

THE RACEMIZATION OF α -PHENYL BUTYRIC ACID IN THE TRIFLUOROACETIC ACID-TRIFLUOROACETIC ANHYDRIDE SYSTEM IN ANHYDROUS SOLVENTS

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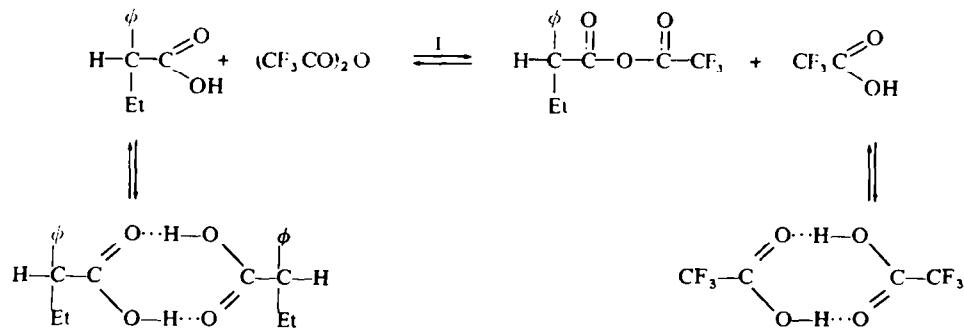
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Abstract—Study of the racemization of α -phenyl butyric acid in the $(CF_3CO)_2O-CF_3CO_2H$ system, indicates that loss of optical activity occurs at the α -phenyl butyric trifluoroacetic mixed anhydride formed in these systems. Kinetic results indicate bifunctional catalysis and the structure of the intermediate complex [mixed anhydride, trifluoroacetic acid] is discussed.

THE INVESTIGATION of catalysis by the carboxylic group is considered a necessary step in studying some enzymatic reaction rates.¹ The use of anhydrous solvents is not a limiting factor as it is known that enzymatic cavities have hydrophobic regions where ionisation is probably suppressed.

This work is part of a study made in our laboratory on reversible inter and intra molecular acyl transfers.

In a previous publication,² we studied the α -phenyl butyric acid—trifluoroacetic acid—trifluoroacetic anhydride system, and established the relative concentrations of these different species, so that the system studied could be represented by the following reversible equations:



Under such conditions, optically active α -phenyl butyric acid racemizes progressively. Here we report our study of this racemization.

Nature of species and bond involved in racemization. α -Phenyl butyric acid does not racemize in CF_3CO_2H either neat or in the presence of solvent. So, when racemization does occur, it must involve the mixed anhydride.

* This study is part of a work to be included in the Dr. es Sc. of H.C. (N° d'ordre C.N.R.S.: A.O. 6532.)

Though loss of optical activity seemed logically attributable to the breaking of the CH bond at the active centre, we would not reject *a priori*, the possibility of racemization by decarbonylation of an α -phenyl butyrylium ion ($C_2H_5CH(C_6H_5)CO^+$); in fact, some hypotheses formulated in the literature^{3,4,5} could possibly lead to the formation of such an intermediate in the media studied.

In our opinion the low acidity of these reactional media makes the formation of such an oxocarbonium ion unlikely.⁶ We attempted to racemize α -ethyl hydratropic acid (2-phenyl propanoic acid) under the same conditions. Formation of an α -ethyl hydratropilium ion should occur at the same rate as that of an α -phenyl butyrylium ion,^{7,8} but its decarbonylation should be much faster since it leads to a tertiary carbonium ion.

Since there is a total absence of racemization of optically active α -ethyl hydratropic acid, we think that loss of optical activity of α -phenyl butyric trifluoroacetic mixed anhydride can only be a result of the breaking of the CH bond at the active centre in the mixed anhydride itself.

The system (defined by equation 1) reaches equilibrium quickly (a few minutes) while the half-life of racemization is several hours (Table 1). So, it is likely that racemization does not occur during the mixed anhydride formation step, but at a later stage.

Kinetic study of the mixed anhydride racemization

Results. From the high value of the equilibrium constant ($K_1 = 10$),² it is clear that, in solutions prepared from low concentrations of active α -phenyl butyric acid in the $(CF_3CO)_2O-CF_3CO_2H$ system, almost all the acid reacts and leads to the active mixed anhydride.

