chloric acid (10 ml) were added. The ether layer was separated, washed several times, and treated with 5 ml of concentrated hydrochloric acid. The deep pink color was dispelled by 25 ml of methanol; the mixture was stirred 30 min and worked up as usual. The ether (1.1 g) boiled at 131° (40 μ) (colorless, viscous oil). The 1-deuterio derivative was prepared similarly using aluminum hydride. Both were characterized by their infrared and nmr spectra.

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A Stereospecific Friedel–Crafts Reaction. The Alkylation of Benzene with γ-Valerolactone

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Abstract: Alkylation of benzene with (*S*)-(−)-γ-valerolactone in benzene solvent with 1.2 equiv of aluminum chloride gives (*R*)-(−)-γ-phenylvaleric acid with 40% net inversion of configuration. The reaction appears to involve racemization of an intermediate species with the alkylation competing with return to starting material.

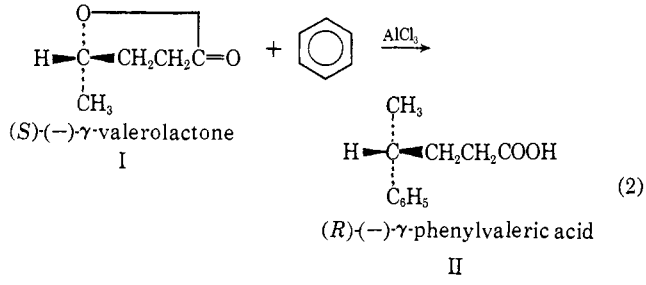
Friedel–Crafts reactions have been studied extensively and used widely in organic chemistry. The entire field has been reviewed recently in great detail[1] and needs little introduction. In the general case, the Friedel–Crafts alkylation can be written as

$$RY + ArH \xrightarrow{\text{Lewis acid}} RAr + HY \qquad (1)$$

where Y can be almost any leaving group.[1] Among the more common RY's are alkyl halides, alcohols, ethers, and esters.

Because of the general utility of this reaction, it is natural to examine the stereochemistry in order to expedite synthetic schemes as well as to help in understanding the reaction. All previous studies have demonstrated at best only minute stereospecificity; the general result in these reactions is extensive racemization and rearrangement. Thus, for example, Price and Lund[2] observed 1% net inversion in alkylation of benzene with 2-butanol and boron trifluoride. Similarly, Burwell and his co-workers found small but measurable inversion in alkylation with alcohols[3] and ethers.[4] In an experiment designed to distinguish racemization occurring independently from rearrangement, Streitwieser and Stang[5] showed that 2-propanol-1,1,1-d_3 gives racemic products in the presence of BF_3, while neither starting material nor products are racemized under the reaction conditions. These experiments suggest that, in general, Friedel–Crafts reactions of secondary and tertiary moieties proceed through intermediates which can racemize (or are racemic) and then give the products without return to starting material. Sharman[6] has discussed a generalized mechanism which includes this requirement and also accounts for the reactions of primary systems. Such reactions apparently proceed by a displacement process since the kinetics are first order in aromatic species and the products are not completely rearranged.[7]

A convenient synthesis of γ-phenyl-substituted carboxylic acids can be achieved by the alkylation of benzene with γ-lactones and aluminum chloride. This reaction has been known for many years and has been studied by Eijkman,[8] Christian,[9] and Truce and Olson.[10] Studies of its scope have shown that it proceeds in good yield and, surprisingly, without rearrangement. In an effort to synthesize γ-phenylvaleric acid-γ-*d*, we attempted the alkylation of benzene with γ-valerolactone-γ-*d*. After observing that this reaction proceeded with more than 96% incorporation of deuterium in the γ position of the product, we then examined the reaction to see whether there was any stereospecificity. We observed that reaction 2 proceeds with as much as 40% over-all net inversion, making it the first-known Friedel–Crafts reaction with extensive stereochemical integrity.



