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CHEMICAL KINETICS AND CATALYSIS

The Mechanism of the Heterogeneous Catalytic Monooxidation of Thiophene Derivatives at the S Position by Hydrogen Peroxide

I. T. Nagieva

Baku State University, Baku, Azerbaijan

e-mail: inara10@yahoo.com

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Abstract—A biomimetic catalytic reaction system for hetero-oriented monooxidation of heteroaromatic compounds was developed experimentally. The system consisted of two interacting synchronous reactions of the decomposition of H_2O_2 and substrate oxidation. The problem related to the preparation, isolation, and identification of thiophene derivative S-monoxides was solved.

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INTRODUCTION

Heterocyclic compounds containing N, O, and S atoms in rings hold an exceedingly important position in living nature. They occur in alkaloids, antibiotics, natural pigments, vitamins, nucleic acids, proteins, etc. Among these compounds, five- and six-membered heteroaromatic compounds are of special importance. They are as a rule divided into π-excessive (five-membered rings with one heteroatom) and π-deficient (six-membered rings). Thiophene and its derivatives are π-excessive heterorings with pronounced aromatic properties. They are active in electrophilic substitution reactions.

Thiophene and its derivatives are comparatively stable toward the action of oxidizers. However, H_2O_2 in an acid medium or peracids oxidize them to sulfoxides (which were not isolated in the free state) or sulfones. Both these products are typical diene systems.

Acyclic sulfoxides are well known. 2,5-Dimethylsulfoxide and petroleum acyclic sulfoxides prepared by the oxidation of sulfur-containing oil components are of the greatest importance. Among heterocyclic thiophene oxides (tetrahydrothiophene-1,1-dioxide), sulfolane and sulfolenes (dihydrothiophene-1,1-dioxide) are well known. Sulfolane has low toxicity, and its alkyl-substituted derivatives are reagents for the extraction of aromatic compounds (benzene, toluene, and cumene) from oil etc.

The use of inorganic biological simulators [1] for the monooxidation of heteroatomic substances in the hetero position opens up new possibilities in fine organic synthesis. This approach can be used to prepare S ⟶ O monoxides by the chemical conjugation mechanism without resort to complex technology. The questions of the synthesis and identification of thiophene-1-monoxide are still open in the chemistry of thiophene, whereas more accessible compounds of the family of thiophene oxides, such as thiophene-1-dioxide and its derivatives, have been studied in much detail [1]. 1-Dioxide, which is easy to synthesize following known procedures, likely passes the stage of formation and accumulation of S-monoxide in the system. For this reason, the problem of the synthesis of 1-monoxide should likely be solved using nontraditional oxidation methods such as the conjugated oxidation of substrates by hydrogen peroxide in the presence of catalytic biological simulators which model the mechanism of monoxygenase reactions that occur in living systems.

It follows that the development of theoretical and experimental methods for the monooxidation of heteroatomic compounds with hydrogen peroxide is of considerable interest, because these reactions give valuable intermediate products with S ⟶ O functional groups.

The purpose of this work was the development of a reaction system for hetero-oriented monooxidation of a heteroaromatic π-excessive compound (five-membered 3,4-dibromo-2,5-dimethylthiophene) consisting of two interacting synchronous reactions of H_2O_2 decomposition and substrate oxidation.

Many thiophene derivatives, in particular, S-disulfides, are used as medicines, and the possibility of the preparation of a new oxidized thiophene form such as S-monoxide can offer promise for the synthesis of a new class of drugs.

EXPERIMENTAL

Gas-phase free radical chain oxidation with hydrogen peroxide is fairly successfully used to prepare N-monoxide of 4-vinylpyridine π-deficient heteroaromatic compound [2].

All attempts to use this variant of synchronous oxidation with hydrogen peroxide for the preparation of

S-monoxides of thiophene derivatives as π-excessive heteroaromatic compounds were, however, unsuccessful. Under the conditions similar to those of the gas phase N-oxidation of 4-vinylpyridine with hydrogen peroxide, almost no S-oxidation was observed; small amounts (~4%) of 3,4-dimethyl-2,5-dibromothiophene underwent oxidative destruction, and the decomposition of H_2O_2 predominantly occurred in the reaction system.

