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THE DECARBOXYLATIVE DEHYDRATION OF 3-HYDROXYCARBOXYLIC ACIDS WITH DIMETHYLFORMAMIDE-DIMETHYLACETAL - EVIDENCE FOR A ZWITTERIONIC INTERMEDIATE

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Summary. Dimethylformamide dimethylacetal (1) and 3-hydroxycarboxylic acids (2) react with formation of esters (4) and olefins (5). Evidence is provided that 5 is generated via an E1/E2-type fragmentation of a zwitterionic intermediate (Z). (Scheme 1).

The decarboxylative dehydration of hydroxycarboxylic acids with dimethylformamide acetals provides a mild and efficient method for the preparation of sensitive olefins and butadienes.[1] Surprisingly, no mechanistic details of this reaction have been reported so far. We studied the interaction of dimethylformamide dimethylacetal (1) with threo-3-hydroxycarboxylic acids (2) (Scheme 1) and found that under standard conditions[2] varying amounts of the methyl esters 4 are formed in competition to the olefins 5 (Table 1). Furthermore we gained evidence that the olefin forming step corresponds to an E1/E2-type fragmentation of a zwitterionic intermediate (Z).

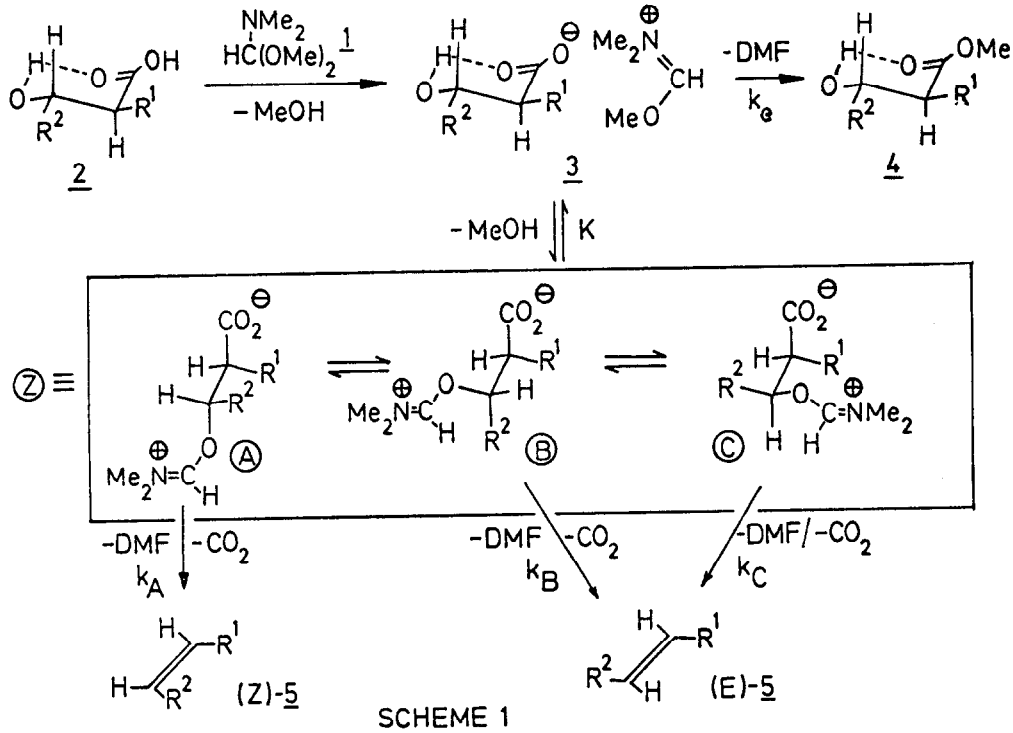
Mechanistic Discussion. We assume that 1 and 2 first form the ion pair 3[3] which generates 4 (S_N2-methyl-transfer to the carboxylate-oxygen[3]) or (Z)[4] (attack at the hydroxyl-oxygen). (Z), which may adopt the conformations (A), (B) or (C), undergoes fragmentation into 5, dimethylformamide, and CO_2. Intermediate 3 was prepared independently for system f: methylating dimethylformamide with methyl fluorosulfonate and adding the triethylammonium salt of 2 f furnished 4 f and 5 f in the same ratio as the reaction of 1 with 2 f.