Establishment of the racemization rate equation. For each solution of α -phenyl butyric acid in the $(CF_3CO)_2O-CF_3CO_2H$ system, we observe a linear variation of $\log \alpha_0/\alpha_t$ with time (α is the optical rotation). This might suggest a first-order rate

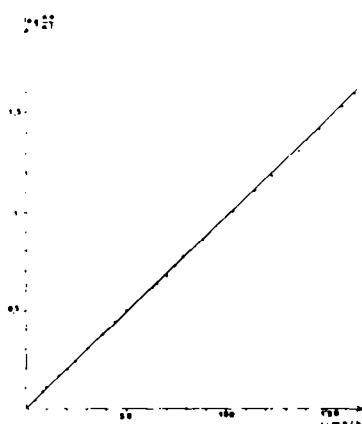


FIG. 1. Linear dependence of $\log \alpha_0/\alpha_t$ with time for the racemization of a solution in CCl_4 of initial composition: $EtCH(Ph)CO_2H$ (0.05 mole, l^{-1})— $(CF_3CO)_2O$ (1 mole. l^{-1}).

equation:

$$v = k_1 [\text{MA}^*] \quad (1)$$

k_1 = experimental rate constant; $[\text{MA}^*]$ = active mixed anhydride conc.

However, changing the relative concentrations in the system causes a variation in rate constant. (Table 1)

TABLE I. APPARENT RATE CONSTANTS FOR THE MIXED ANHYDRIDE RACEMIZATION MEASURED FOR DIFFERENT INITIAL CONCENTRATIONS

$\text{EtCH}(\text{Ph})\text{CO}_2\text{H}$ mole.l ⁻¹	$(\text{CF}_3\text{CO})_2\text{O}$ mole.l ⁻¹	$\text{CF}_3\text{CO}_2\text{H}$ mole.l ⁻¹	$k_1 \cdot 10^5$ s ⁻¹
0.05	1	0	0.28
0.05	0.9	0.1	0.43
0.05	0.8	0.2	0.57
0.05	0.6	0.4	0.77
0.05	0.4	0.6	1.03
0.05	0.2	0.8	1.13
0.05	0.1	0.9	1.09

This implies a degeneracy in the reaction order, which can be explained by the chemical invariance of the medium (once equilibrium is reached, the active mixed anhydride concentration is the only one which changes). In fact, k_1 is an increasing function of the trifluoroacetic acid concentration (Fig. 2).

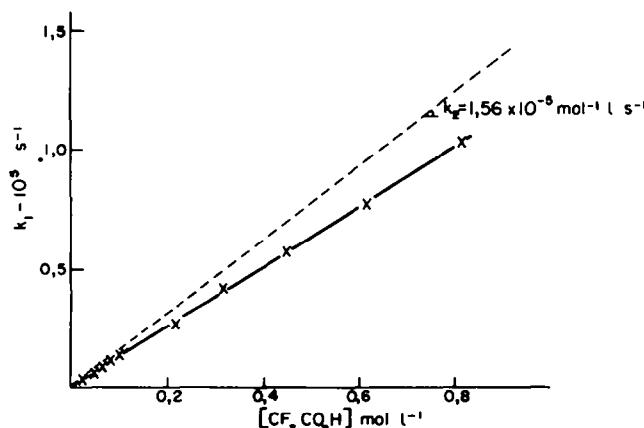


FIG. 2. Dependence of apparent rate constant (k_1) on $\text{CF}_3\text{CO}_2\text{H}$ concentration, for 0.05 mole.l⁻¹ mixed anhydride solutions in CCl_4 solvent. ----- theoretical, —— experimental

For acid concentrations varying between 0 and 0.1 mole.1⁻¹, k_1 is found to conform to eq. 2:

$$k_1 = k_2 [\text{AH}] \quad (2)$$

k_2 = kinetic constant; $[\text{AH}]$ = trifluoroacetic acid conc.

For concentration ranges between 0.1 and 1 mole.1⁻¹, k_1 increases less rapidly than expected: the difference between the experimental curve and the theoretical (established on the basis of eq. 2) increases with acid concentration. This fact could be explained by dimerization of the trifluoroacetic acid. Therefore, the monomeric form could act as the reaction's catalyst*.

The rate equation becomes:

$$v = k_2 [\text{MA}^*] [\text{AHm}] \quad (3)$$

$[\text{AHm}]$ = monomeric trifluoroacetic acid conc.

Solvent effects. We studied similarly the racemization of the mixed anhydride in the solvents CH_2Cl_2 , CCl_4 and C_6H_{14} †. The variations of k_2 observed on changing solvents are in Table 2.

