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Spontaneous reaction of malonyl peroxides with methanol

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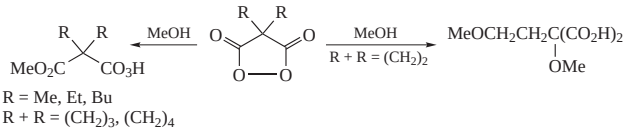
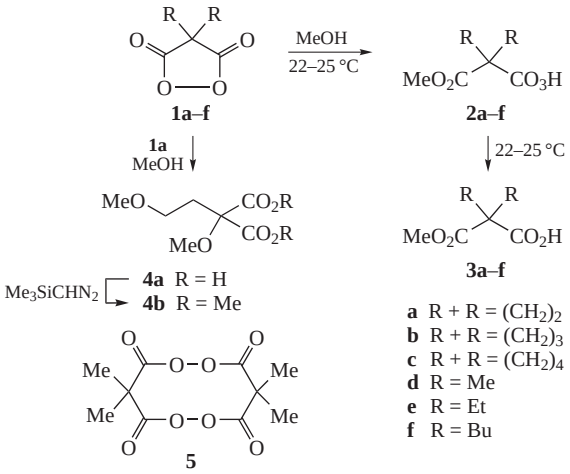
The spontaneous reaction of disubstituted malonyl peroxides (MPOs) with methanol affording monopermalonic acid monomethyl esters is fast (minutes) for lower homologues but is sharply decelerated (days) for the higher ones. Spirocyclopropyl-MPO is an exception in which the nucleophilic opening of the spiroactivated cyclopropane ring leads to 2,4-dimethoxy-2-carboxybutanoic acid.



Within the first decade after their discovery in 1971,[1] malonyl peroxides (MPOs, stable cyclic diacylperoxides, *e.g.*, compounds of type **1e**–**f** in Scheme 1) were intensively investigated as convenient substrates for generation of α-lactones, malonic anhydrides, and other types of low-stable compounds by photolysis or thermolysis.[2] Interest in MPOs returned in 2010 with the discovery of their capability of the *cis*-dihydroxylating of olefins without using reagents with heavy metals.[3] In recent years, the use of MPOs as oxidizing agents is expanding, as exemplified by *trans*-dihydroxylation of olefins,[4] hydroxylation of arenes[5] and acyloxylation of β-dicarbonyl compounds.[6,7]

At the same time, the transformations of MPOs themselves, other than photolysis and thermolysis, are little known. Slow solvolysis (up to 2500 h at 22 °C) of di-*n*-butyl-MPO (**1f**, see Scheme 1) with methanol gave monomethyl ester **3f** as a main product, whereas with ethanol it resulted in free di-*n*-butylmalonic acid.[8] Recently, we described fast (15 min at 25 °C) alcoholysis of MPOs **1a**–**c** catalyzed by potassium acetate, which led to monoesters (at carboxyl group) of monopermalonic acids **2a**–**c** partially converted into monoesters **3a**–**c** under mild reaction conditions.[9]

Herein, we report our results of more thorough investigations on methanolysis of some representative MPOs **1a**–**f**.† We have unexpectedly found that spirocyclobutyl-MPO **1b** rapidly reacts with methanol without any catalysts giving the same mixture of products **2b** and **3b** as those with potassium acetate catalysis (Table 1).‡ This transformation proceeds equally well in carefully purified (from traces of basic impurities) methanol (Method A) as well as in methanol acidified to pH 2–3 (Method B). Similar results were obtained with methanolysis of MPOs **1c**,**d**§ (see Table 1, entries 5 and 6). Due to the high volatility of the lowest



Scheme 1

† Starting MPOs **1a**–**c**,**e**,**f** were synthesized as described.[3(a),6,10] The use of compound **1d** was multiply reported[1,2(a),10] without its synthesis and properties. In ref. 2(*d*) an attempted preparation of **1d** by the standard for MPOs procedure was reported to give the product to which dimeric structure **5** was ascribed on the basis of cryo- and ebullioscopic data. On repeating this synthesis (with minor modification), we obtained the product which was identical with the already described one by melting point, IR and ^{1}H NMR spectra (see below). However, the monomeric structure of the product was proved as its methanolysis brings about only monoesters of diacids **2d** and **3d**. In case of dimeric structure **5**, other dimethylmalonic acid derivatives should also be expected, namely, diester, bisperacid and reduction products of the latter.