Olefin vs. Ester Formation. The kinetic analysis of Scheme 1 yields the following expressions:

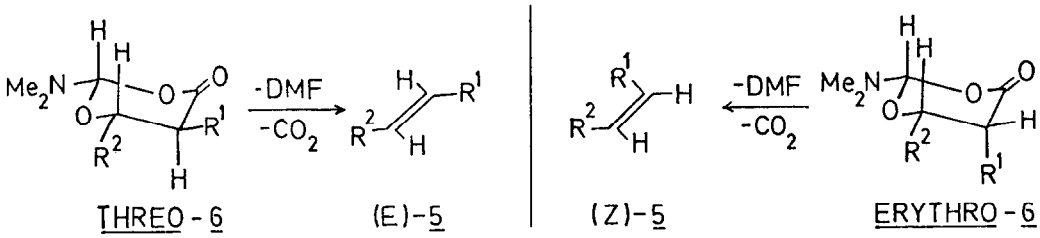
$d[4]/dt = k_e[3]$ and $d[5]/dt = k_o[Z] = k_o \cdot K[3]/[MeOH]$, where $K = [Z][MeOH]/[3]$, and $k_o = k_A[A]/[Z] + k_B[B]/[Z] + k_C[C]/[Z]$, and $[Z] = [A] + [B] + [C]$.

Hence $\frac{d[5]}{d[4]} = \frac{k_o \cdot K}{[MeOH] \cdot k_e}$, $\frac{[5]}{[4]} = r = \frac{k_o \cdot K}{k_e \cdot I}$ (Equ. 1), with $I = \int_0^\infty [MeOH]\,dt$.

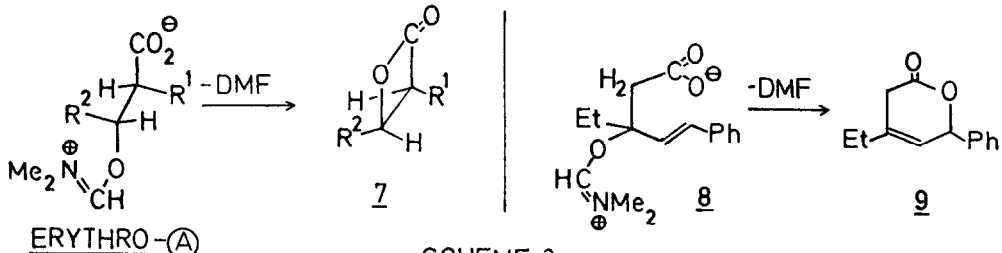
Discussion of Equ. 1: As the step 3 → 4 involves the carboxylate-oxygen only, k_e must be practically independent of R^2; K and I are not likely to vary much with R^1 and R^2 anyhow. Therefore, at least in a series with constant R^1 (= Ph) and sterically not too different R^2s (Table 1, runs a-j), $r = [5]/[4]$ may be considered as an estimate of k_o, the rate of the fragmentation step (Z) → 5, which - due to the complexity of the system - cannot be determined directly. Table 1 shows that r, and hence k_o, quite in agreement with the postulated E1/E2-fragmentation mechanism, is dramatically increased if R^2 stabilizes a carbenium center well. So r is very low for R^2 = alkyl (runs a-c) and grows from 0 to ∞ in the Hammett-sequence d-i. The validity of Equ. 1 is further demonstrated by the data given in Table 2. To dilute the reaction mixture means to decrease I, which - in accordance with Equ. 1 - leads to an increase of r (Table 2, runs a,b,c). In turn, an addition of methanol should increase I and decrease r. Again, this is confirmed by the experiment (Table 2, runs d,e). These results are in agreement with



SCHEME 1



SCHEME 2



SCHEME 3

a mobile equilibrium 3 ⇄ Z and give evidence that 5 must be formed via an intermediate which has been generated from 3 by elimination of methanol.

The Stereochemistry of the Olefin Formation. E2-elimination and, hence, formation of (Z)-5 can only occur from (A) where the two eliminatable groups are in the required anti-position. By contrast, (B) and (C) are suitable for E1-elimination only and generate (E)-5, the more stable olefin isomer. In estimating the E1/E2-ratio two factors have to be considered: a. the ratio of k_A vs. k_B, k_C: It can be expected that the E1-processes (k_B and k_C) are more accelerated by a carbenium-ion-stabilizing R^2 than the E2-step (k_A)[5]. Thus, for a constant R^1 (= Ph) the ratio of (E)-5: (Z)-5 should be increased considerably on going from R^2 = alkyl to R^2 = aryl. Table 1 shows that this is actually the case (runs a, b vs. runs e to j).

b. the relative population of (A) vs. (B)+(C): R^1 and R^2 are syn in (A) and (B) and anti in (C). Thus, an increased repulsion between R^1 and R^2 should clearly favor (C), which means that E1-elimination (= formation of (E)-5) will gain more and more over E2-elimination (= formation of (Z)-5). To avoid an interference from effect a R^2 is kept constant (= Ph), and, indeed, with growing bulkiness of R^1 (Table 1, runs k to n) the ratio of (E)-5: (Z)-5 rises from 1 : 2 to > 99 : 1.