TABLE 2. VARIATION OF RACEMIZATION RATE CONSTANT WITH SOLVENT

Solvents	CH_2Cl_2 $\epsilon = 9.08$	CCl_4 $\epsilon = 2.238$	C_6H_{14} $\epsilon = 1.89$
$k_2 \cdot 10^5$ mole ⁻¹ ·l. s ⁻¹	1.47	1.56	3.24

Salt effects. We studied the influence of the trifluoroacetates of Li, Na, and K, on the reaction rate. The results obtained are in Table 3.

For the same concentrations of trifluoroacetic acid, the apparent constant k_1 decreases with respect to both nature and concentration of the salts.

The introduction of CF_3CO_2^- ions by a common ion effect lessens the protonic activity of the solution. In addition, there is a specific salt effect which increases with decrease in cation volume.‡

TABLE 3. SALT EFFECTS ON THE APPARENT CONSTANT (k_1) OF THE RACEMIZATION OF THE INITIAL SYSTEM: $\text{EtCH}(\text{Ph})\text{CO}_2\text{H}$ (0.1 mole.1⁻¹)— $(\text{CF}_3\text{CO})_2\text{O}$ (2 mole.1⁻¹)— $\text{CF}_3\text{CO}_2\text{H}$ (9 mole.1⁻¹), IN CCl_4 SOLVENT

$\text{CF}_3\text{CO}_2\text{M}$ mole.1 ⁻¹	0	0.05	0.1	0.3	0.5
(Li)					
k_1 (h ⁻¹)	0.541	0.566	0.522	0.533	0.496
(Na)					
k_1 (h ⁻¹)	0.568	0.532	0.497	0.428	0.375
(K)					
k_1 (h ⁻¹)	0.552	0.434	0.347	0.322	0.222

* In a previous publication,² we attributed a similar decrease of activity of $\text{CF}_3\text{CO}_2\text{H}$ to dimerization.

† In ether, the mixed anhydride does not racemize.

‡ With Li at low salt concentrations, this specific salt effect is stronger than the common ion effect.

Thermodynamic constants. By measuring the rate constant at 35°, 25° and 10° C (Table 4), we obtained values for the enthalpy and entropy of activation:

$$\Delta H^* = 22 \text{ kcal/mole}$$

$$\Delta S^* = -22 \text{ e.u.}$$

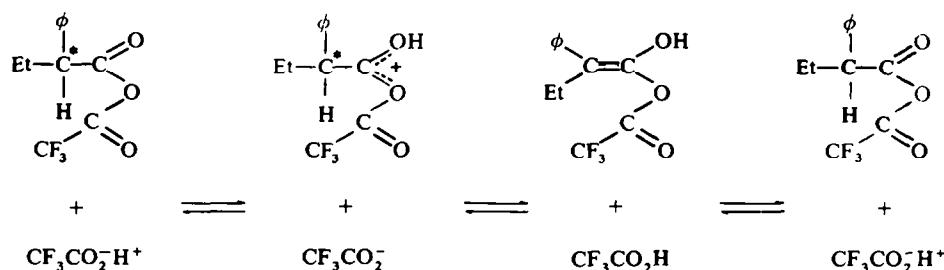
TABLE 4. VARIATION OF RATE CONSTANT (k_2) WITH TEMPERATURE FOR AN INITIAL SYSTEM:
EtCH(Ph)CO₂H (0.5 mole.l⁻¹)—(CF₃CO)₂O (1 mole.l⁻¹)

Temperatures	35°	25°	10°
$k_2 \cdot 10^5 \text{ mole}^{-1} \cdot \text{l. s}^{-1}$	0.239	0.075	0.012

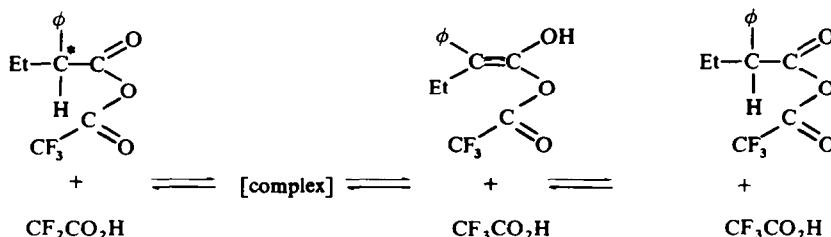
Analysis of results. The kinetic study of the racemization reaction stresses the intervention of a bimolecular mechanism involving the mixed anhydride and the monomeric form of the trifluoroacetic acid. When the concentration of CF₃CO₂H is zero, there is no racemization (extrapolation of the curve presented in Fig. 2 passes through the origin). This excludes all possibilities of a competitive monomolecular mechanism.*

More information is required about the way trifluoroacetic acid acts on the mixed anhydride: there are two hypotheses:

(a) A mechanism in which the first step would be protonation of the mixed anhydride, followed by enol formation.



