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Regioselective alkane oxygenation with H_2O_2 catalyzed by titanosilicalite TS-1

Georgiy B. Shul'pin,[a,*] Tawan Sooknoi,[b] Vladimir B. Romakh,[c]
Georg Süss-Fink[c] and Lidia S. Shul'pina[d]

[a]*Semenov Institute of Chemical Physics, Russian Academy of Sciences, ulitsa Kosygina, dom 4, Moscow 119991, Russia*
[b]*Department of Chemistry, King Mongkut's Institute of Technology Ladkrabang, Ladkrabang, Bangkok 10520, Thailand*
[c]*Institut de Chimie, Université de Neuchâtel, Avenue de Bellevaux 51, CH-2009 Neuchâtel, Switzerland*
[d]*Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, ulitsa Vavilova, dom 28, Moscow 119991, Russia*

Abstract—Titanosilicalite TS-1 catalyses oxidation of light (methane, ethane, propane and *n*-butane) and normal higher (hexane, heptane, octane and nonane) alkanes to give the corresponding isomeric alcohols and ketones. The oxidation of higher alkanes proceeds in many cases with a unique regioselectivity. Thus, in the reaction with *n*-heptane the CH_2 groups in position 3 exhibited a reactivity 2.5 times higher than those of the other methylene groups. This selectivity can be enhanced if hexan-3-ol is added to the reaction mixture, the $3\text{-}CH_2/2\text{-}CH_2$ ratio becoming 10. It is assumed that the unusual selectivity in the oxidation of *n*-heptane (and other higher alkanes) is due to steric hindrance in the catalyst cavity. As a result, the catalytically active species situated on the catalyst walls can only easily react with certain methylenes of the alkane, which is adsorbed in the cavity taking U-shape (hairpin) conformations.
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Oxidative functionalization of inert saturated hydrocarbons is a challenging goal of contemporary catalytic chemistry.[1–3] Hydrogen atoms at primary, secondary and tertiary carbons of branched alkane chains (e.g., in 2-methylhexane) usually react with oxidizing reagents with different reactivities, which change in the following order: $1° < 2° < 3°$. The value of the parameter $1°{:}2°{:}3°$ which is normalized (i.e., calculated taking into account the number of hydrogen atoms at each position) gives the relative reactivities of hydrogen atoms at primary, secondary and tertiary carbons, respectively and allows us to make conclusions about the nature of an oxidizing species. For example, this parameter (which reflects the so-called 'bond-selectivity') is noticeably lower in the case of very reactive hydroxyl or chlorine radicals in comparison with the cases of oxidations by weaker oxo or peroxy derivatives of metals. At the same time,

methylene groups in higher normal alkanes are not discriminated in reactions by the 'usual' oxidizing reagents. 'Regioselectivity' (i.e., the selective functionalization of only certain positions in a long alkane chain) can be, however, enhanced if an investigator uses reagents in which reaction centres are surrounded by bulky substituents or are situated in hydrophobic pockets. In these cases, not all regions of a substrate can approach the reaction centre due to steric reasons. Enzymes,[2,4,5] certain metal-complex catalysts[2,6–8] and metal-based biomimetic systems[2,9–13] are known to induce regioselective transformations of alkanes.

Micro- and mesoporous materials containing relatively small cavities or narrow channels are excellent examples of catalysts for regioselective functionalization of long-chain alkanes.[14–17] Thus aerobic oxidation of *n*-dodecane over Mn-ALPO-18 (with 0.38×0.38 nm pores) gave, preferentially, products of oxidation at C_1 and C_2 whereas oxidation over Mn-ALPO-5 (0.73×0.73 nm pores) produced only the C_3, C_4 and C_4 oxygenates.[18] Microporous titanosilicalite TS-1 is known as a catalyst for H_2O_2 oxidation of various organic compounds[19–21] including alkanes.[22–27] This solid is based upon the

silicalite (MFI) framework, which contains a system of straight and sinusoidal intersecting channels of approximately 0.55 nm in diameter.[28] Due to its relatively narrow pores, TS-1 catalyzes efficiently the H_2O_2 oxidation of small organic molecules whereas the bulky oxidant, *tert*-butyl hydroperoxide, is inactive in TS-1-catalyzed reactions. Nevertheless, cyclohexane can react with H_2O_2, and addition of acetic acid to the reaction mixture leads to activity enhancement.[29]

In the present letter, we report the first results on TS-1-catalyzed oxidation of linear short- and long-chain alkanes with 35% aqueous hydrogen peroxide without any organic solvent and in the presence of certain alcohols.

