Effect of Supramolecular Inclusion on the 1,2-Rearrangement of Free Radicals

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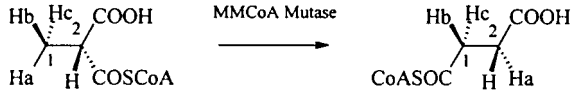
Dedicated to Professor *André M. Braun* on the occasion of his 60th birthday

The free radicals 3-ethoxy-2-(ethoxycarbonyl)-3-oxopropyl (**1**•) and 3-ethoxy-2-(ethoxycarbonyl)-2-methyl-3-oxopropyl (**2**•) were generated by photolysis of perester precursors in *i*) hexane solution, *ii*) in the presence of β-cyclodextrin, and *iii*) in NaY zeolite. While free radicals in solution are reluctant to rearrange, they do so when encapsulated in β-cyclodextrin or NaY zeolite. The coenzyme-B_{12}-dependent enzymic rearrangement of methylmalonyl-CoA to succinyl-CoA could be mimicked by photochemical generation of an analogue of the putative intermediate radical in a molecular container.

Introduction. – Coenzyme-B_{12}-dependent enzymic rearrangements occur *via* radical intermediates that would be highly unstable and reactive in solution or gas-phase chemistry. It has been postulated that, at the enzyme's active site, these reactive species are protected from possible reaction partners thereby preventing undesired side reactions [1]. Such a device prolongs the lifetime of the radical intermediate, thus allowing its rearrangement, which is not a typical reaction of the radicals in solution. For the selective prevention of reactions of highly unstable intermediates by enzymes, the term 'negative catalysis' has been coined [1].

One of the most thoroughly investigated and physiologically important coenzyme-B_{12}-dependent rearrangements is that of methylmalonyl-CoA to succinyl-CoA (*Scheme 1*).

Scheme 1. *The MMCoA Mutase Reaction*

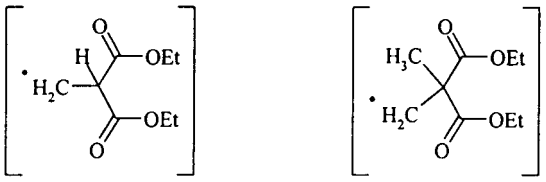


methylmalonyl CoA succinyl CoA

Homolysis of the Co–C bond of coenzyme B_{12} leads to a short-lived 5′-deoxyadenosyl radical, which abstracts an H-atom from the Me group of methylmalonyl-CoA to yield the substrate radical. The rearrangement of the substrate radical produces the product radical [2]. Evidence for these chemically unprecedented events came from isotope labeling [3] and EPR experiments [4]. More recently, the protective function of the enzyme has been shown by the X-ray structure of a mutant of methylmalonyl-CoA mutase in which the channel to the active site has been partially

opened. The oxygen sensitivity of the mutant was 80 times higher than that of the wild-type [5].

Chemical devices to stabilize highly unstable species are also known. When such species like cyclobutadiene [6], *o*-benzyne [7], or cycloheptatetraene [8] are generated in a molecular container, called hemicarcerand, they show a prolonged lifetime and different chemical behavior than they do in free solution. Naturally occurring materials like cyclodextrin and zeolite have also been investigated as molecular containers [9][10]. Here we examine the behavior of the photochemically generated free radicals 3-ethoxy-2-(ethoxycarbonyl)-3-oxopropyl (**1**$^{\bullet}$), and 3-ethoxy-2-(ethoxycarbonyl)-2-methyl-3-oxopropyl (**2**$^{\bullet}$) (*Figure*) *i*) in hexane solution, *ii*) in the presence of *β*-cyclodextrin, and *iii*) in zeolite NaY.

