6** have been described in previous papers.[9,33,36] Each of the compounds **3–6** was

(37) J. F. Lane and H. W. Heine, *J. Amer. Chem. Soc.*, 73, 1348 (1951).
(38) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich.
(39) Nmr spectra from Varian Associates A-60 spectrometer with internal tetramethylsilane reference.
(40) Mass spectra from A.E.I.-MS 12 spectrometer. We are indebted to Mr. Oliver Norton for preparation of the spectra.

purified until vpc analysis of the methyl ester (diazomethane) indicated >99% purity.

$\Delta^{4,10}$-Octalin-9-carboxylic Acid. The ethyl ester was prepared from a redistilled commercial mixture of methyl and ethyl esters of cyclohexanone-2-carboxylic acid with methyl vinyl ketone.[41-43] Hydrolysis of the ester was accomplished by means of potassium *tert*-butoxide in dimethyl sulfoxide.[44] The free acid was recrystallized from hexane: mp 86–87°, with no change after sublimation at 55–60° (1.5 mm). The infrared and nmr spectra are consistent with the assigned structure.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.44; H, 9.09.

***trans*-10-Bromodecalin-9-carboxylic Acid.** The preceding unsaturated acid was treated with hydrogen bromide in toluene containing a few milligrams of hydroquinone. The product was isolated by evaporation and purified by recrystallization from ether: mp 155–157° dec; mass spectrum, 100% peak, *m/e* 135; highest peak, *m/e* 181 (compound less HBr and CO_2H); nmr, broad multiplet at τ = 7.3–8.9, similar to that observed for a sample of *trans*-9,10-dibromodecalin (τ = 7.2–8.4).[45]

Anal. Calcd for $C_{11}H_{17}BrO_2$: C, 50.59; H, 6.57; Br, 30.60. Found: C, 50.61; H, 6.59; Br, 30.71.

Solvolyses of the Decalin Acid. In both water and 80% ethanol the sole product was $\Delta^{9,10}$-octalin. Attempts to obtain kinetic data by means of a Warburg apparatus (see below) or by means of a continuous infrared analyzer down to −45.3° were unsuccessful. The reaction was complete in less than 2 min (~10 sec, very likely instantly). The reaction in 80% ethanol at −78° gave inconclusive results owing to partial solidification of the solution. We estimated at least a 10^6-fold acceleration over **6**.

***cis*-Cyclopentane-1-carbo-2-lactone (7).** This substance was isolated by preparative vpc from the analysis runs for the solvolysis of **3** (see below): $n^{30.5}$D 1.4520; mol wt 115 (calcd 112); infrared, 1820 cm^{-1}; nmr C_1–H 228 Hz, octet (*J* values ~6.6, 4.1, 1 Hz), C_2–H 292 Hz, 1:2:1 triplet (*J* ~ 3.5 Hz), six proton complex multiplet, 115 Hz.

Anal. Calcd for $C_6H_8O_2$: C, 64.20; H, 7.14. Found: C, 63.98; H, 7.19.

Product Analyses for Reactions in Water (Table III). For each isomer (**3–6**) three to six runs were made: 0.200 mmol of the acid was placed in a sealed glass bubble with a small lead weight, and the bubble was placed in a 55 × 200 mm borosilicate glass test tube containing 20 ml of water, 10 ml of chloroform, and 120.8 mg of potassium carbonate. The test tube was cooled to −60° and sealed and then was placed in boiling water. After 5 min the test tube was vigorously shaken to break the bubble and then was returned to the boiling water. After 30 min, with occasional shaking, the test tube was removed and cooled until solidification began, and then it was opened.

The cycloalkene (chloroform layer) was treated with bromine in chloroform, excess bromine being removed with thiosulfate, and the dibromocycloalkane was recovered (rotary evaporator) and analyzed by vpc, using bromobenzene as internal standard in carbon disulfide solution.

The original aqueous layer (basic) containing the acids produced was partially neutralized (0.2 *N* hydrochloric acid) and most of the water removed (rotary evaporator). The remaining 1–2 ml was acidified (0.2 *N* hydrochloric acid) and extracted four times with ether which was then dried over anhydrous magnesium sulfate. The ethereal solution was filtered and treated with diazomethane and analyzed by vpc, using comparisons with authentic samples of the possible products.

Calibration runs for the cycloalkenes indicated 90% efficiency (due to volatility), and an appropriate correction was applied in each case for the final analytical data in Table III.

Product Analyses in 80% Ethanol. The solvent is 80 vol % absolute ethanol, 20 vol % water. The reaction was carried out as for water solution. Upon opening the test tube, *ca.* 12 ml of purified pentane and 20 ml of saturated aqueous sodium chloride were added. The pentane solution of cycloalkene was treated as for the chloroform solution (above). Calibration runs indicated 92% efficiency, and appropriate corrections were made in the data displayed in Table III.

The acidic components were isolated essentially as for the water cases (above), all water-containing solutions being kept saturated with sodium chloride.

In the case of **5**, 2-bromo-1-ethoxycyclohexane was formed during bromination of cyclohexene. Its identity was established by reaction of cyclohexene with bromine–chloroform in the presence of ethanol and silver trifluoroacetate. An nmr spectrum confirms the assigned structure.[46]

Kinetics by Bromide Release. An Aminco-Cotlove automatic chloride titrator was used as described in a previous paper.[33]

Kinetics by Carbon Dioxide Release. The reaction vessel for single runs is described elsewhere[47] and was modified to permit rapid circulation (pump) of thermostated water. Carbon dioxide evolution was followed by pressure increase at constant volume and temperature with appropriate corrections for its solubility in the buffered solutions (see below). For multiple runs a Warburg apparatus[48] was used. Determination of the flask constant for conversion of pressure change to quantity of carbon dioxide was achieved by the mercury method.[49] The solid bromo acids were introduced into the magnetically stirred buffered solutions at the required reaction temperature. Readings were taken at 2-min intervals for 50 min and thereafter at 4-min intervals, and all readings were corrected by means of a thermobarometer. The final pressure was reached after from 5 (**3**) to 36 (**6**) hr; and for each run there was obtained a set of 20–30 pressure–time values. Rates were calculated from $P_\infty - P_{corr}$ and by the Guggenheim method[50] which is independent of the final pressure. Methods agree within 2% of recorded values. The corrected pressure values take into account the solubilities of carbon dioxide in the buffered solutions.[51]

Acknowledgment. The senior author is indebted to Mr. Don Phillips and Mr. Edmund B. Ross (University of Michigan) for checking certain of the carbon dioxide kinetic data by the bromide automatic titrator method.

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(49) Reference 48, pp 46–47.
(50) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961, pp 49–50.
(51) Reference 48, p 31.