We believe that π-deficient heteroaromatic compounds, such as pyridines, easily participate in various free radical reactions, whereas π-excessive thiophenes are stable toward free radical attacks. Bearing this in mind, we changed our approach to performing synchronous oxidation by hydrogen peroxide from free radical to biomimetic catalytic. We had to synthesize a biomimetic catalyst on which an oxidative intermediate would form (as a result of the catalytic decomposition of H_2O_2) with "active oxygen" electrophilic in character, because thiophenes, which are π-excessive heteroaromatic compounds, easily participate in electrophilic interactions.

In recent years, a new area of catalysis has been intensely explored. This is the creation of new-generation catalysts, so-called biomimetics, which model separate enzyme functions in usual chemical systems. They differ by the method of synthesis of mimetics themselves, their functions, and types of modeled biochemical oxidation reactions. One of successful oxidation models is $PPFe^{3+}OH$ (iron protoporphin) deposited on alumina, which models catalase, peroxide, and monooxygenase reactions [3].

A method for the perfection of these systems is the modification of the organic ligand of the redox center or its replacement by simpler and more accessible organic ligands with similar action. This was performed for the $PPFe^{3+}OH/Al_2O_3$ biomimetic, in which the iron ion (Fe^{3+}) was coordinated with ethylenediaminotetraacetic acid (EDTA) rather than protoporphin [4]. The selection of EDTA as an organic ligand was not fortuitous. For instance, the broadly known Hamilton and Udenfried oxidative systems contain di- and trivalent iron linked with EDTA. An analysis of the mechanism of enzymatic reactions with the participation of hydrogen peroxide (catalase and peroxidases) excluded reactions with radical chain mechanisms, which have nothing in common with enzymatic oxidation.

In enzymatic catalysis, we observe concerted participation of catalytic redox and acid-base centers in selective oxidation. A new inorganic biomimetic (catalyst) should contain acid-base and redox catalytic centers on the one hand and be able to perform oxidation by the mechanism of coherent-synchronous reactions on the other. In addition, in liquid phase oxidation with hydrogen peroxide, EDTA is much more stable to the destructive action of the oxidizer compared with porphin. This allows oxidation to be performed in a static system for a long time. We synthesized biomimetics of two types, which only differed in the valence state of the iron ion. They were tested in synchronous oxidation of simple thiophene derivatives for the preparation of thiophene-1-monoxide derivatives.

The synthesis of catalytic biomimetics was performed as follows. NH_4OH was added to an aqueous solution of $Fe_2(SO_4)_3$ (to prepare active centers containing Fe^{3+} ions) to completely precipitate $Fe(OH)_3$. The solution was filtered, and the precipitate was washed with hot water. The precipitate was then dissolved in an aqueous solution of EDTA. The adsorption of this solution was performed by depositing it on alumina. Catalysts with Fe^{2+} in active centers was prepared by adding an aqueous solution of EDTA to an aqueous solution of $FeSO_4$. The complex obtained was deposited on Al_2O_3. The monosodium salt of the EDTA Fe^{3+} complex was adsorbed from an aqueous solution on a certain amount of Al_2O_3. Alumina was used in the neutral or basic form.

The experimental unit was a three-neck flask with a backflow condenser and a tap for gaseous products. The flask was connected with a gasometer by a rubber hose. A thermometer and a pipe for taking liquid samples were placed inside the flask. The unit was also equipped with a stirrer and furnace for heating it.

The products were identified and quantitatively estimated using gas-liquid and liquid chromatography, chromato-mass spectrometry, and ^1H NMR spectroscopy.

The substrates were thiophene derivatives 3,4-dibromothiophene, 2,5-dimethylthiophene, and 3,4-dibromo-2,5-dimethylthiophene. We used acetone, methanol, and dichloromethane as solvents and hydrogen peroxide of "reaktivnyi" (reactive) grade as a solvent.