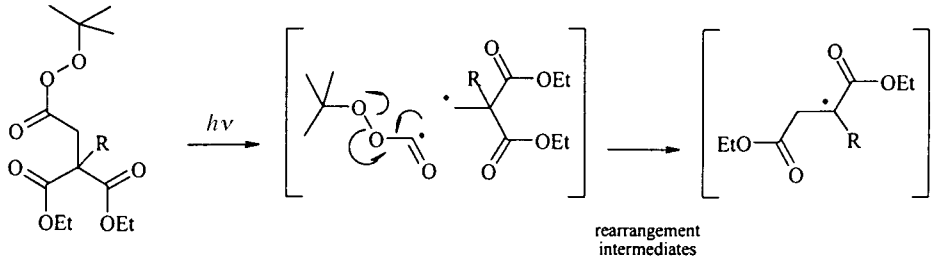


1$^{\bullet}$ **2**$^{\bullet}$

Figure. *Studied 3-Ethoxy-2-(ethoxycarbonyl)-3-oxopropyl Radicals*

Results. – As precursors for the radicals **1**$^{\bullet}$ and **2**$^{\bullet}$, the peresters *tert*-butyl 4-ethoxy-3-(ethoxycarbonyl)-4-oxobutaneperoxoate (**3**) [11] and its 3-methyl derivative **4** were prepared (*Scheme 2*). The expected products were in part commercially available and characterized by NMR spectroscopy and elemental analysis. All were identified by GC/MS. Photoirradiation of the peresters **3** [11] and **4** was carried out in a quartz vessel at room temperature with a low-pressure Hg lamp. Upon irradiation, **3** and **4** underwent homolytic cleavage with concomitant decarboxylation, generating a *tert*-butoxy radical and radicals **1**$^{\bullet}$ and **2**$^{\bullet}$, respectively (*Scheme 2*) [11–13].

Scheme 2. *Generation and Rearrangement of the 3-Ethoxy-2-(ethoxycarbonyl)-3-oxopropyl Radicals*

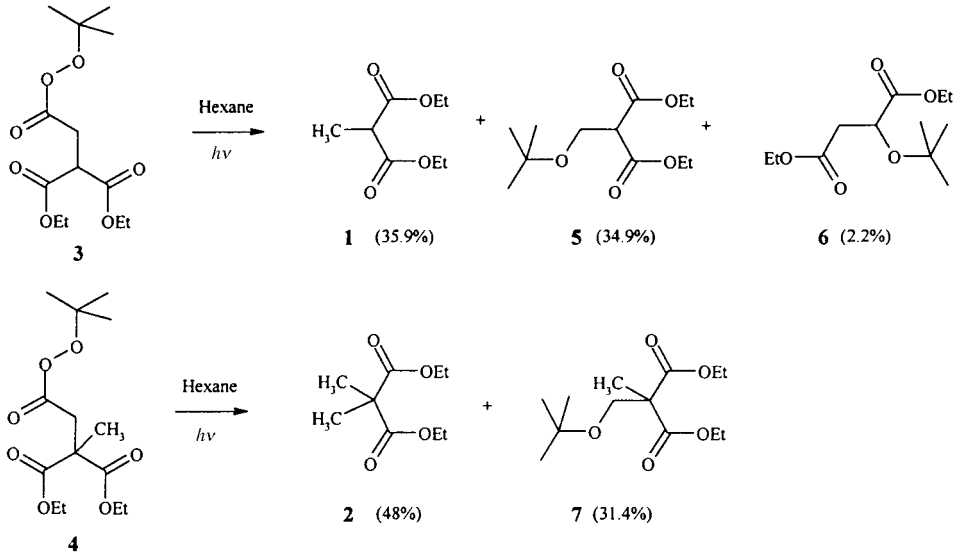


3 R=H
4 R=Me

The main products of the irradiation of **3** and **4** in hexane consisted of both recombination products with the *tert*-butoxy radical and H-abstraction products (*Scheme 3*), *i.e.*, 2-[(*tert*-butoxy)methyl]malonic acid diethyl ester (**5**) and methyl-

malonic acid diethyl ester (**1**) for **3**, and 2-[(*tert*-butoxy)methyl]-2-methylmalonic acid diethyl ester (**7**) and dimethylmalonic acid diethyl ester (**2**) for **4**. The ratios of the two kinds of products **1**/**5** was *ca.* 1:1, whereas it was 0.7:1 for the products **2**/**7**. Only very small amounts of rearranged product **6** (2.2%) were detected in the irradiation experiment with **3**, while none was found in the corresponding experiment with **4**. These results are in agreement with the work of *Keese*'s group [11] who found 1.7% of rearrangement product upon photolysis of **3** in cyclohexane.