(2)

Results

In order to determine the stereochemical course of this reaction, it is necessary to know the absolute configurations of starting material and product. Fortunately these have both been related through unequivocal chemical means to lactic acid. Most of the relationships are known from the work of Levene and Haller. The configurations are related as follows:

(1) G. A. Olah, Ed., "Friedel–Crafts and Related Reactions," Interscience Publishers, Inc., New York, N. Y., 1963.
(2) C. C. Price and M. Lund, *J. Am. Chem. Soc.*, **62**, 3105 (1940).
(3) R. L. Burwell, Jr., and S. Archer, *ibid.*, **64**, 1032 (1942).
(4) R. L. Burwell, Jr., L. M. Elkin, and A. D. Shields, *ibid.*, **74**, 4570 (1952).
(5) A. Streitwieser, Jr., and P. J. Stang, *ibid.*, **87**, 4953 (1965).
(6) S. H. Sharman, *ibid.*, **84**, 2945 (1962).
(7) H. Jungk, C. R. Smoot, and H. C. Brown, *ibid.*, **78**, 2185 (1956), and earlier papers cited therein.
(8) J. F. Eijkman, *Chem. Zentr.*, [I] 1416 (1904).
(9) R. V. Christian, *J. Am. Chem. Soc.*, **74**, 1591 (1952).
(10) W. E. Truce and C. E. Olson, *ibid.*, **74**, 4721 (1952).

Table I. Reaction Stereochemistry

Run	Solvent (M)	Time, sec	% reaction[a]	Recovered lactone, % racemized	γ-Phenylvaleric acid, % Inverted	γ-Phenylvaleric acid, % Racemized
1[b]	C_6H_6 (11.3)	7200	100	...	40	60
2	C_6H_6 (11.3)	82	46	10	36	64
3[b]	CS_2 + C_6H_6 (1.9)	4800	100	...	10	90
4	CS_2 + C_6H_6 (1.9)	143	26	18	...	...
5	CS_2 + C_6H_6 (1.9)	415	70	80	10	90
6	CS_2 + Et_6C_6 (0.7)	143	...	35	...	...
7	CS_2	143	...	56	...	...

[a] Based on recovered lactone; see text. [b] Reaction carried out by slow addition of lactone.

(*R*)-(−)-lactic acid → (*R*)-(−)-1,2-propanediol[11] → (*R*)-(−)-β-hydroxybutyric acid[12] → (*R*)-(−)-γ-hydroxyvaleric acid[13] → (*R*)-(+)-γ-valerolactone;[13] and (*R*)-(−)-lactic acid → (*R*)-(−)-1,2-propanediol[11] → (*R*)-(−)-β-hydroxybutyric acid[12] → (*R*)-(−)-1,3-butanediol[13] → (*R*)-(−)-2-butanol[14] → (*S*)-(+)-2-phenylbutane[15] → (*S*)-(+)-β-phenylbutyric acid[16] → (*S*)-(+)-γ-phenylvaleric acid.[17] Consequently, reaction 2 with the observed signs of rotation occurs with over-all inversion of configuration, since (−)-lactone gives (−)-γ-phenylvaleric acid.

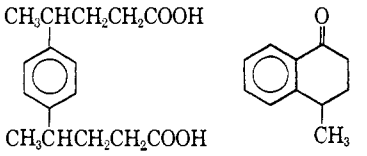
In studies of reactions which have some stereospecificity it is often possible to obtain significant information by isolating products and unreacted starting material from the reaction before it is completed. From this it may be possible to demonstrate whether starting material or product racemizes under the reaction conditions and, if so, to correct the observed stereochemistry in order to determine the true stereochemical properties of the reaction. To this end, we have studied the stereochemical consequences of the reaction with different concentrations of benzene by quenching the reaction mixture before all of the starting lactone had undergone reaction.