In all experiments, a substrate (0.1 g) dissolved in one of the solvents was loaded into the static reactor, and Perhydrol was added in the amount corresponding to the S (substrate) : H_2O_2(Perhydrol) = 1 : 1.5 or 2.0 ratio. This reaction mixture was heated to 50–55°C, the catalyst (0.1–0.15 g) was added to it, and the magnetic stirrer was switched on. At the first stage, the reaction continued for ~5 h. After this, a sample was taken and analyzed. The gasometer was used to monitor the rate of oxygen release. In ~5 h, the intensity of oxygen release sharply decreased, which was evidence of a low concentration of H_2O_2. During this time, the catalyst became active in the main. Product yields were easy to determine from the mass spectra. Next, H_2O_2 in an amount 10 times larger than its initial amount was added to the system to create the most favorable conditions for conjugated oxidation. The reaction continued for more than a day. Samples for analyses were taken systematically to draw conclusions about the depth of transformations. The intensity of oxygen release was monitored using the gaso-

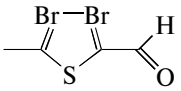
meter; the results were evidence of the presence of H_2O_2 and catalyst activity.

After twofold separation on a liquid chromatograph, the supposed basic product 3,4-dibromo-2,5-dimethylthiophene-1-monoxide was isolated from reaction products. This allowed us to record the ^1H NMR spectrum of 1-monoxidedimethylthiophene for the first time; its mass spectrum contained an ion with $m/e = 44$ (the C–S fragment), which was more intense than all the other ions and could probably be used as a characteristic mass for the identification of thiophene-1-monoxide and its derivatives. Note that the ion with the mass 44 for thiophene and its derivatives, including thiophene-1-dioxide, does not have the intensity characteristic of monoxides. The reaction was considered complete when the release of molecular oxygen ceased. The heterogeneous catalyst was easy to separate from the liquid reaction mixture (which was its obvious advantage). It was tested for activity in the decomposition of H_2O_2. Every time, it exhibited high activity and could be repeatedly used in the oxidation of the substrate. We performed control experiments with pure solvents (without substrates) to check their stability to oxidation with hydrogen peroxide under catalysis conditions.

RESULTS AND DISCUSSION

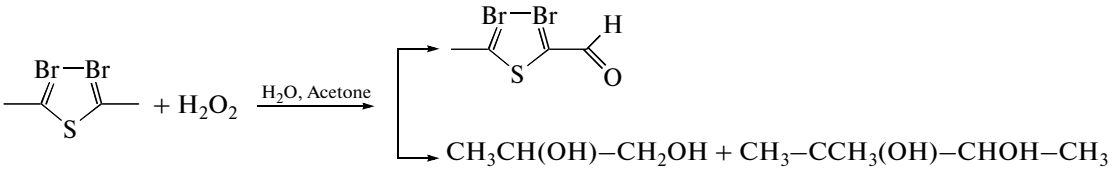
A series of experiments with the catalytic oxidation of thiophene derivatives to the corresponding 1-monoxide in the presence of the EDTA $Fe^{3+}OH/Al_2O_3$ catalyst was performed with 3,4-dibromo-2,5-dimethylthiophene. We had to minimize the participation of unsaturated bonds in oxidation and the influence of substituents on the predominant direction of the reaction toward the formation of 1-monoxide. It is shown below that both factors strongly influence the formation of 1-monoxide and the rate of its formation. Oxidation was performed under the conditions described above using three different solvents; qualitatively different results were obtained. The use of CH_2Cl_2 did not lead to a noticeable change in the substrate, because the presence of water (aqueous solution of hydrogen peroxide) contributed to reaction mixture layering with the formation of three phases that did not mix. Two of these were liquid and one solid (catalytic). Such a system had low efficiency. We used acetone and methanol as solvents which formed a homogeneous mixture with the substrate and water.