Scheme 3. *Products of the Photolysis in Hexane*



Photolysis of the peresters **3** and **4** in cyclodextrin and in zeolite afforded dramatically different results (see *Schemes 4* and *5* and *Table*). Supramolecular encapsulation in β-cyclodextrin favored the 1,2-rearrangement of the generated radicals. Moreover, recombination with the simultaneously generated *tert*-butoxy radical was also favored with respect to H-atom capture. The corresponding product ratios were 5.3:1 and 9.6:1 for **1**$^{\bullet}$ and **2**$^{\bullet}$, respectively. Obviously, the 'cage effect' in the cyclodextrin cavity prevents the escape of the *tert*-butoxy radical.

In contrast, during irradiation in the presence of the zeolite NaY, the proportion of the recombination products decreased (*ca.* 10%) and that of the products arising from H-abstraction increased (56% for **1**$^{\bullet}$ and 61% for **2**$^{\bullet}$) (*Scheme 5*). The rearrangement products **10** and **11** (14 and 9%, resp.) arising from **1**$^{\bullet}$ and **2**$^{\bullet}$ were formed exclusively by H-atom abstraction. Photolysis of **3** afforded 21% of methylidenemalonic acid diethyl ester (**9**), while that of **4** gave 20% of methylmalonic acid diethyl ester (**1**), implying the loss of a Me group from **2**$^{\bullet}$. These Me groups must have been lost as methyl radicals since a minor amount (4.3%) of 2-ethyl-2-methylmalonic acid diethyl ester (**12**) was detected in the product mixture (*Scheme 5*); **12** is supposed to be the recombination product of **2**$^{\bullet}$ with a methyl radical.