‡ Literature statement of the fast (10 min at room temperature) reaction of MPO **1b** with methanol[11(a)] is erroneous. In fact, it was performed with a MeONa/MeOH solution.[11(b)]

§ *Dimethylmalonyl peroxide* **1d**. A suspension of dimethylmalonic acid (1.98 g, 15 mmol) in solution of $H_2O_2 \cdot OC(NH_2)_2$ (6.27 g of 90% purity, 60 mmol) in methanesulfonic acid (10 ml) was stirred at room temperature until total dissolution (2.5 h), and the mixture was left overnight. The formed colourless solution was cooled in an ice bath and treated with saturated ammonium sulfate aqueous solution (2 ml) pre-cooled to 4 °C. The white precipitate thus formed was filtered, washed with the same ammonium sulfate solution, dissolved in chloroform (20 ml), and the small aqueous layer thus emerged was discarded. The organic layer after rapid drying (with $MgSO_4$ + 10% MgO) was concentrated on a rotary evaporator without warming to leave a semi-crystalline mass. This was dissolved in minimum methyl *tert*-butyl ether, the solution was diluted (3–4 fold) with hexane. After the crystallization ceased, the suspension was evaporated *in vacuo* (no longer than 1 min at 1 Torr) to afford white crystals of **1d** with a strong pungent odour (be careful!), yield 800 mg (41%), mp 49–51 °C (lit.,[2(d)] mp 48–49 °C). ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 1.59 (s). ^{13}C NMR (75.48 MHz, $CDCl_3$) δ: 21.6 (Me), 39.0 (C), 174.6 (CO). IR ($CHCl_3$, ν/cm^{-1}): 1800, 1815 (1 : 2). Mass spectrum of **1d** corresponds to a monomer.[2(d)] The substance is volatile, small crystals evaporating in air at 21 °C within 15 min. Probably, this volatility distorted the results of cryo- and ebullioscopic methods in ref. 2(*d*).

Table 1 Spontaneous reaction of MPOs with methanol.

Entry	MPO	Method[a]	Time of 50% conversion[b] at 25 °C/h	Products[c] and their ratios[d]
1	**1a**	A	6	**2a** + **3a** + **4a** + polymer, 4 : 11 : 49 : 36
2	**1a**	B	6	**3a** + **4a** + polymer, 10 : 53 : 37
3	**1b**	A, B[e]	0.06	**2b** + **3b**, 56 : 44
4	**1b**	D	> 500[f]	none
5	**1c**	A, B[e]	0.25	**2c**, ~100
6	**1d**	A, B[e]	0.05	**2d** + **3d**[g]
7	**1d**	C	1.0[f]	**1d** + **2d** + **3d**, 24 : 72 : 4
8	**1d**	D	> 500[f]	none
9	**1e**	A	41	**1e** + **2e** + **3e**, 20 : 18 : 62
10	**1f**	A	96	**1f** + **2f** + **3f**, 50 : 33 : 17

[a] *Method A*. A solution of MPO **1a**–**f** (0.05–0.1 mmol) in carefully purified methanol (1.00 ml) was stored at 22–25 °C under control of the MPO conversion and the corresponding peracid **2** formation (TLC, visualization by aqueous sodium iodide). After complete (or partial) MPO conversion, the solution was evaporated to dryness without warming, and the residue was dissolved immediately in $CDCl_3$. The product composition was analyzed by ^{1}H NMR. *Method B*. As Method A, but 0.01 M solution of CF_3COOH in methanol (pH 2–3) was used. *Method C*. As Method A, but 2.3 M concentration of MPO was used. *Method D*. A solution of MPO (0.05 mmol) and methanol (0.1 mmol) in dichloromethane (1.00 ml) was stored at 22–25 °C under control as in Method A. [b] Assuming quasi-first order in MPO reaction rate. [c] Products **2a**–**c** and **3a**–**c** were identified by comparison with the previously[9] obtained samples. [d] Yields of product sums ~100%. [e] Results on using Methods A and B are the same. [f] These values are for comparison only because the reaction rate order was higher in Methods C and D due to MeOH : MPO ratios < 10 : 1. [g] Product isolation was impossible due to its volatility with methanol.

homologue **2d** with methanol vapors, its isolation from the resulting 0.1 M solution was impossible (complete volatilazing during evaporation of the solution). Isolation of peracid **2d** turned possible from 2.3 M methanolic solution (Method C), however, at this concentration the methanolysis rate drops sharply (entry 7). With 0.1 M solution of methanol in dichloromethane (Method D), MPOs **1b**,**d** do not react at all (entries 4 and 8), as reported for compound **1a**.[9]

Under the most favourable conditions (Method A), MPOs **1e**,**f** react 800–2000 times slower (entries 9 and 10). Low speed of **1f** methanolysis is in accordance with the previously described data (566 h at 50 °C for full conversion[8]). However, methanolysis of MPO **1f** catalyzed by potassium acetate[9] proceeds as fast as those of MPOs **1a**–**c**, with complete conversion in 15 min.¶

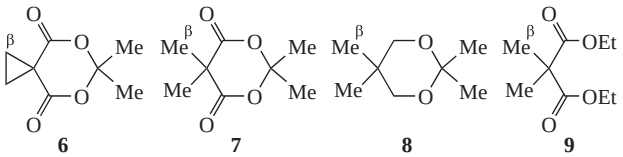
The ratio between peracids **2** and the corresponding carboxylic acids **3** formed in reactions of MPOs **1** with methanol is strongly dependent of stability of the peracids. An almost quantitative formation of peracid **2c** from spirocyclopentyl-MPO **1c** (entry 5) is of special note.