A fairly noticeable selective oxidation of the substrate with hydrogen peroxide is observed when acetone is used as a solvent. The yield of the product with the mass number 283 then reaches ~25 wt %. The compound (mass number 284) has the structural formula



Substrate oxidation is accompanied by solvent oxidation with the formation of hydrogenation and hydroxylation products, that is, glycols, in fairly large amounts.

Generally, the transformations observed in the system can be described by the scheme

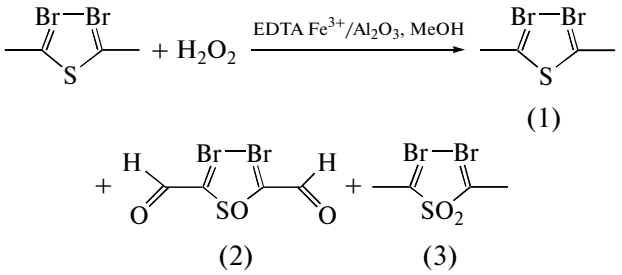


The formation of glycols from acetone in this reaction can be of interest of its own. Acetone behaves as an active component of the system and influences the formation of the oxidation product. This causes the necessity to exclude the additional source of active interference into the formation and consumption of reaction intermediates. If only hydrogen peroxide participates in the formation of intermediates, quite selective and predictable substrate oxidation can be expected.

The oxidation of acetone (solvent) itself in the absence of a substrate is of certain scientific interest. For instance, initially, the reaction proceeds with the formation of isopropanol, and only small amounts of destructive oxidation products (acetaldehyde and acetic acid) are observed. This leads us to conclude that the H_2O_2–H_2O–EDTA $Fe^{3+}OH/Al_2O_3$–acetone mixture has reducing properties thanks to the combined presence of hydrogen peroxide, acetone, and the mimetic.

Before using methanol as a solvent for the oxidation of 3,4-dibromo-2,5-dimethylthiophene, we checked its stability to oxidation in the absence of a substrate under the conditions similar to those described above. We found that it was completely indifferent with respect to oxidation with hydrogen peroxide for a long time, which was evidence of its minimum influence of CH_3OH on chemical transformations. In addition, the absence of oxidation products leads us to conclude that the decomposition of

H_2O_2 on the mimetic occurs as a heterogeneous catalytic reaction, that is, there is no ejection of free radicals into solution. Otherwise, free OH radicals, which are highly reactive particles, would react with methanol. We used methanol as a solvent to study the oxidation of 3,4-dibromo-2,5-dimethylthiophene with hydrogen peroxide in the presence of EDTA $Fe^{3+}OH/Al_2O_3$. We were able to synthesize 1-monoxide in a fairly simple way according to the scheme

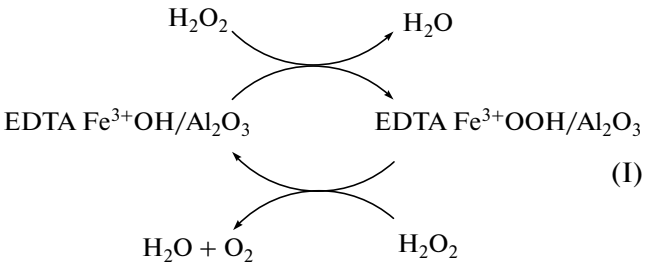


(yield, wt %: 1, 30.0; 2, 16.0; 3, 10.0).

The products were for the first time characterized by ^1H NMR and mass spectrometry. 3,4-Dibromothiophene formed in an amount of ~8.0% (36.0% based on the unreacted initial substance). The mass spectrum (m/z) of the purified reaction product formed from 3,4-dibromo-2,5-dimethylthiophene over the m/z range 487–509 is shown in Fig. 1a. The mass (m/z) 286 corresponds to the 3,4-dibromo-2,5-thiophene-1-monoxide molecule, and the intense peak at $m/z = 44$, which can be assigned to the C–S fragment, can be used as a characteristic peak for the identification of thiophene-1-monoxide and its derivatives. The ^1H NMR spectrum of 3,4-dibromo-2,5-dimethylthiophene-1-monoxide is shown in Fig. 1b.