(b) Trifluoroacetic acid could act as a bifunctional catalyst, and thus form a complex [anhydride–acid] which, in turn, would rearrange to the above enol, and then to the racemic mixed anhydride.



* Disproportionation reaction of the mixed anhydride leading to a ketene and to trifluoroacetic acid.

In this case, trifluoroacetic acid could protonate the most basic oxygen of the carbonyl of the mixed anhydride (the carbonyl α to the active centre). It could also react by the use of its carbonyl group either on the H_{12} proton (complex C_I), or on the C_{10} carbon (to form a tetracoordinated complex C_{II}) (Fig. 3).

By a concerted electronic transfer, C_I and C_{II} can lead to the above enol, thus causing racemization. One also can imagine a rearrangement of C_{II} following a different process, which would lead to a mixed anhydride similar to the initial one, but with exchange of the trifluoroacetate groups of the anhydride and the acid.

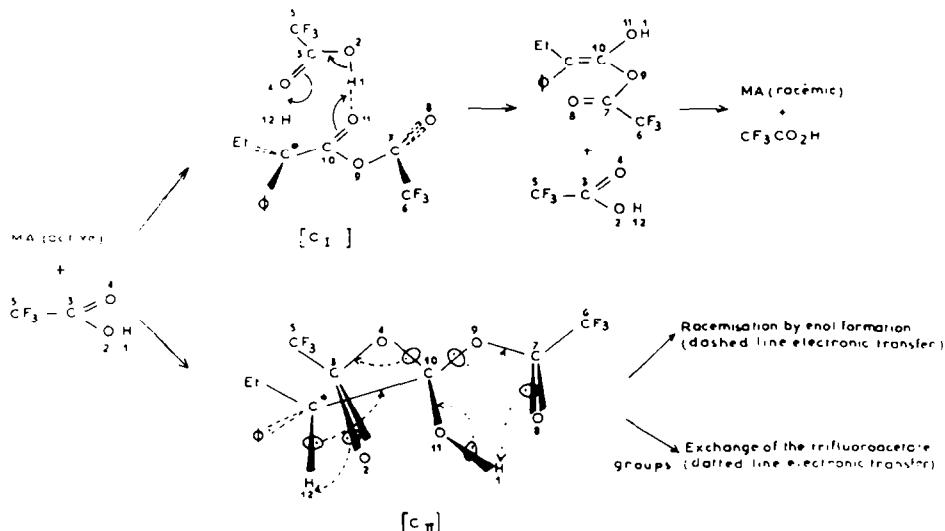


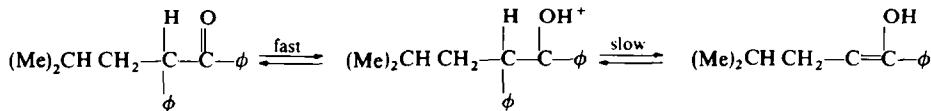
FIG. 3. Structure and rearrangement of the C_I and C_{II} complexes.

The kinetic results do not yet enable us to decide between mechanisms (a) or (b). Indeed, the acceleration observed with the increase of solvent dielectric constant can be understood as an increase of either the ionic dissociation of CF_3CO_2H , or the concentration in the monomeric form. In the same way, a decrease of reaction rate, by introduction of $CF_3CO_2^-$ ions, indicates a decrease of protonic activity of the solution, either by removal of the acid ionization equilibrium, or by solvation of the acid by the anion. The negative and relatively high value of $\Delta S^* = -22$ e.u., indicates a transition state, with less degrees of freedom than the initial one. This indicates the hypothesis of bifunctional catalysis in which a complex of type C_I or C_{II} , would be energetically very near the transition state.* Since the reaction occurs in an aprotic solvent of low dielectric constant ($\epsilon_{CCl_4} = 2.238$), the existence of an ionization equilibrium for CF_3CO_2H seems unlikely. However, this does not eliminate racemization process (a).