The oxidations of gaseous saturated hydrocarbons were carried out in glass-lined stainless steel autoclaves with intensive stirring (the reaction mixture consisted of 1 mL of aqueous H_2O_2 solution and a solid TS-1 sample and the total volume of the autoclave was 100 mL). Before the oxidation, the autoclave was charged with air under atmospheric pressure and then with the gaseous alkane under an appropriate pressure. (CAUTION: the combination of air or molecular oxygen and H_2O_2 with organic compounds at elevated pressures and temperatures may be explosive!) The reactions were stopped by cooling with ice, and acetonitrile containing a small amount of nitromethane (an internal standard for the GC) was then added to the reaction mixture in order to obtain (after filtering off the solid TS-1) a homogeneous solution. The reactions of *n*-heptane and other liquid alkanes were carried out in air in a triphase (solid–liquid–liquid) system in thermostated (50 °C) Pyrex cylindrical vessels with vigorous stirring and developed as described above for the case of gaseous hydrocarbons. Other details are given in Table 1.

A titanium-containing zeolite TS-1 was prepared by hydrothermal crystallization of a silicon–titanium gel containing a tetrapropylammonium salt as described previously.[29] The Si/Ti ratio of 20 was obtained by spectroscopic methods and the specific surface area, measured by gas adsorption (BET), was approximately 373 $m^2 g^{-1}$. A 35% aqueous solution of hydrogen peroxide ('Fluka') was used for the reactions.

The reaction solution was analyzed by GC (a DANI-86.10 chromatograph with capillary column 50 m × 0.25 mm × 25 μm, Carbowax 20 M, integrator SP-4400 and a 3700 chromatograph with FFAP/OV-101, 20/80

w/w capillary column, 30 m × 0.2 mm × 0.3 μm; helium was the carrier gas). Each sample was analyzed twice, that is, before and after the addition of an excess of solid PPh_3. Triphenylphosphine reduces hydrogen peroxide to water and the alkyl hydroperoxide to the corresponding alcohol, and comparison of the reaction chromatograms before and after the reduction allowed us to check if the alkyl hydroperoxide was present in the reaction mixture. This method was used by us previously[2,30–33] for the analysis of reaction mixtures obtained from various alkane oxidations.

The results of the alkane oxidations are summarized in Table 1. We found that *n*-heptane was oxidized at a relatively low temperature (50 °C) in the absence of any organic additives to give a mixture of isomeric alcohols and ketones. We analyzed the reaction solutions both before and after addition of triphenylphosphine[2,30–33] and demonstrated that only a very small amount of the corresponding alkyl hydroperoxide was formed. The second feature of the reaction, which is in accordance with literature data,[27] is the oxidation of only methylene groups whereas the reactivity of the more inert methyl groups is negligible (the CH_2 groups are 80–100 times more reactive than the CH_3 groups). This observation clearly testifies that the alkane oxidation does not involve free hydroxyl radicals or, possibly, metal-oxo species. Indeed, the selectivity parameter C(1):C(2):C(3):C(4) which is normalized (i.e., calculated taking into account the number of hydrogen atoms at each position) gives the relative reactivities of hydrogen atoms in positions 1, 2, 3 and 4 of the hydrocarbon chain as approximately 1:9:7:7 for the reaction of *n*-heptane with known generators of hydroxyl radicals (the 'vanadate ion–pyrazine-2-carboxylic acid–H_2O_2' reagent, hv–H_2O_2, $FeSO_4$–H_2O_2).[34–37] This parameter was found to equal 1:46:35:35 for the oxidation with the 'H_2O_2–$[LMn^{IV}(O)_3Mn^{IV}L]^{2+}$–$MeCO_2H$' system, where L = 1,4,7-trimethyl-1,4,7-triazacyclononane.[38–40] The latter oxidation is believed to proceed via abstraction of hydrogen atoms from the alkane by the M=O fragment. Thus, it is reasonable to assume that alkane oxygenation with the H_2O_2–TS-1 system occurs with participation of certain titanium-peroxy species.[41–43] If a light alkane does not contain methylene groups, as in ethane and methane molecules, the C–H bonds can be, nevertheless, functionalized by the same H_2O_2–TS-1 system, although the efficiency is low (entries 5 and 6). Methylene groups are predominantly oxidized in the two other gaseous alkanes, propane and *n*-butane

Table 1. Oxidation of various alkanes with hydrogen peroxide catalyzed by TS-1[a]

Entry	Alkane	TS-1 (mg)	Temperature (°C)	Pressure (bar)	Time (h)	Products (μmol)
1	*n*-Heptane	5	50	atm	0.5	Isomeric alcohols + ketones (4.5)[b]
2	*n*-Heptane[c]	5	50	atm	0.5	Isomeric alcohols + ketones (0.6)[b]
3	*n*-Butane	10	60	2	4	Butan-2-one (12), butan-2-ol (1.5)
4	Propane	10	60	5	4	Acetone (10), isopropanol (4.7)
5	Ethane	10	60	30	12	Acetaldehyde (28), ethanol (1.7)
6	Methane	10	60	50	24	Methanol (1.1)