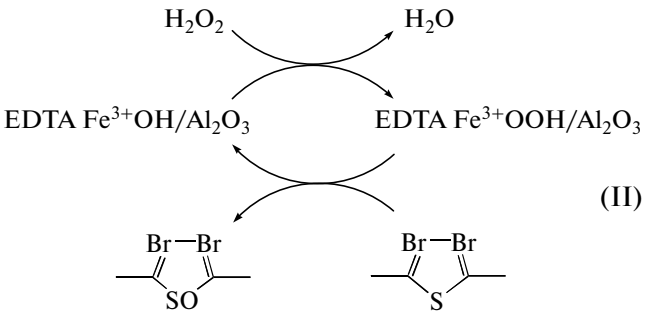
The chemical shift value observed for 3,4-dibromo-2,5-dimethylthiophene-1-monoxide (1.7 ppm) is situated behind the chemical shifts of 3,4-dibromo-2,5-dimethylthiophene (2.38 ppm) and 3,4-dibromo-2,5-dimethylthiophene-1-dioxide (2.19 ppm). As regards compounds 2 and 3, their identification was mainly based on the mass spectra and, with 3, liquid chromatography. Of course, the identification of 2 on the basis of its mass spectrum only is not very reliable.

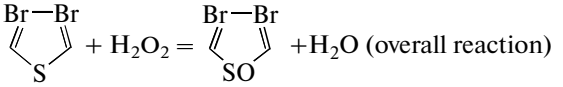
As in similar oxidative systems, the oxidation of the substrate in the system under consideration follows a synchronous mechanism. Accordingly, the mechanism of the reaction can be described by the following schemes taking into account the overall transformations in the system:



$2H_2O_2 = 2H_2 + O_2$ (overall reaction)

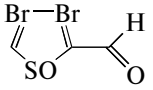
Secondary reaction





Scheme (I) describes the formation of the intermediate product in the conjugation of two reactions. According to scheme (II), this product induces and accelerates the secondary reaction synchronized with the first one.

We studied the influence of the valence state of iron using a different catalyst with Fe^{2+} as the central ion. The oxidation of 3,4-dibromo-2,5-dimethyl-thiophene in the H_2O_2–H_2O–CH_3OH–EDTA $Fe^{2+}OH/Al_2O_3$ system was performed under identical conditions. The activity of this system in oxidation was found to be very low. The total yield of the products with the mass numbers 299 and 301, which we assigned to the



compound (molecular weight 300) and the compound with molecular weight 302 was less than 1%. It follows that the valence state of iron in the active catalyst center predetermines oxidation results.

It was no less important to determine the influence of the character and number of thiophene substituents on its oxidation. Vigorous reaction of H_2O_2 decomposition was only observed in the system H_2O_2–H_2O–CH_3OH–EDTA $Fe^{2+}OH/Al_2O_3$–3,4-dibromothiophene under identical conditions. Transformations of 2,5-dimethylthiophene were character-