We have tried to establish a parallel between possible racemization of the protonated mixed anhydride (mechanism (a)) and racemization of a protonated ketone

* A. Kergomard and M. Renard¹¹ obtained a value of $\Delta S^* = -22$ e.u. for the mutarotation reaction of tetramethylglucose catalyzed by a carboxylic acid. They proposed a bifunctional attack of the catalyst acid of the C_I complex type.

possessing an asymmetric carbon atom bound to a hydrogen atom in position α to the carbonyl group. The racemization of D- α -phenyl isocaprophenone in the $\text{H}_2\text{SO}-\text{H}_2\text{O}$ system, studied by Swain and Rosemberg⁹ seemed a suitable model for comparison:



These authors showed that the H_2O and HSO_4^- anions take part in the elimination of the proton; the kinetic constants being: $k_{\text{H}_2\text{O}} = 3.46 \times 10^{-4}$ and $k_{\text{HSO}_4^-} = 3.3 \times 10^{-6}$.

By analogy, the rate equation of the mixed anhydride racemization could be written as follows:

$$v = k [\text{MAH}^+] [\text{CF}_3\text{CO}_2^-] \quad (4)$$

$[\text{MAH}^+]$ = protonated mixed anhydride concentration; $[\text{CF}_3\text{CO}_2^-]$ = trifluoroacetate ion concentration.

With the inclusion of the dissociation constants of the protonated mixed anhydride and the trifluoroacetic acid, respectively: K_{MAH^+} and $K_{\text{CF}_3\text{CO}_2\text{H}}$, eq. 4 takes the following form:

$$v = k \frac{K_{\text{CF}_3\text{CO}_2\text{H}}}{K_{\text{MAH}^+}} [\text{MAH}^*] [\text{CF}_3\text{CO}_2\text{H}] \quad (5)$$

Under these conditions, by comparing eqs. 4 and 5, we see that constant k_2 (1.56×10^{-5} mole⁻¹.l.s⁻¹) previously determined would not be the kinetic constant of the reaction since:

$$k_2 = k \frac{K_{\text{CF}_3\text{CO}_2\text{H}}}{K_{\text{MAH}^+}} \quad (6)$$

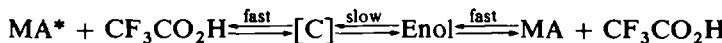
In this relation, if we give $K_{\text{CF}_3\text{CO}_2\text{H}}$ its value measured in water, that is 5×10^{-1} (though in the system studied, this constant is necessarily much lower) and if we admit that K_{MAH^+} has a value near that of the dissociation constant of the protonated ketone, that is 2×10^{-7} (actually, the mixed anhydride basicity being certainly lower than the ketone basicity, it is likely that K_{MAH^+} is much higher), we get a value of k :

$$k > \frac{1.56 \times 10^{-5} \times 2 \times 10^{-7}}{5 \times 10^{-1}} \simeq 6 \times 10^2$$

The constant k would then be at least 10^7 times higher than the ones observed by Swain and Rosemberg in the racemization reaction of D- α -phenyl isocaprophenone. Such a difference seems too important to be solely attributable to an inductive effect of the trifluoroacetate group; so, we consider as unlikely mechanism (a).

The formation of a complex $\text{EtCH}(\text{Ph})\text{COOC CO}_2\text{H} \dots \text{CF}_3\text{CO}_2\text{H}$ by bifunctional attack of $\text{CF}_3\text{CO}_2\text{H}$ on the oxygen of the most basic carbonyl, and on an electrophilic centre of the mixed anhydride seems more likely. For the present, intermediates

C_1 and C_{II} both seem equally possible. Under these conditions, the reaction mechanism becomes:



The rate equation can be expressed in the form:

$$v = k[C] = k \cdot K \cdot [MA^*] \cdot [CF_3CO_2H] \quad (7)$$

k = kinetic constant, $[C]$ = complex conc., K = complex dissociation constant, $[MA^*]$ = active mixed anhydride conc., $[CF_3CO_2H]$ = trifluoroacetic acid conc., MA = racemic mixed anhydride conc.

Thus, the measured value of k_2 would not be the kinetic constant of the reaction. Indeed, in such a case, it would be linked to the dissociation constant of the complex by the relation:

$$k_2 = k \cdot K \quad (8)$$

Swain and Di Nilo,¹⁰ and more recently Kergomard¹¹ suggested intermediates of type C_{II} , underlining the bifunctional character of the carboxylic acids.