[a] Conditions. In the case of gaseous alkanes (entries 3–6) the oxidations were carried out in an autoclave under the pressure of hydrocarbon; H_2O_2, 1 mL. In the case of *n*-heptane (entries 1 and 2) the reaction was carried out in air; *n*-heptane, 0.05 mL; H_2O_2, 0.5 mL.
[b] For the composition of isomers, see Figure 1.
[c] The reaction was carried out in the presence of hexan-3-ol (0.05 mL); *n*-heptane, 0.05 mL; H_2O_2, 0.25 mL.

(entries 4 and 3, respectively). We also found that a branched isomer of heptane, 2-methylhexane gives only a very small amount of oxygenates. In the case of the more bulky 3-methylhexane, we did not detect any traces of products. It can thus be concluded that the oxidation of light and higher linear alkanes proceeds only in the narrow channels of TS-1.

The most striking peculiarity of the reaction with *n*-heptane is an unusual distribution of regioisomers formed by the functionalization of methylene groups (Fig. 1A). It can be seen that the normalized reactivities of the methylenes in positions 2 and 4 are approximately two times lower than that of the 3-CH$_2$ group. If hexan-3-ol is added to the reaction mixture (Fig. 1B) the regioselectivity increases dramatically: the reactivity of the 3-CH$_2$ group is now 10 and 5 times higher than the reactivities of hydrogens in positions 2 and 4. It is noteworthy that in this case, the 3- and 4-oxygenates consist of the almost pure isomeric alcohols whereas the mixture
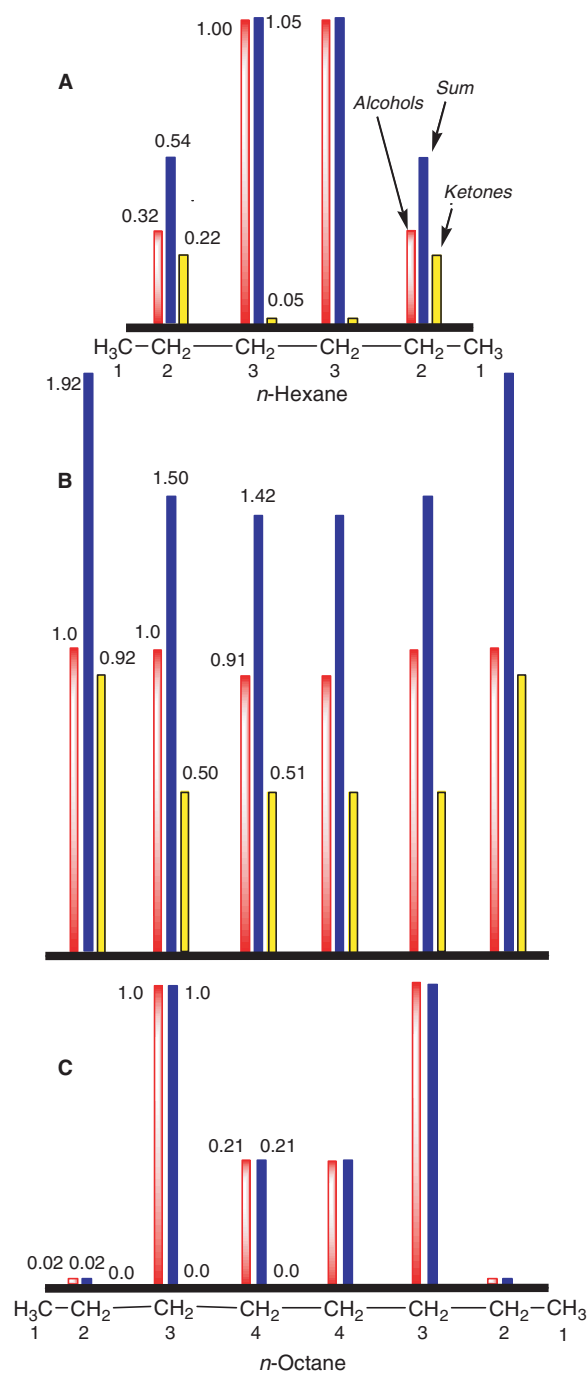

Figure 1. Distribution of isomers (normalized reactivities of methylenes in positions 2, 3 and 4) in the oxidation of *n*-heptane with H$_2$O$_2$ catalyzed by TS-1 (for conditions, see Table 1). The reactivity of the 3-methylene hydrogens in the corresponding isomeric alcohol formation is accepted to equal 1.00. A: without additives (Table 1, entry 1); B: in the presence of hexan-3-ol (Table 1, entry 2); C: in the presence of butan-2-ol (TS-1, 5 mg; H$_2$O$_2$, 0.25 mL; *n*-heptane, 0.05 mL; butanol-2, 0.05 mL; 0.5 h, 50 °C).