It was found that in order to isolate unreacted starting material this reaction must be quenched after 1 or 2 min; the reaction is complete within about 5 min. There is an inherent difficulty in controlling reactions such as this which have very large heats of mixing of reactants and are heterogeneous. Normally, these reactions are run by adding reactants slowly, thereby keeping the temperature low. We observed that the stereochemistry was relatively insensitive to the reaction temperature (5–60°). Therefore, in order to analyze starting material, we cooled all the reactants to 5°, then mixed them rapidly. The temperature then rose to about 25° and remained at this point until the reaction was quenched by pouring it into ice water.

The results of a number of experiments are tabulated in Table I. The specific rotations are listed in the Experimental Section. In addition, we have subjected optically active 2-butyl acetate to these reaction conditions and have recovered 2-phenylbutane with >99.9% racemization.

The following facts can be deduced from the data in Table I. First, the reaction products are not racemized under the reaction conditions. Thus, in run 2, in which lactone is little racemized, the product stereochemistry is independent of reaction time. Furthermore, we observe no product racemization on prolonged heating of the solutions. Second, lowering the benzene concentration causes an increase in racemic lactone and racemic product relative to active product. Third, an aromatic compound is not required for racemization to occur. Fourth, a nonreactive aromatic (hexaethylbenzene) actually suppresses the racemization of lactone.

In order to analyze the data, it is necessary to know the ultimate disposition of products. The primary product, about 70–80%, is γ-phenylvaleric acid. The other two main products are the dialkylated material III and the cyclized tetralone IV. These two compounds, together with II, account for almost all of the material.[9,10]



III IV

Since III and IV must arise from II, it is reasonable to assume that *II recovered from the reaction represents all of the reaction product in terms of stereochemistry.* Thus, we base our analysis of extent of reaction on recovered lactone. It is readily apparent that the observed racemization of II results in part from concurrent racemization of the lactone, I. We can correct at least crudely for this by the following method.[18] Racemization of lactone is first order in active lactone. Disappearance of lactone is first order in total lactone but independent of optical activity. For a given experiment we know, from the data in Table I, the extent of reaction and racemization at the same time. The ratio of pseudo-first-order rate constant for racemization, k_α, to pseudo-first-order rate constant for reaction, k_p, is k_α/k_p = log [fraction of remaining optical activity]/log

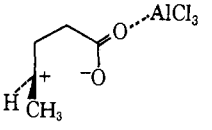
(11) P. A. Levene and H. L. Haller, *J. Biol. Chem.*, 67, 329 (1926).
(12) P. A. Levene and H. L. Haller, *ibid.*, 65, 49 (1925).
(13) P. A. Levene and H. L. Haller, *ibid.*, 69, 165 (1926).
(14) P. A. Levene, H. L. Haller, and A. Walti, *ibid.*, 71, 465 (1926–1927).
(15) J. Kenyon, H. Phillips, and V. Pittman, *J. Chem. Soc.*, 1072 (1935).
(16) D. J. Cram, *J. Am. Chem. Soc.*, 74, 2137 (1952).
(17) P. A. Levene and R. E. Marker, *J. Biol. Chem.*, 110, 329 (1935).

(18) Estimates of reaction rate constants are made by *assuming* that the reaction is homogeneous. These estimates will be approximately correct if complex formation between the aluminum chloride and lactone is relatively fast compared to the other steps and if only dissolved complex undergoes reaction (racemization, alkylation, etc.).

[fraction of remaining lactone]. From run 2, $k_\alpha/k_p \approx 0.17$; from run 4, $k_\alpha/k_p \approx 0.66$. The product, when all lactone has disappeared, will be racemized by the fraction $1/(1 + k_p/k_\alpha)$. In terms of our data, this means that in run 1 some 15% of the observed racemization in the product is due to concurrent racemization of lactone; therefore the "true" stereochemical consequence of the reaction is about 47% net inversion, 53% racemization. Similarly, from run 3, we observe 40% racemization due to starting material; thus about 83% racemization, 17% inversion under these conditions is the "true" stereochemistry for product formation.

