Side-product inhibition of the catalyst in electrophilic aromatic substitutions and Friedel–Crafts reactions

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Received 25 August 1992; accepted 1 October 1992

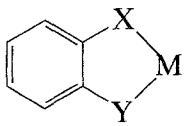
Electrophilic substitutions on aromatics such as C_6H_5X often lead to mixtures of the ortho- and para-disubstituted products C_6H_4XY. The former can chelate a metallic center and hence be a potential catalyst inactivator, whenever the (X, Y) substituents have atoms with lone pairs. This general principle operates in the Friedel–Crafts acylation of anisole, a reaction of industrial importance.

Keywords: Modified clay catalyst; "clayzic"; catalyst poisoning; chelation

1. Introduction

Electrophilic aromatic substitutions are foremost in importance among organic reactions for their numerous industrial uses, for their significance to mechanistic studies and for their historical impact. Ortho–para product distributions are frequent. In quite a few cases, the para isomer is the desired product and the ortho is viewed as a fairly innocuous bystander. Common knowledge is sometimes plainly wrong, as we now proceed to show.

Common sense will suffice for the demonstration in principle. Let us denote as X the ortho–para directing group; Y will be the entering group. Let us further assume that X and Y both include heteroatoms. This frequent situation is the mug shot for an excellent chelator, i.e. for an excellent inhibitor of most metallic catalytic sites:



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Hence, we can issue the following extremely general warning:

whether under homogeneous or heterogeneous catalysis, the catalyst is liable to inactivation by the ortho product.

We now proceed to provide a clear-cut example of such catalyst inactivation. The reaction is the Friedel–Crafts [1]. We have provided novel catalysts for it, in the form of montmorillonite clays exchanged or impregnated with metallic Lewis acids [2]. These obviate the need for stoichiometric amounts of Lewis acids as catalysts [3] and are thus less of an environmental nuisance. We shall be dealing here specifically with Friedel–Crafts acylations [4]. "Clayzic", i.e. clay-supported zinc chloride, is an outstanding catalyst for such reactions [2,5]. Enzyme-like, it displays impressive substrate selectivities [6–9]. It improves substantially upon earlier clay catalysts: Super-Filtrol catalyzed acylation of anisole by acetic anhydride, in the para position, but the yield was about four times less than by the use of 85% orthophosphoric acid as the catalyst [10]. We shall bring forth presently experimental support for the above conjecture of catalyst poisoning by the ortho product.

2. Experimental

2.1. PREPARATION OF THE CATALYST

"Clayzic" is the acronym for montmorillonite clay K10-supported zinc chloride. It is prepared by dissolving 5 g of zinc chloride in 100 ml of warm (40°C) acetonitrile in a 500 ml flask. To this vigorously stirred solution, 20 g of clay (H10, Süd-Chemie, Munich) is added in small increments. Stirring is maintained for another 30 min after the addition of the clay. The solvent is then removed under reduced pressure in a rotary evaporator on a 50°C water bath for 30 min and at 95°C for another 30 min. The resulting solid is powdered in a mortar and dried overnight in an oven at 120°C in air at atmospheric pressure. Upon removal from the oven, the catalyst is, if necessary, ground again in a mortar, and kept at 120°C under air at atmospheric pressure.

2.2. GENERAL

Anisole and acetic anhydride (Janssen Chimica, Beerse, Belgium) are distilled before use. Gas phase analysis of product mixtures is carried out with a Varian 3300 gas chromatograph equipped with a flame ionisation detector, and a Varian 3400 integrator and a 30 m $\times$ 0.324 mm DB1 fused silica capillary column (J&W Scientific, 0.25 mm thickness). The acetylation products are identified and their yield determined after calibration of the instrument using authentic samples and *n*-hexadecane as the internal standard. IR spectra were obtained with a Perkin-Elmer FTIR spectrophotometer of the 1600 series.

2.3. TYPICAL PROCEDURE

A mixture of the anisole substrate (10.8 ml ≈ 100 mmol) also serving as the solvent and of *o*-acetylanisole (0.025–2.5 mmol), with acetic anhydride (10 mmol), and with hexadecane (56 mg, 0.25 mmol) is preheated at 160°C in a round-bottomed 50 ml flask equipped with a magnetic stirrer, an upright condenser and a $CaCl_2$ tube to guard against humidity. The solid catalyst (0.1 g) was added into the mixture. The reaction is followed by gas chromatography. After disappearance of the acylating reagent, denoting its 100% conversion in the excess aromatic substrate as solvent, the mixture is cooled, filtered, and the solid catalyst is washed with two or three 20 ml portions of diethylether or dichloromethane. Then, the solvent is removed under reduced pressure (20 mm Hg) from the gathered liquid phases.