Figure 2. Reactivities of methylenes in various positions of the alkane chain in the oxidation *n*-hexane (A) and *n*-octane (B, C) with H$_2$O$_2$ catalyzed by TS-1. The reactivity of the 3- or 2-methylene hydrogens in the corresponding isomeric alcohol formation is accepted to equal 1.00. Graph C: in the presence of hexan-3-ol.

of 2-oxygenates (formed in a very small amount) consists of approximately equal portions of the alcohol and ketone. In the course of the reaction, hexan-3-ol is oxidized to hexan-3-one with a conversion of only 2.5%. Added butan-2-ol also enhances the regioselectivity (Fig. 1C), although less efficiently in comparison with hexan-3-ol. The oxidation of *n*-hexane (Fig. 2A) occurs under the same conditions with the predominant formation of the 3-oxygenate (consisting of the almost pure alcohol). In contrast, the oxidation of *n*-octane gives the 'usual' distribution of regioisomers (Fig. 2B), that is, the amount of the 2-oxygenates is a bit larger than that of the other isomers. However, as in the case of *n*-heptane, adding hexan-3-ol dramatically improves the selectivity to give only the 3- and 4-alcohols (Fig. 2C). The reaction with *n*-nonane (Fig. 3) gives an isomer distribution in which the amount of C_2 oxygenates is 2.5 times higher than the amount of the 3-isomers.

We can assume that this unusual regioselectivity is due to the narrow hydrophobic cavities of TS-1 in which the oxygenation of alkanes proceeds. If adsorbed[44,45] in the silicalite, *n*-heptane adopts a U-shape conformation,[46,47] and the C–H bonds in position 3 will be in close contact with the reaction centres (titanium-peroxy species) whereas the 4-CH_2 groups are situated (in the form of a 'hairpin bend') in the middle of the channel and cannot be efficiently attacked by the oxidizing species. Molecules of higher alcohols are apparently adsorbed in the cavity modifying it and this leads to an increase in the regioselectivity. Recently, we found[40] that in the reaction of *n*-heptane with the 'H_2O_2–[LMn^{IV}(O)$_3$Mn^{IV}L]$^{2+}$–carboxylic acid' system (L = 1,4,7-trimethyl-1,4,7-triazacyclononane) in water, the CH_2 groups in position 4 are oxidized more easily than the methylenes in positions 3 and 2. This phenomenon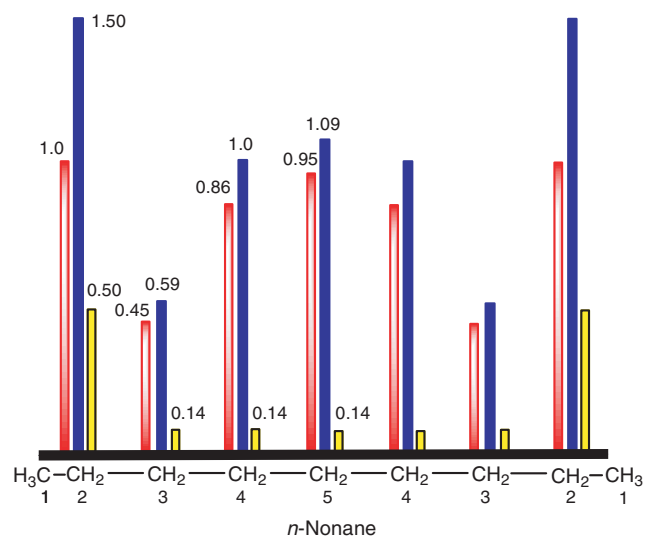 can also be explained if we assume that *n*-heptane in aqueous solution adopts U-shape conformations and the 4-CH_2 group has some preference in approaching the Mn-containing reaction centre situated between two voluminous macrocyclic ligands.

In summary, this work demonstrates that by using solid catalysts with nanopores we can control regioselectivity in the functionalization of higher normal alkanes and this selectivity can be improved if we introduce into the reaction mixture certain other molecules such as alcohols.

Figure 3. Normalized reactivities of methylenes in various positions of the *n*-nonane chain in its oxidation with H_2O_2 catalyzed by TS-1. The reactivity of the 2-methylene hydrogens in the corresponding isomeric alcohol formation is accepted to equal 1.00.

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