Discussion

There are a number of observations to be accounted for in this reaction if one is to formulate a mechanism. First, there is stereochemistry (inversion plus racemization); second, there is the lack of rearrangement; third, there is the dependence of stereochemistry on benzene concentration. The first two observations are undoubtedly associated; the same factors probably account for stereochemical integrity and lack of rearrangement. The mechanism in Figure 1 is consistent with these observations. The asterisk indicates optically active species. For convenience in the analysis we formulate this mechanism in terms of active and racemic species, although use of the enantiomers would be equally valid. X is an intermediate species which is capable of optical activity (X*). One might reasonably assume that X is an ion-pair species with appreciable interaction between the leaving group and the carbonium ion center. A possible structure is shown below. Equally reasonable alternatives can easily be visualized. For example, it may be that a chloride is coordinated with the carbonium ion center. The stereochemistry is maintained provided that rotation around the C–C bond does not occur. That is, the carbonium ion center may be planar but in an asymmetric environment and thus not racemic. Because of the stereochemical integrity as well as the absence of rearrangement, it is probable that there is a close association between the leaving group and carbonium ion. This association makes rearrangement a relatively unfavorable process here as compared with more "free" carbonium ions. This association also accounts for the return to starting material under the reaction conditions. Typically, in Friedel–Crafts reactions catalyzed by aluminum halides one cannot recover rearranged or racemized starting material. Instead, carbonium ions, once formed, give only products. The return, then, is further evidence for this ion pair. Naturally, the precise nature of the bonding or other properties of this intermediate are difficult to determine, but we anticipate further studies in this area. In this mechanism racemization occurs by rotation around the C–C bond. Since reaction of X* by k_r converts one molecule of optically active material to one molecule of racemate, the rate constant for rotation is actually one-half of k_r.



X

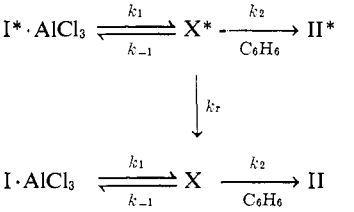


Figure 1.

This mechanism accounts for the effect of benzene concentration on stereochemistry. If we assume a steady-state concentration of X*, then decreasing the benzene concentration will increase total racemic material relative to active product and will also increase racemic lactone relative to racemic product. This is consistent with the data, and it can be placed on a nearly quantitative basis.[18] By assuming the steady state, the relative value of k_r to k_2[benzene] is given by the amount of racemic lactone plus racemic product relative to active product. Similarly, the ratio of k_{-1}/k_2[benzene] is given by racemic lactone/racemic product, with racemic product corrected for the amount derived from racemic lactone as analyzed previously. Somewhat surprisingly, in view of the heterogeneous reaction, the results for neat benzene (11.3 *M*) and CS_2 (1.9 *M* benzene) are quite consistent. In benzene solvent, the ion pair X* partitions as follows: for every time it returns, it reacts four times and rotates four times (racemizes eight times). Thus, k_{-1} is roughly 2 times k_2, and k_r is about 22 times k_2. This mechanism also predicts that racemization should occur in the absence of benzene, consistent with the observations of runs 6 and 7. In fact, run 6 which approximates run 4 in solvent conditions shows that X* partitions in the usual way exclusive of the benzene pathway in the absence of benzene. Thus, racemization in run 6 is equal to racemization of lactone plus total product formation in run 4.[19]

Friedel–Crafts reactions of primary systems are thought to proceed in part by a displacement process.[6,7] One observes some primary alkylates, and the kinetics are first order in aromatic species.[7] A displacement process appears highly unlikely in our reaction. We observe at least as much disappearance of active lactone in the absence of benzene, and it thus appears that an intermediate intervenes as postulated. That the stereochemical result is not due to the heterogeneous nature of the reaction has been shown by the observation of about 20% net inversion in the reaction of I carried out in 1,2,4-trichlorobenzene with aluminum bromide catalyst, a homogeneous reaction.