3. Results and discussion

To test for minor product inhibition, this product, *o*-acetylanisole, was added to the reaction mixture before bringing it to the 160°C reaction temperature. The results are displayed graphically in figs. 1–3.

Obviously, the presence of the minor product from the beginning of the reaction, provided that its amount be greater than 0.25%, has a pronounced effect on the rate of product formation. At the 0.5% level, its influence is negligible during the first 30 min, following which a slowdown occurs (fig. 1). At

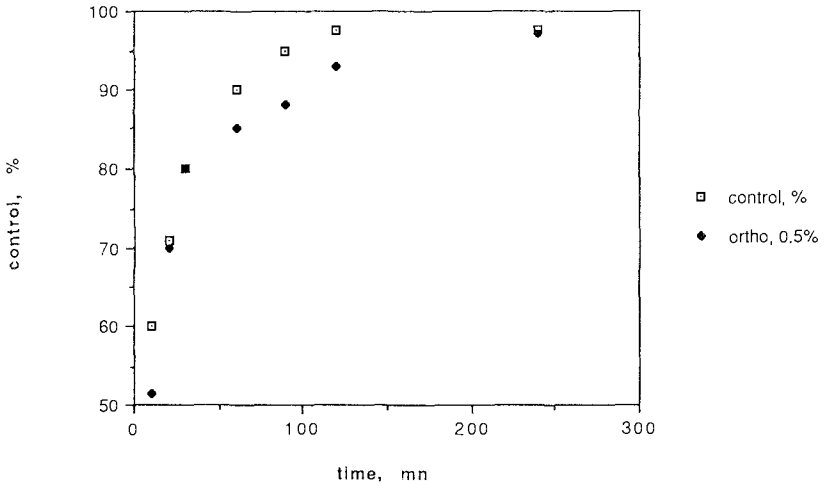

Fig. 1. Yield in the major, para product monitored as a function of time during 4 h. Data for the control experiment, in the absence of the minor, ortho product, are uncorrected for inhibition by this minor product. Its relative amount at the end of the reaction is 2.5%. This control experiment is compared with the effect of adding 0.5% of the minor product.

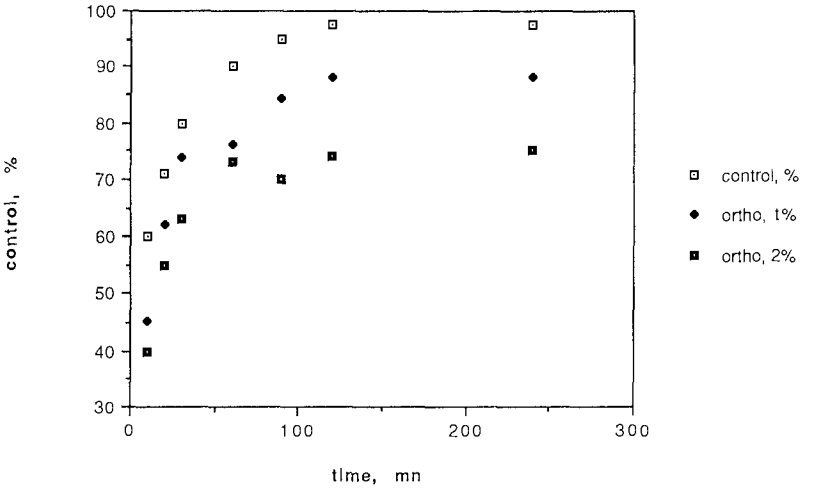

Fig. 2. Same as in fig. 1, with 1 and 2% of added ortho product.

the 1–2% level, there is significant inhibition (fig. 2). At levels greater than 5%, considerable inhibition is observed (fig. 3). The dominant effect is reduction of the yield at which production of the major regio isomer levels off. It reaches asymptotic values of about 70, 60, and 50% for amounts of the minor product of 15, 20, and 25%, respectively. These results show conclusively that the minor reaction product poisons the catalyst.