Scheme 4. *Products of the Photolysis in the Presence of β-Cyclodextrin*

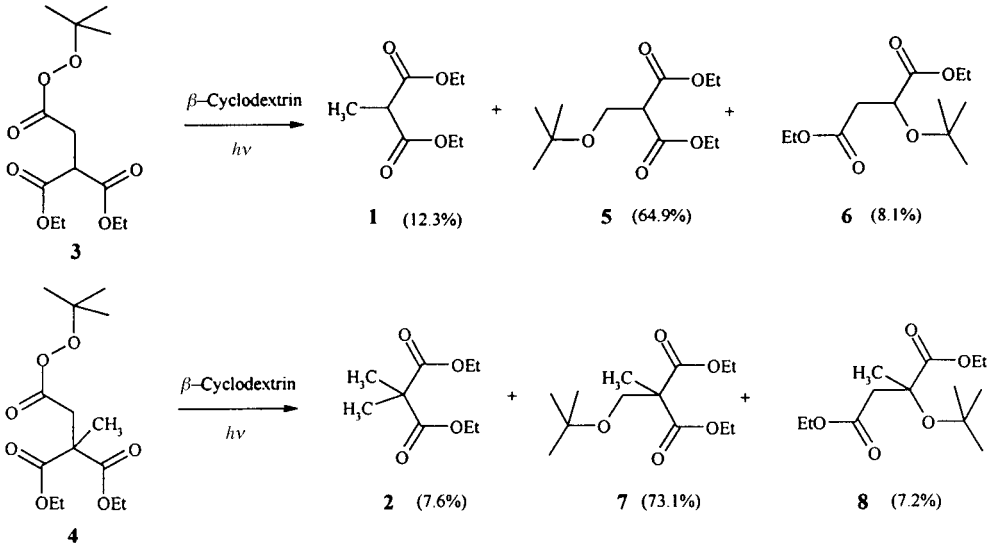


Table. *Yields of Rearrangement Products under Different Conditions*

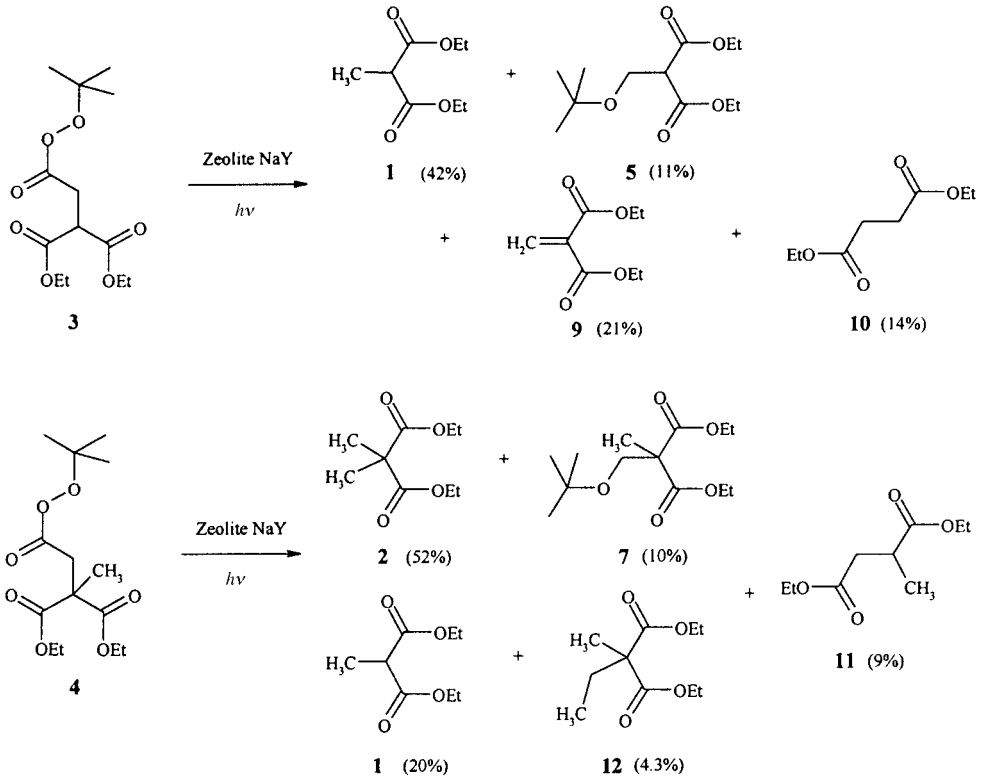
Substrate	Yields of rearrangement products (GC % of products)		
	hexane	β-cyclodextrin	zeolite NaY
3	2.2	8.1	14
4	0	7.2	9

Discussion. – The present results are relevant for the rearrangement reactions catalyzed by coenzyme-B_{12}-dependent enzymes. It has been postulated that the radicals generated at the active site of the corresponding enzymes are protected from bimolecular reactions by a 'cage effect' [1]. Photochemical generation and inclosure of putative radical intermediates of a model reaction, namely **1**$^{\bullet}$ and **2**$^{\bullet}$ in β-cyclodextrin or zeolite NaY, can be regarded as models for the events at the enzyme active site. Indeed, the percentage of rearrangement products was increased by factors of 4 and 7, respectively. The simultaneous generation of the *tert*-butoxy radical favored, however, recombination with the rearranged and unrearranged radicals in the β-cyclodextrin cage. Interestingly, such a recombination was suppressed when the same radicals were generated in the zeolite cage. A possible explanation for this may be the presence of easily abstractable H-atoms, so that H-abstraction can successfully compete with the recombination of the radicals generated in the cage.

Experimental Part

1. *General.* Column chromatography (CC): *Merck* silica gel *60* column; solvents distilled before use. NMR Spectra: *Bruker AC-250* or *DRX-500* instruments; δ in ppm, residual nondeuteriated solvent peak as an internal standard, *J* values in Hz. GC/MS: *Hewlett-Packard 5890* series *II* gas chromatograph with a *Hewlett-Packard*

Scheme 5. *Products of the Photolysis in the Presence of Zeolite NaY*



5972 mass selective detector; *Hewlett-Packard HP-5* trace analysis capillary column (25 m × 0.2 mm); *m/z* (rel. %). Elemental analyses were performed with a *CHN-O-Rapid* instrument from *Heraeus.*

2. *Precursors.* tert-*Butyl 4-Ethoxy-3-(ethoxycarbonyl)-4-oxobutaneperoxoate* (**3**) was synthesized as described [11]: 90% yield. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.29 (*t*, *J* = 7.3, *Me*CH_2); 1.33 (*s*, ^{t}Bu); 2.94 (*d*, *J* = 7.3, $CH_2CO_2{}^t$Bu); 3.88 (*t*, *J* = 7.3, *CH*$(CO_2Et)_2$]; 4.24 (*q*, *J* = 7.3, MeCH_2). ^{13}C-NMR (126 MHz, $CDCl_3$): 13.9 (*Me*CH_2); 26.0 (*Me*$_3$C); 30.3 ($CH_2CO_3{}^t$Bu); 47.5 (*CH*$(CO_2Et)_2$); 62.0 (MeCH_2); 83.9 (Me$_3$*C*); 167.9 (C=O). Anal. calc. for $C_{13}H_{22}O_7$; C 53.78, H 7.64; found: C 53.70, H 7.62.