Our stereochemical results strongly disagree with the assumption [1a] that 5 is generated via a concerted fragmentation of 6 (Scheme 2) which could be easily formed from (Z) by ring closure. In this case, however, from threo-2 always (E)-5 should be generated (which, according to Table 1, is not true), whereas erythro-2 should furnish only (Z)-5. We prepared erythro-2a, b, f, k, l, m, n and reacted them with 1; in each case the olefin fraction consisted of the (E)-isomer exclusively !

Additional Evidence for the Intermediate (Z) (Scheme 3). In addition to the fragmentation (A) should also be able to collapse to a ß-lactone via an internal S_N2-process. For threo-(A) this reaction suffers from the cis-interaction between R^1 and R^2 and cannot be observed. In erythro-(A), however, R^1 and R^2 are trans and the ß-lactone 7 is formed in addition to (E)-5 and the erythro-ester. If R^2 is a vinyl group, (Z) (= 8) undergoes an internal S_N2'-reaction and lactone 9 is found besides the "normal" butadiene. To exclude ß-lactones as intermediates in the formation of 5 from 1 and 2 we converted 2a, b, k, l, m, n into the corresponding ß-lactones independently and found them absolutely stable under the conditions described in lit. 2.

Preparative Consequences. Quite in accordance with the mechanism delineated in Scheme 1 dimethylformamide dineopentylacetal [1b] converts 2 into the olefins and no esters are formed (e.g. in the systems a, b, k, l, m, n). This is of advantage from the synthetic point of view; for our mechanistic studies we preferred 1 due to the highly informative competition between ester and olefin formation. However, high olefin yields may be obtained even with 1 in many cases if diluted reaction mixtures are used (Table 2 !).

References and Notes

1. a. Hara, S., Taguchi, H., Yamamoto, H., Nozaki, H., Tetrahedron Lett. 1975, 1545.
b. Rüttimann, A., Wick, A., Eschenmoser, A., Helv.Chim.Acta 1975, 58, 1450.
c. Mulzer, J., Kühl, U., Brüntrup, G., Tetrahedron Lett. 1978, 2953.

2. $CHCl_3$, 0.05 M solution, molar ratio of 1 : 2 = 1.5 : 1, 2 hrs at 22°C, product analysis by ^{1}H-NMR, isolation by TLC (silicagel, ligroin/ether 3 : 1).

3. Brechbühler, H., Büchi, H., Hatz, E., Schreiber, J., Eschenmoser, A., Helv.Chim.Acta 1965, 48, 1746. Vorbrüggen, H., Liebigs Ann.Chem. 1974, 821.

4. An intermediate similar to (Z) has been postulated in the fragmentation of 3-bromo-carboxylic acids: Noyce, D.S., Banitt, E.H., J.Org.Chem. 1966, 31, 4043, and cited lit. See also Grob, C.A., Angew.Chem.Int.Ed.Engl. 1969, 8, 535.

5. See, for example, March, J., Advanced Organic Chemistry, 2nd ed., McGraw-Hill, N.Y., 1977, p. 914.

Table 1 Product Distributions and Total Yields in the Reaction of 1 and threo-2.

Run	R^1	R^2	yields (%) of 5	yields (%) of 4	r = [5] : [4]	(E)-5 / (Z)-5
a	Ph	Me	7	69	0.10	1/26
b	"	Et	7	68	0.10	1/3.7
c	"	i-Pr	< 1	74	~ 0.0	-
d	"	4-CN-C_6H_4	< 1	83	~ 0.0	-
e	"	4-Cl-C_6H_4	27	58	0.47	5.0/1
f	"	Ph	58	22	2.6	6.8/1
g	"	4-Me-C_6H_4	85	5	17	17/1
h	"	4-OMe-C_6H_4	82	< 1	~ ∞	> 99/1
i	"	4-NMe_2-C_6H_4	85	< 1	~ ∞	>99/1
j	"	2-furyl	94	< 1	~ ∞	>99/1
k	Me	Ph	50	31	1.6	1/2.0
l	Et	"	65	13	5.0	1.5/1
m	i-Pr	"	80	8	10	98/2
n	t-Bu	"	85	4	21	>99/1

Table 2 Influence of the Initial Concentration of 2 (= $(2)_i$) and of Methanol Additions on r.

Run	R^1	R^2	$(2)_i$ (mole/l)	CH_3-OH- Addition (mole equiv.)	r
a	Ph	Ph	0.05	-	2.6
b	"	"	0.15	-	0.63
c	"	"	1.5	-	0.32
d	"	"	1.5	5	0.22
e	"	"	1.5	13	0.14

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