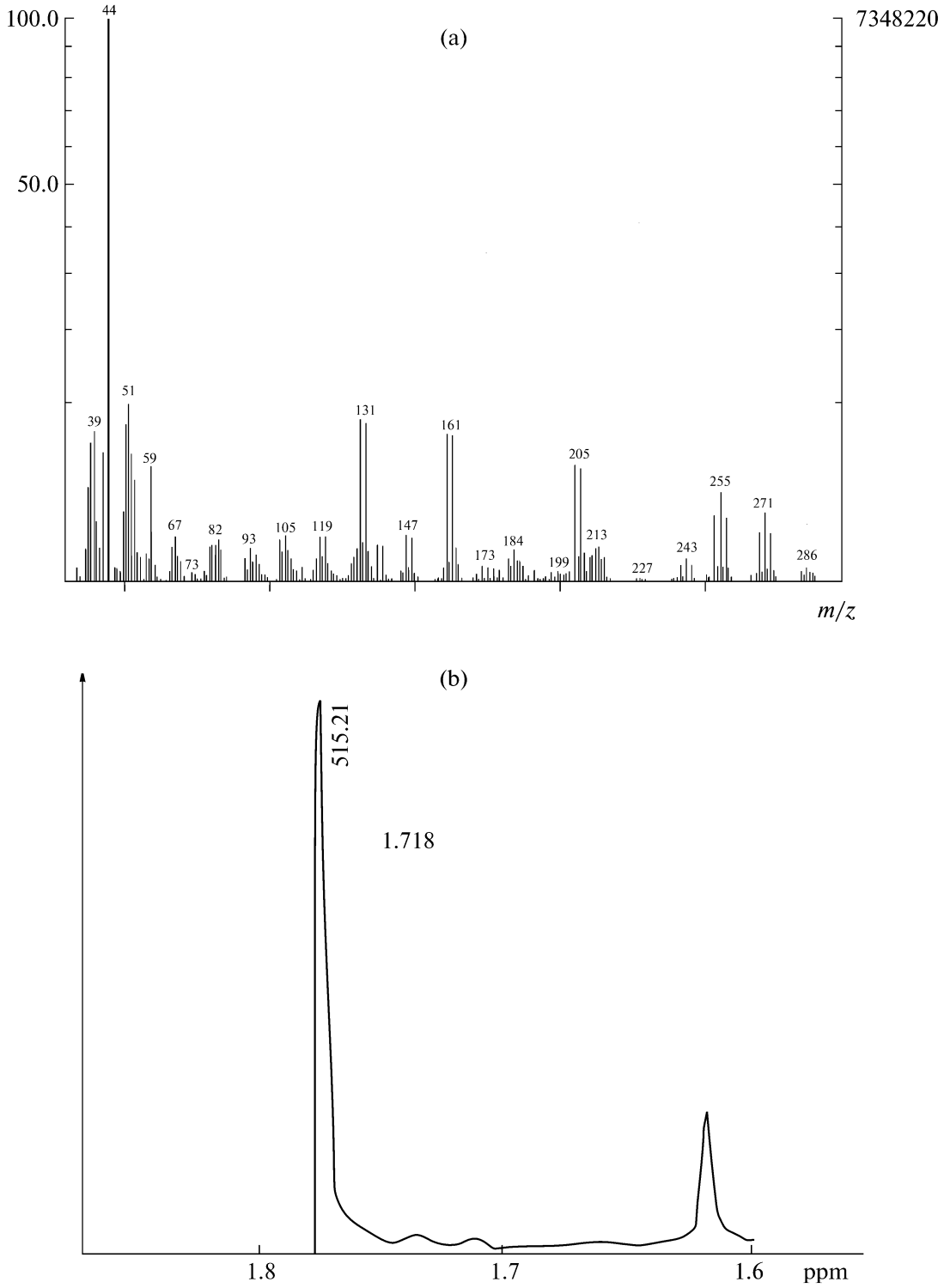


Fig. 1. (a) Mass spectrum and (b) ^{1}H NMR spectrum of 3,4-dibromo-2,5-dimethylthiophene-1-monoxide.

ized by a high percentage of its participation in the reaction, but the main products had the masses 154, 222, and 279, which was evidence of its deeper oxidation.

It follows that the nature and number of substituents substantially influence the qualitative and quantitative characteristics of biomimetic oxidation with hydrogen peroxide, which shows that we correctly

selected 3,4-dibromo-2,5-dimethylthiophene as the principal substrate.

The high-efficiency reaction system developed in this work offers a solution to the problem of the preparation, isolation, and identification of thiophene S-monoxide derivatives. This reaction system consisting of two coherent synchronous reactions of the decomposition of H_2O_2 and hetero-oriented monooxidation of heteroaromatic compounds allowed us to effectively perform liquid-phase monooxidation of thiophene and its derivatives as π-excessive heteroaromatic compounds in the presence of a heterogeneous biomimetic catalyst (EDTA, $Fe^{3+}OH/Al_2O_3$).

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