tert-*Butyl 4-Ethoxy-3-(ethoxycarbonyl)-3-methyl-4-oxobutaneperoxoate* (**4**). Dry benzene (6 ml) was added to a 60% suspension of NaH in oil (0.87 g, 20 mmol), followed by dropwise addition of methylmalonic acid diethyl ester (3.48 g, 20 mmol) to the stirred mixture. Then *tert*-butyl bromoacetate (3.90 g, 20 mmol) was added dropwise, and the mixture was stirred overnight at r.t. Filtration and evaporation gave the crude product, which was purified by CC (hexane/^{t}BuOMe 4 : 1): propane-1,2,2-tricarboxylic acid 1-(*tert*-butyl) 2,2-diethyl ester (4.5 g, 78%). ^{1}H-NMR (250 MHz, $CDCl_3$): 1.25 (2*t*, *J* = 7.3, 2 *Me*CH_2); 1.42 (*s*, ^{t}Bu); 1.52 (*s*, $CH_2C(Me)(CO_2Et)_2$); 2.85 (*s*, $CH_2CO_2{}^t$Bu); 4.19 (*q*, *J* = 7.3, 2 MeCH_2).

The *tert*-butyl diethyl ester (2.02 g, 7 mmol) was cleaved as described [11] above giving propane-1,2,2-tricarboxylic acid 2,2-diethyl ester (1.45 g, 89%). The acid (0.80 g, 3.4 mmol) was reacted with *tert*-butyl hydroperoxide to give **4** (0.82 g, 78%). ^{1}H-NMR (500 MHz, $CDCl_3$): 1.24 (*t*, *J* = 7.2, 2 *Me*CH_2); 1.30 (*s*, ^{t}Bu); 1.55 (*s*, $CH_2C(Me)(CO_2Et)_2$); 2.93 (*s*, $CH_2CO_3{}^t$Bu); 4.19 (*q*, *J* = 7.2, 2 MeCH_2). ^{13}C-NMR (126 MHz, $CDCl_3$): 13.9 (*Me*CH_2); 20.2 ($CH_2C(Me)(CO_2Et)_2$); 26.0 (*Me*$_3$C), 37.1 ($CH_2CO_3{}^t$Bu); 51.5 (*C*$(CO_2Et)_2$); 61.9 (MeCH_2); 83.6 (Me$_3$*C*); 167.9, 170.6 (C=O). Anal. calc. for $C_{14}H_{24}O_7$: C 55.25, H 7.95; found: C 55.34, H 7.77.

3. *Inclusion Compounds from Perester* **3** *or* **4** *and β-Cyclodextrin.* A 1 : 1 (molar ratio) mixture of **3** or **4** and *β*-cyclodextrin (*β*-CD) was dissolved in H_2O by stirring overnight. The resulting soln. was lyophilized. The

complex formation in the aq. soln. was confirmed by ^{1}H-NMR the inner protons of β-CD (H–C(3), H–C(5), and H–C(6) being shifted upfield to various extents, thus providing evidence for the inclusion of **3** and **4** into the hydrophobic cavities of β-CD.

3/β-CD: ^{1}H-NMR (500 MHz, D_2O): 1.30 (t, J = 7.2, 6 H, *Me*CH_2); 1.35 (s, 9 H, ^{t}Bu); 2.98 (t, J = 7.0, 2 H, $CH_2CO_3{}^t$Bu); 3.62 (t, J = 9.5, 7 H, H–C(4) of β-CD); 3.66 (dd, J = 9.9, 3.6, 7 H, H–C(2) of β-CD); 3.83 (m, 7 H, H–C(5) of β-CD); 3.87 (m, 14 H, H–C(6) of β-CD); 3.93 (t, J = 9.5, 7 H, H–C(3) of β-CD); 4.00 (t, J = 7.1, 1 H, $CH(CO_2Et)_2$); 4.29 (m, 4 H, MeCH_2); 5.08 (d, J = 3.7, 7 H, H–C(1) of β-CD).