It is important to know what causes the lactone to differ from other substrates in this reaction. A simple ester, 2-butyl acetate, gives more than 99.9% racemization, and we thus conclude that it is not the ester function which is important. The unique feature of lactones is the enforced proximity of the leaving group by virtue of its being a part of the same molecule. Significantly, the literature indicates that lactones alone among secondary substrates do not rearrange. Thus, stereospecificity may be general for all reasonably sized lactones. There are few analogies for opening lactone

(19) Aromatic compounds appear to moderate the effectiveness of the aluminum chloride, possibly by complex formation. Hexaethylbenzene, which cannot be alkylated, approximates benzene in its solvent effect. Therefore run 6 is chosen over run 7 for comparison.

Table II. Specific Rotations and Optical Purities

Run[a]	[α] of starting lactone (neat), deg	OP of starting lactone, %[b]	[α] of γ-phenylvaleric acid (neat), deg	OP of acid, %[c]	[α] of recovered lactone (neat), deg	OP of recovered lactone, %[b]
1	$[\alpha]^{24}D$ −14.2	51.2	$[\alpha]^{25}D$ − 4.52	20.4	...	...
2	$[\alpha]^{24}D$ −14.7	52.8	$[\alpha]^{23}D$ − 4.19	19.0	$[\alpha]^{23}D$ −13.3	47.9
3	$[\alpha]^{25}D$ −14.2	51.2	$[\alpha]^{25}D$ − 1.09	4.93	...	...
4	$[\alpha]^{25}D$ −14.8	53.3	...	...	$[\alpha]^{18}D$ −12.2	44.0
5	$[\alpha]^{16}D$ +7.91	28.5	$[\alpha]^{17}D$ + 0.65	2.94	$[\alpha]^{18}D$ +1.59	5.73
6	$[\alpha]^{17}D$ −5.87	21.1	...	...	$[\alpha]^{18}D$ −3.83	13.8
7	$[\alpha]^{18}D$ −13.4	48.3	...	...	$[\alpha]^{18}D$ −5.87	21.2

[a] See Table I for solvent composition. [b] Based on $[\alpha]^{20}D$ −27.75° for pure lactone.[13] [c] Based on $[\alpha]^{20}D$ −22.1° for pure acid.[17]

rings by a unimolecular process. It is interesting, however, that Noyce and Banitt[20] have recently concluded that a β-lactone can open to an ion pair which decarboxylates faster than it can rotate. This suggests that it is possible to maintain stereochemistry in ion-paired species of this type.

The scope of stereospecific Friedel–Crafts reactions has not been fully explored. If proximity is the important factor, then cyclic ethers, for example, may show stereospecificity as well as lactones. It is quite possible that different Lewis acids may affect the stereochemistry. We assume that the effect of hexaethylbenzene in run 6 may be due to its complexing with the aluminum chloride. To the extent that such a complex is a weaker Lewis acid than aluminum chloride alone, racemization would decrease, as observed. On the basis of our mechanism, we would expect that more nucleophilic aromatics will give more inversion. It is not yet clear whether our system will serve as a good model for other Friedel–Crafts reactions, but it should provide considerable insight into these processes.

Experimental Section[21]

(*S*)-(−)-γ-Valerolactone. γ-Valerolactone (Eastman Kodak, practical) was resolved through the cinchonidine salt of the hydroxy acid according to the procedure of Levene and Haller.[13] After four recrystallizations, (−)-valerolactone was obtained about 50% optically pure. The (+) enantiomer was recovered from the mother liquors. γ-Valerolactone resolved in this fashion had bp 72–73° (7.6 mm), and the infrared spectrum was identical with that of pure material.