When the yield of the major product, *p*-methoxyacetophenone, is plotted after 2 h of reaction time as a function of the amount of inhibitor present (fig. 4), it is seen to consist of a steep descent followed by a plateau, leading in turn to another, less abrupt decrease. We interpret this pattern as consistent with coexistence of at least two types of catalytic sites: "fast" sites poisoned by the

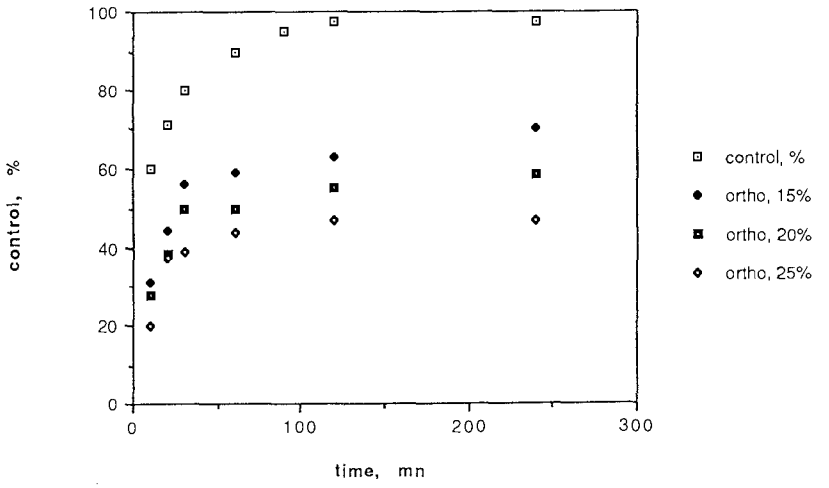

Fig. 3. Same as in fig. 1, with 15, 20, and 25% ortho product added.

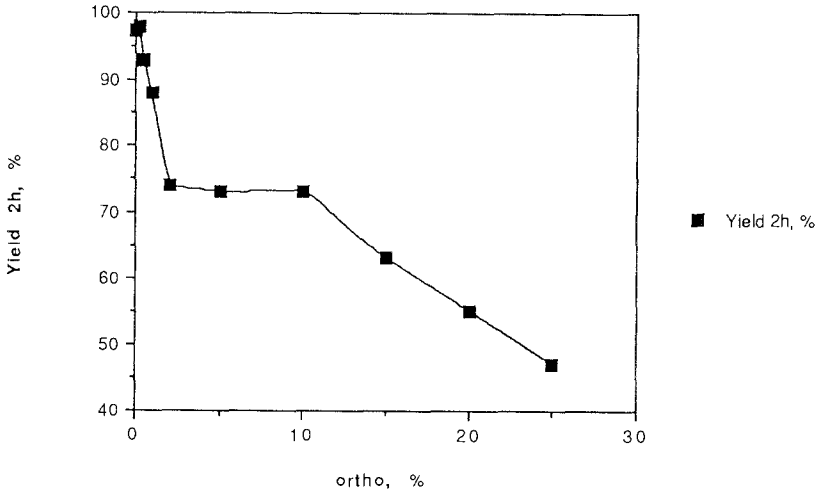

Fig. 4. Plot of the yield in major product (*p*-methoxyacetophenone) obtained after 2 h of reaction time as a function of the relative amount of the *o*-methoxyacetophenone inhibitor.

smallest amounts of *o*-methoxyacetophenone, and "slow" sites only poisoned by amounts of *o*-methoxyacetophenone greater than 10%. This duality of catalytic sites makes it difficult to quantitate accurately the inhibition. Nevertheless, if one limits consideration to the results of greatest practical import, i.e. to the range of 0–5% inhibitor, it is possible to plot the results as a double reciprocal, Lineweaver–Burk-type plot (fig. 5). From this plot, it appears that the dissociation constant $K_d = 0.87 \times 10^{-3}$ M of the "complex" formed between the minor

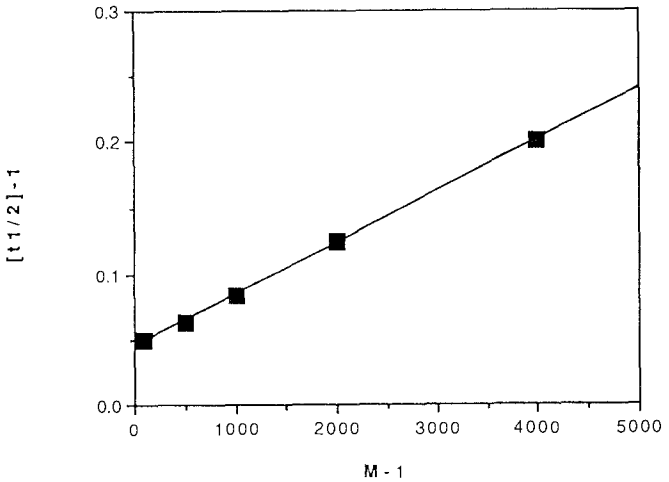

Fig. 5. Double reciprocal plot. $t_{1/2}$ denotes the time necessary to reach 50% yield in *p*-methoxyacetophenone and M is the concentration of the inhibitor. Correlation coefficient = 0.999 for five data points.