Spontaneous alcoholysis of MPOs is not limited to methanol. Recently described ethanolysis of MPO **1c** occurs with 91% conversion in 6 h at 20 °C and produces ethyl homologues of monoesters **2c** and **3c** (70 : 18).[7]

Such a great difference in the rates of spontaneous methanolysis between the MPO higher representatives **1e**,**f** and the lower ones **1b**–**d** is remarkable. This can be caused by the effect of *gem*-dialkyl groups which create steric shielding of carbonyl groups being attacked in the course of methanolysis.

In an attempt to assess the role of these substituents, energy of transition states during methanolysis was calculated by *ab initio* method (for details, see Online Supplementary Materials). Energy barriers for the reaction of MPOs **1d** and **1e** with one MeOH molecule were found to be correspondingly 41.9 and 44.3 kcal mol^{-1} in a vacuum, 30.6 and 33.5 kcal mol^{-1} in methanol environment, and 28.1 and 31.4 kcal mol^{-1} for the reaction model with the simultaneous participation of two MeOH molecules. For the much slower reacting MPO **1e**, the energy barrier is higher by ~3 kcal mol^{-1}. This difference is not large enough for more than 800-fold slowing the reaction.

Benzene assisted shift (BAS) of signals in ^{1}H NMR spectra is particularly significant for carbonyl compounds.[13,14] Nature of BAS consists in formation of a complex in which the benzene molecule is associated and coordinated with the carbonyl group of substrate. For our case, benzene may be considered as a probe allowing one to estimate accessibility of MPO carbonyl groups towards methanol. Compound **1a** manifested the unusually high BAS,[2(f)] the greatest one observed for compounds with CHO composition. Table 2 shows BAS values measured for β-located protons with respect to the carbonyl groups in MPOs **1a**–**f** and some reference compounds **6**–**9** (for full NMR spectral data for benzene solutions, see Online Supplementary Materials). For compounds **1b**–**e** and **6** BAS values are also unusually large. This fact can be attributed to two features of the structures in question: two identical carbonyl groups situated with respect to the observed proton induce a double effect, and 1,2-dioxolane cycle of MPOs or 1,3-dioxane cycle in **6** and **7** can make a small contribution to the total BAS. The value of this contribution can be estimated by noticeable BAS in 1,3-dioxanes **8** and some other related molecules,[15] as compared with the absence of BAS for β-protons in acyclic malonate **9**.



6 **7** **8** **9**

The most interesting seems the parallelism between BAS values (see Table 2) and 50% reaction times (see Table 1, Method A) in the series of MPOs **1b**–**f** with a correlation coefficient of 0.96. It testifies to the same factor affecting the two phenomena, which can be only shielding of carbonyl groups by the adjacent *gem*-dialkyl groups in malonyl moieties.

An exception from this correlation is MPO **1a** exhibiting the largest BAS value but only a moderate rate of methanolysis (see Table 1, entries 1 and 2). This is apparently due to geometry distortion of its 1,2-dioxolane cycle caused by a spiro-annulated cyclopropane ring (according to X-ray analysis, the value of

Table 2 Benzene-d_6 induced shifts of signals for protons at carbons β-positioned to carbonyl carbon.

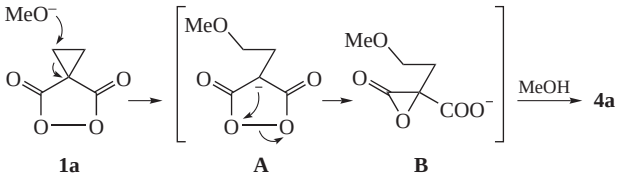
Compound	$\Delta\delta$ (C_6D_6–$CDCl_3$)[a]/ppm	Compound	$\Delta\delta$ (C_6D_6–$CDCl_3$)[a]/ppm
1a	–1.22	**1f**	–0.43
1b	–0.97	**6**	–0.52
1c	–0.81	**7**	–0.31
1d	–0.91	**8**[b]	–0.18
1e	–0.65	**9**	+0.04

[a] Negative ASIS implies upfield shift. [b] Position of 'carbonyl carbon' in **8** is assumed to be as in **7**.