4/β-CD: ^{1}H-NMR (500 MHz, D_2O): 1.29–1.32 (m, 15 H, *Me*CH_2, ^{t}Bu); 1.55 (s, 3 H, *Me*$C(CO_2Et)_2$); 2.99 (s, 2 H, $CH_2CO_3{}^t$Bu); 3.63 (t, J = 9.5, 7 H, H–C(4) of β-CD); 3.67 (dd, J = 9.9, 3.6, 7 H, H–C(2) of β-CD); 3.80 (m, 7 H, H–C(5) of β-CD); 3.86 (m, 14 H, H–C(6) of β-CD); 3.92 (t, J = 9.6, 7 H, H–C(3) of β-CD); 4.30 (m, 4 H, MeCH_2); 5.08 (d, J = 3.6, 7 H, H–C(1) of β-CD).

Pure β-CD: ^{1}H-NMR (500 MHz, D_2O): 3.60 (t, J = 9.2, 7 H, H–C(4)); 3.67 (dd, J = 9.9, 3.7, 7 H, H–C(2)); 3.88 (m, 7 H, H–C(5)); 3.90 (m, 14 H, H–C(6)); 3.99 (t, J = 9.5, 7 H, H–C(3)); 5.09 (d, J = 3.7, 7 H, H–C(1)).

4. *Inclusion of Perester* **3** *or* **4** *with Zeolites.* Weighed amounts of substrates **3** or **4** and activated NaY zeolite were stirred in hexane for *ca.* 10 h. In a typical experiment, 400 mg of zeolite and 5 mg of the perester were added to 20 ml of hexane. The solid was isolated by filtration, washed with hexane twice, and dried *in vacuo*.

5. *Reference Compounds for the Rearrangement Products. 2-(*tert-*Butoxy)butanedioic Acid Diethyl Ester* (**6**) was prepared by the reaction of diethyl malate (= diethyl hydroxybutanedioate) and 2-methylpropene in the presence of *Amberlyst 15* [7]. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.20 (s, ^{t}Bu); 1.26 (t, J = 7.3, 1 *Me*CH_2); 1.27 (t, J = 7.0, 1 *Me*CH_2); 2.63–2.67 (m, $CH_2CHO{}^t$Bu); 4.08–4.24 (m, 2 MeCH_2); 4.45 (m, C*H*O^{t}Bu). GC/MS: 231(2), 173(12), 145(5), 118(6), 117(100), 101(3), 99(2), 89(7), 87(3), 75(4), 73(6), 71(13), 59(6), 58(4), 57(88), 56(7), 55(7), 45(2), 43(10), 42(2), 41(13).

*2-[(*tert-*Butoxy)methyl]-2-methylpropanedioic Acid Diethyl Ester* (**7**) was prepared by the reaction of 2-(hydroxymethyl)-2-methylpropanedioic acid diethyl ester [8] and 2-methylpropene in the presence of *Amberlyst 15* [7]. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.14 (s, ^{t}BuO); 1.24 (t, J = 7.3, 2 *Me*CH_2); 1.47 (s, Me–C(2)); 3.69 (s, CH_2–C(2)); 4.17 (q, J = 7.0, 2 MeCH_2). GC/MS: 204(2), 203(18), 187(13), 174(6)), 159(16), 157(2), 141(2), 131(7), 130(5), 129(34), 128(8), 115(8), 114(3), 113(5), 103(6), 102(3), 101(14), 100(7), 99(2), 87(15), 86(9), 85(17), 84(3), 83(6), 75(3), 73(2), 72(3), 70(2), 69(27), 68(2), 59(28), 58(6), 57(100), 56(9), 55(6), 47(3), 45(9), 44(2), 43(27), 42(6), 41(73).