γ-Phenylvaleric Acid. To a stirred mixture of 4.95 g (37.2 mmoles) of aluminum chloride and 20 ml of dry benzene was added 2.93 g (29.3 mmoles) of (−)-γ-valerolactone ($[\alpha]^{23.5}D$ −14.2°) at a rate sufficient to maintain the temperature at 33–35°. The reaction mixture, which was homogeneous at the end of lactone addition, was then heated on a steam bath for 30 min, cooled to 0°, and added to 20 ml of cold 6 *N* hydrochloric acid. The benzene layer was separated and extracted with three 100-ml portions of saturated sodium bicarbonate solution. The bicarbonate extracts were acidified with hydrochloric acid and extracted with three 80-ml portions of ether. The ether was dried with sodium sulfate, and the solvent was evaporated to give 4.52 g of crude product. This was distilled on a microcolumn, bp 122–123° (0.1 mm), to give 2.92 g (55%) of γ-phenylvaleric acid, $\alpha^{25}D$ −2.37° (0.5 dm, neat); $[\alpha]^{25}D$ −4.51°. An analysis was obtained on a sample of optically active γ-phenylvaleric acid isolated as above.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.86; H, 7.83.

The observed rotation would require 32% of the unracemized starting material to be present if all of the activity were due to the starting material. γ-Valerolactone is readily identified by its intense absorption at 1775 cm^{-1}; this absorption was absent. In addition, vpc analysis of the product showed no lactone or other impurities to be present. Control experiments indicate that 0.1% lactone would be easily detected. Since the starting material and the product have comparable specific rotations, the activity must be due to the γ-phenylvaleric acid. These conditions are typical for reactions allowed to go to completion.

γ-Phenylvaleric Acid. To a cooled (5°) suspension of 3.60 g (27.1 mmoles) of aluminum chloride in 15 ml of dry benzene was added, all at once, 2.07 g (20.7 mmoles) of (−)-γ-valerolactone ($[\alpha]^{24}D$ −14.7°, neat), and the reaction mixture was swirled for 82 sec. The reaction mixture was then poured into cold dilute hydrochloric acid. The benzene layer was separated and extracted twice with 60 ml of water. The combined aqueous layers were continuously extracted with ether for 24 hr. The ether solution was dried with sodium sulfate. Distillation gave 1.12 g (54%) of γ-valerolactone, bp 78–79° (7.0 mm), $[\alpha]^{23.6}D$ − 13.3°, neat.

The benzene layer was then extracted with saturated sodium bicarbonate solution. The aqueous extract was acidified and extracted with ether. The ether solution was dried with sodium sulfate, and distillation gave 1.30 g (35%) of γ-phenylvaleric acid, bp 110.0–110.5° (0.1 mm), $[\alpha]^{23}D$ −4.19°, neat.

γ-Phenylvaleric acid worked up in this manner showed no absorption at 1775 cm^{-1}. In addition, the methyl ester of (−)-γ-phenylvaleric acid prepared by treatment with oxalyl chloride followed by methanol and isolated by preparative vpc showed <0.5% of γ-valerolactone present. The methyl ester isolated by preparative vpc had a rotation essentially equal to that of the free acid.

Control experiments carried out on known mixtures showed that almost all of the material could be extracted by the above procedure. These conditions are typical for reactions stopped before completion.

Observed rotations and optical purities are summarized in Table II.

Acknowledgment. We thank Professor Harry S. Mosher for a sample of optically active 2-butanol. We are indebted to the Research Corporation for partial support of this work.

(20) D. S. Noyce and E. H. Banitt, *J. Org. Chem.*, 31, 4043 (1966).

(21) Boiling points are uncorrected. Rotations were taken neat with a Zeiss polarimeter in an end-filled, 0.5-dm tube. Microanalyses were carried out by Messrs. E. Meier and J. Consul, Stanford Microanalytical Laboratory.