¶ A solution of MPO **1f** (20 mg, 0.09 mmol) and AcOK (9 mg, 0.09 mmol) in MeOH (1 ml) was stored for 15 min at room temperature (TLC indicated full conversion). The mixture was acidified with CF_3COOH to pH 2, chloroform (3 ml) and water (2 ml) were added, the organic layer was separated, dried ($MgSO_4$) and evaporated to dryness *in vacuo*. Yield 23 mg (~100%) of a mixture of **2f** and **3f** (43 : 57), clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.89 (t, ~3 H, 2 Me in **3f**, *J* 7.2 Hz), 0.91 (t, ~3 H, 2 Me in **2f**, *J* 6.6 Hz), 1.05–1.25 (m, 4 H, 2 β-CH_2), 1.25–1.40 (m, 4 H, 2 γ-CH_2), 1.80–2.05 (m, 4 H, 2 α-CH_2), 3.75 (s, 1.3 H, OMe in **2f**), 3.80 (s, 1.7 H, OMe in **3f**).

OC–C–CO angle in **1a** reaches 107.6°, which is significantly higher than those in other MPOs[3(*a*),(*b*)]). The other exception for compound **1a** is the direction of its reaction with methanol leading mainly to dimethoxy diacid **4a**, a product of three-membered and then five-membered cycle disclosures. Product **4a** was characterized as its diester **4b** (see Scheme 1).[††] Methanolysis of MPO **1a** towards the 'normal' products **2a** and **3a** occurs only to a minor extent.

The easy nucleophilic opening of cyclopropane ring in MPO **1a** by methanol to form product **4a** is a consequence of the well-known 'spiro-activation' of cyclopropanes by two orthogonally arranged carbonyl groups. An attack of **1a** by methoxide anion results in malonyl-anion **A** (Scheme 2). However, unlike reactions of other spiroactivated cyclopropanes,[16(*b*)] the most rapid reaction for carbanion **A** is its intramolecular oxidation by the adjacent peroxide group to form α-lactone **B**. Methanolic medium partially protects α-lactone **B** from polymerization through the reaction with a second methanol molecule, which leads (after carboxylate anion protonation) to product **4a**. The direction of methanolysis with formation of α-methoxy acid but not α-hydroxy acid methyl ester as well as easy polymerization are typical of α-lactones.[1,2(*e*)]



Scheme 2

The observed spontaneous alcoholysis of MPOs may be used for a fast *in situ* generation of peracids **2b**–**d** and should be taken into consideration when carrying out reactions with MPOs in the presence of alcohols.[7] Spiro-activation of cyclopropane ring in MPO **1a** was also demonstrated in reactions with other nucleophiles and will be described elsewhere.

[††] *2,4-Dimethoxy-2-carboxybutanoic acid* **4a** was isolated from the crude product after the conversion of MPA (Method B, see Table 1) by preparative TLC [Merck silica gel plate, hexane–EtOAc–HCOOH (60:40:5), double development, R_f 0.09]. Viscous oil, yield 35%. ^{1}H NMR (300.13 MHz, $CDCl_3$ + 1 equiv. of MeOH) δ: 2.42 (t, 2H, C^3H_2, *J* 6.0 Hz), 3.32 (s, 3H, C^4OMe), 3.43 (s, 3H, C^2OMe), 3.55 (t, 2H, C^4H_2, *J* 6.0 Hz). ^{13}C NMR (75.48 MHz, $CDCl_3$ + 1 equiv. of MeOH) δ: 31.84 (C^3H_2), 53.77 (2-OMe), 58.59 (4-OMe), 66.92 (C^4H_2), 82.67 (C^2), 171.18 (2COOH). MS (ESI, positive ions), *m*/*z*: 193.0707 [M+H$^+$], 210.0973 [M+NH$_4^+$], 215.0522 [M+Na$^+$], 231.0264 [M+K$^+$] (calc. for $C_7H_{12}O_6$, *m*/*z*: 193.0707, 210.0972, 215.0526, 231.0265).

Diacid **4a** was converted into dimethyl ester **4b** by a treatment with Me_3SiCHN_2 in MeOH. Clear oil, yield 68%. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 2.37 (t, 2H, C^3H_2, *J* 6.0 Hz), 3.27 (s, 3H, C^4OMe), 3.37 (s, 3H, C^2OMe), 3.46 (t, 2H, C^4H_2, *J* 6.0 Hz), 3.79 (s, 6H, 2COOMe). ^{13}C NMR (75.48 MHz, $CDCl_3$) δ: 32.90 (C^3H_2), 52.78 (2COO*Me*), 53.65 (2-OMe), 58.82 (4-OMe), 66.84 (C^4H_2), 82.94 (C^2), 169.03 (2*C*OOMe). MS (ESI, positive ions), *m*/*z*: 221.1019 [M+H$^+$], 243.0842 [M+Na$^+$], 259.0574 [M+K$^+$] (calc. for $C_9H_{16}O_6$, *m*/*z*: 221.1020, 243.0839, 259.0578).

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.05.008.

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