Although it seems that tetracoordination at the carbonyl invoked in C_{II} has never been observed for an anhydride, its presence has been proved at the carbonyls of both ketones and esters.^{1, 12, 13} In our case C_{II} could be a common intermediate for exchange reactions of trifluoroacetate groups and the racemization reaction of the mixed anhydride. Moreover bifunctional addition of CF_3CO_2H , of the same type to the carbonyl of the mixed anhydride, could lead to the reaction intermediate involved in the formation of $(CF_3CO)_2O$, and by reversibility, of the mixed anhydride. The difference of relative basicity of the two carbonyls of the mixed anhydride with respect to CF_3CO_2H , could thus be an important kinetic factor in the high value of the formation constant ($K = 10$) of the mixed anhydride.

EXPERIMENTAL

Formation time of the mixed anhydrides. IR spectra were recorded on a Perkin-Elmer 257 spectrometer using CaF_2 cells. Optical rotations were taken on a Perkin-Elmer 141 polarimeter, using a sodium lamp (wavelength 589 nm) and a thermostated cell compartment maintained at $25^\circ \pm 0.1^\circ C$.

IR Data. Near 1200 – 1900 cm^{-1} , the IR spectra of the solutions present the characteristic bands of the mixed anhydride² about 2 min after the components are mixed and remains constant.

Polarimetric data. Table 5 contains the specific rotatory power of α -phenyl butyric anhydride, of α -phenyl butyric acid and of α -phenyl butyric acetic mixed anhydride.

TABLE 5.

Species	$(Et-CO_2)_2O$	$Et-CO_2H$	$Et-C(Ph)-C(=O)-O-C(=O)-Me$
$[\alpha_S]_{(C_6H_6)}$	150°	95.4°	138.2°
$[\alpha_S]_{(Et_2O)}$			117.7°

A solution of optically active α -phenyl butyric acid in $(CH_3CO)_2O$ or $(CF_3CO)_2O$ undergoes an exalta-

tion of the rotatory power; this occurs when we operate at such concentrations that, there is no formation of symmetric anhydride but of mixed anhydride. The latter would then be responsible for this exaltation of the rotatory power. It has therefore been possible to follow polarimetrically the formation of mixed anhydrides: trifluoroacetic α -phenyl butyric and acetic α -phenyl butyric. The results are in the following Table 6.

TABLE 6.

Solvents	$\begin{array}{c} \text{H} \\ \\ \text{Et}-\text{C}-\text{CO}_2\text{H} \text{ mole} \cdot \text{l}^{-1} \\ \\ \text{Ph} \end{array}$	Time min.
$(\text{CF}_3\text{CO})_2\text{O}$	0.558	6
$(\text{CF}_3\text{CO})_2\text{O}$ +	0.185	2
CCl_4		
$(\text{CH}_3\text{CO})_2\text{O}$	0.702 0.201	55 15

The polarimetric and IR results therefore stress the rapidity of formation of the trifluoroacetic α -phenyl butyric mixed anhydride.

Kinetic study of the racemization. We followed polarimetrically the racemization of the solution of α -phenyl butyric acid in the $(\text{CF}_3\text{CO})_2\text{O}-\text{CF}_3\text{CO}_2\text{H}$ system. For this, we used a spectropolarimeter Spectropol I (FICA) using a xenon lamp and "Suprasil" cells. We worked at $\lambda = 400$ nm. On the whole, the rotary power of such a solution is given by the relation:

$$[\alpha] = [\text{MA}^*][\alpha_s]_{\text{MA}} + [\text{AH}^*][\alpha_s]_{\text{AH}} \quad (9)$$

$[\text{MA}^*]$ = concentration of the mixed anhydride formed

$[\text{AH}^*]$ = concentration of the α -phenyl butyric acid remaining

$[\alpha_s]_{\text{MA}}$ = specific rotatory power of the mixed anhydride

$[\alpha_s]_{\text{AH}}$ = specific rotatory power of the acid.

However, by operating under concentration conditions such that $(\text{CF}_3\text{CO})_2\text{O}$ would be in excess with respect to $\text{EtCH}(\text{Ph})\text{CO}_2\text{H}$, almost the whole of this acid reacted and formed the mixed anhydride. The second term of the relation $[\text{AH}^*]$ is indeed near zero. Moreover, the specific rotatory power of the acid being slightly lower than that of the mixed anhydride, the second term of relation (9) becomes negligible. Under these conditions, the optical activity of the solution is given by:

$$[\alpha] = [\text{MA}^*], [\alpha_s]_{\text{MA}} \quad (10)$$

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