*2-(*tert-*Butoxy)-2-methylbutanedioic Acid Diethyl Ester* (**8**) could not be synthesized but was identified by GC/MS: 245 (2), 215 (2), 201(11), 187(15), 174(5), 173(5), 159(7), 141(6), 132(4), 131(94), 129(7), 128(12), 127(4), 114(3), 113(9), 112(7), 103(5), 101(4), 100(6), 99(3), 87(8), 86(5), 85(16), 83(2), 75(3), 74(3), 73(4), 69(13), 59(7), 58(7), 57(100), 56(8), 55(6), 45(5), 44(6), 43(10), 41(23).

*2-(*tert-*Butoxy)-3-methylbutanedioic Acid Diethyl Ester* was prepared by the reaction of 2-hydroxy-3-methylbutanedioic acid diethyl ester and 2-methylpropene in the presence of *Amberlyst 15* [7]. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.10 (d, J = 7.0, *Me*CH); 1.17 (s, ^{t}BuO); 1.14 (t, J = 7.0, 1 *Me*CH_2); 1.16 (t, J = 7.0, 1 *Me*CH_2); 2.78 (m, MeC*H*); 4.11–4.25 (m, 2 MeCH_2, ^{t}BuOC*H*). GC/MS: 159(2), 141(2), 132(3), 131(40), 113(2), 103(3), 102(2), 87(5), 86(2), 85(15), 75(3), 74(3), 73(2), 69(7), 59(7), 58(9), 57(100), 56(8), 55(3), 45(4), 43(9), 43(2), 41(33).

2-Methylbutanedioic Acid Diethyl Ester (**11**) was obtained from the corresponding commercially available carboxylic acid (1 g, 8 mmol) by refluxing it in EtOH containing 5% conc. HCl soln.: 1.1 g (77%) of **11**. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.24 (m, 2 *Me*CH_2, Me–C(2)); 2.56 (m, CH_2); 2.90 (m, CH); 4.14 (m, 2 MeCH_2). GC/MS: 144(8), 143(100), 142(34), 117(2), 116(15), 115(93), 114(23), 113(3), 101(17), 99(3), 89(3), 88(16), 87(36), 86(7), 85(2), 74(2), 73(40), 71(8), 70(6), 69(16), 60(4), 59(2), 56(2), 55(6), 45(23), 44(2), 43(34), 42(31), 41(26), 40(4).

2-Hydroxy-2-methylbutanedioic Acid Diethyl Ester was obtained from the corresponding carboxylic acid (1 g, 8 mmol) by refluxing in EtOH soln. containing 5% conc. HCl soln.: 1.0 g (73%) of ester. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.25 (t, J = 7.1, 1 *Me*CH_2); 1.30 (t, J = 7.2, 1 *Me*CH_2); 1.44 (s, *Me*C(OH)); 2.81 (J_{AB} = 16.3, CH_2COOEt); 3.785 (s, OH); 4.14 (q, J = 7.9, 1 MeCH_2); 4.26 (q, J = 7.0, 1 MeCH_2). GC/MS: 159(3), 132(7), 131(100), 115(2), 113(2), 103 (18), 89(4), 88(3), 86(4), 85(74), 61(5), 60(3), 58(8), 57(2), 45(3), 44(2), 43(77), 42(5), 41(3).

6. *Photolysis Experiments and Product Analysis.* Photoirradiation of perester **3** or **4** in hexane soln. was carried out in a quartz vessel at r.t. by irradiation with a low-pressure Hg lamp for 2 h. The irradiation products were analyzed by GC/MS.

Aq. solns. of the perester/β-CD inclusion complexes were prepared by dissolving the complexes and an excess of β-CD in H_2O. The solns. were first purged with Ar for 30 min and then irradiated in quartz tubes with a low-pressure Hg lamp. After irradiation, the products were extracted with $CHCl_3$ and analyzed by GC/MS.

The precursors included in the dry NaY zeolite were irradiated as solids with a low-pressure Hg lamp. After irradiation, the products were extracted with $CHCl_3$ after dissolving the zeolite with 1N HCl at r.t. and analyzed by GC/MS. The structures of the products were assigned either by comparison of the retention times and MS with the standard or by the fragmentation pattern in their MS. For the estimation of the product ratios, the peak areas of the GC signals were considered. Only those esters that were formed from the irradiation of perester were considered. The percentage of the rearrangement product was quite reproducible in at least three independent experiments (errors for irradiation in hexane and β-CD aq. soln, $\pm 0.5\%$; for irradiation in NaY, $\pm 2\%$).

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