product and the "fast" catalytic sites is of the order of 10^{-3} M, which of course ties in nicely with the concentration at which the effect of the inhibitor becomes significant. The present use of a double reciprocal, Lineweaver–Burk-type plot may be a little unusual in an inhibiting study. The common form is the plotting of the reciprocal of the rate versus the reciprocal of the substrate concentration for several concentrations of inhibitors. The dissociation constant for the catalyst–inhibitor complex is then found from a replot of the inhibitor concentration versus either the slopes of the various lines or their X-axis or Y-axis intercepts. Since we did not perform a full-fledged kinetic study, we have built on the analogy with pharmacological studies, in which the dissociation constant of an agonist–receptor complex is obtained from such a double reciprocal plot: a plot of 1/effect versus 1/dose has a slope of $-1/K_d$ and an intercept of 1/maximum effect. Furthermore, $t_{1/2}^{-1}$ has the dimension of a rate constant for the pseudo-first-order reaction studied when the anisole substrate is in large excess with respect to the acetylating reagent. Hence, the above value of K_d should be considered only as an order-of-magnitude, rather than as a highly accurate determination.

Given the specific surface area of "clayzic" (107 m^2/g^{-1}), the total number of zinc(II) catalytic sites in each sample is of the order of 2.2×10^{22}. The critical concentration of 0.2 mM for the poisoning of the "fast" sites indicates that about one site out of 200 belongs to that category. It is tempting to identify these "fast sites" with the edges of the platelets. A back-of-the-envelope calculation gives 3×10^{19} edge sites per sample, given square platelets with sides of 10000 Å. In reality, the sides are jagged rather than smooth, which increases the actual perimeter of the platelets; and correspondingly the number of edge sites, perhaps by one order of magnitude. This is nicely consonant with the number of poisoning particles, i.e. 1.2×10^{20}.

By recovery of the catalyst during an on-going reaction and recording the IR spectrum in KBr, we were able to observe carbonyl stretching frequencies at 1662 and 1649 cm^{-1}. The corresponding C≡O absorptions are 1677 and 1675 cm^{-1} for the isolated para and ortho product, respectively, as liquid films. Accordingly, product adsorption onto the catalytic surface and the attendant interaction with the metallic zinc(II) centers induces low frequency shifts $\Delta\nu$ of 15 and 26 cm^{-1} respectively. The latter value is consistent indeed with chelation of zinc by the *o*-methoxyacetophenone.

p- and *o*-methoxyacetophenone also display shifts of the C≡O absorption upon formation of a 1:1 complex with $ZnCl_2$. The free bands at 1677 and 1673 cm^{-1}, respectively, shift to 1656 and to 1621 cm^{-1}, in the solid state (nujol mull) for $\Delta\nu$ values of 21 and 52 cm^{-1}. The literature indicates that *p*-methoxyacetophenone interacts with $ZnCl_2$ in the solid state (nujol mull) to form a 1:1 complex characterized by $\Delta\nu = 45$ cm^{-1} (1675 free; 1630 bound) [11]. The smaller value of 15 cm^{-1} observed here for the adsorbate indicates that the zinc metallic ion impregnated on the clay has reduced Lewis acidity compared to the

free ion. The literature also indicates for the complex between *o*-methoxyacetophenone and mercuric chloride a $\Delta\nu = 33$ cm^{-1} (1678 free; 1645 bound) [12].

4. Conclusions

This study demonstrates inhibition of a Friedel–Crafts electrophilic aromatic substitution. The minor isomer inactivates the "clayzic" catalyst by chelation of the zinc(II) active sites. These are likely to be edge sites on the periphery of the clay platelets. The dissociation constant of the *o*-methoxyacetophenone–catalyst complex is of the order of millimolar, which corresponds to the concentration at which the minor product acts as an inhibitor of the catalyst.

Acknowledgement

We thank Tessenderlo NV for their generous support and Dr. Loosen, director of research, for his continued interest. We thank Mr. Noville, from Professor Pirard's laboratory, at the University of Liège for determining the specific surface of "clayzic".

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