

Retrospective Hit-Deconvolution of Mixed Metal Oxides: Spotting Structure-Property-Relationships in Gas Phase Oxidation Catalysis Through High Throughput Experimentation

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Abstract: Complex multi-element lead structures of mixed metal oxides that may be identified as hits during high throughput experimentation (HTE) campaigns, can be deconvoluted retrospectively on the basis of simple binary and ternary oxides as illustrated in the current example of a hit found in an ammoxidation reaction. On the basis of the performance of the simple binary and ternary mixed metal oxides structure property relationships can be established, that give insight into the roles of the different components of the complex mixed metal oxides and may also help in establishing a reaction mechanism and converting the hit into a development candidate.

INTRODUCTION

Partial oxidation reactions of alkanes to aldehydes, carboxylic acids, anhydrides or nitriles in the gas phase using heterogeneous catalysts are among the most challenging catalytic conversions that can be encountered. Although many years of research in industry and academia have been devoted to this topic, only a minor amount of processes have made it to the commercial size, certainly the most important one being the oxidation of n-butane to maleic anhydride [1]. Nevertheless the interest in these conversions in both industry and academia is undiminished. From an industrial perspective the high attractiveness of these conversions is evident: alkanes are a largely abundant and cheap feedstock and the compelling advantage of a one step direct conversion of an alkane to a partial oxygenate is evident if compared to the multi-step conversions of the well established oxidation and ammoxidation technologies based on allylic oxidation olefins [1-4] or benzylic oxidation of aromatics [5] as feedstock. It is common for heterogeneously catalysed partial oxidation reactions that the solution to the scientific and technical problem of converting the paraffin to the partial oxygenate is closely related to materials. Specific mixed metal oxides are required for each specific reaction, and even with a handful of known structural types of mixed metal oxides in the hand of the scientific community it seems currently impossible to predict new potential lead candidates for oxidation reactions. Regarding the challenges of multi-step partial oxidation reactions it becomes clear why some of them without any known lead structures are considered "dream reactions" or "holy grails of oxidation catalysis". One of these very challenging reactions is surely the direct conversion of n-hexane or cyclohexane to adipodinitrile *via* heterogeneously catalysed gas phase ammoxidation. Reports about the successful accomplishment of this reaction in the scientific literature are sparse, apart from two reports from Reddy *et al.* [6] and

Simon *et al.* [7]. The work of Reddy describes the use of an antimony doped γ -alumina supported vanadyl pyrophosphate catalyst system as catalyst for the oxidation of cyclohexane to adipodinitrile. The obtained yields are around 35% and apart from this sole report, no other group has ever reported yields that high in an ammoxidation reaction of this type. Simon *et al.* report the use of different hydrocarbon feedstocks n-hexane, cyclohexane and benzene for the target reaction. Their findings are that a) n-hexane does not lead to product formation and both cyclohexane and benzene are both converted to muconitrile (dicyanobutadiene), with the reaction pathway going over benzene as intermediate when employing cyclohexane as hydrocarbon feedstock. Simon *et al.* [7] found that V-Mo-O and Ti-Mo-O systems proved to be most useful for the conversion of cyclohexane and benzene to muconitrile, but obtained also only moderate yields with maleo- and fumaro-dinitrile, maleine-imide and HCN as main by-products. The work of Ovitser should also be mentioned here [8], most of the work was performed as TAP experiments (temporal analysis of products). Still Ovitser claims the usefulness of cyclohexane conversion to adipodinitrile over Ti-Sb-O catalysts.

The state of the art summarized above is representative for a number of cases in heterogeneous catalysis where little or virtually nothing is known about potential lead structures that would render themselves useful in a target reaction. From a viewpoint of the experimental planning this is not an easy case. There are some approaches on how to tackle problems similar to the one described on a very principle level by the groups of Schüth and Mirodatos [9, 10]. The general approach of this work of cause may lead to databases and algorithms that may in the long run help predicting new lead structures from scratch. Generally speaking, most of the other methodologies for library planning relate on the chemical intuition of the scientists working on the project. Examples for statistical aids or optimization algorithms that may be used to structure the search for a suitable catalyst are for instance statistical experimental designs [11, 12], genetic algorithms [13] or alternative iterative design methods [14]

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and fully randomised algorithms [15]. To apply such tools, starting points have to be defined from which the further experimentation is done. If a confinement strategy is followed, these starting points and the corresponding variations of the variables connecting them can be interpreted as the boundaries of the experimental plan (i.e. hyperplanes in the multidimensional search space). Unfortunately, the number of points required to cover the entire search space increases with the number of dimensions (n) as an exponent. The method of lead deconvolution attempts to reduce the dimensionality in a systematic way: A lead-centred simplex-centroid design [16] is generated. If fully expanded, this results in $n + \binom{n}{2} + \binom{n}{3} + \dots + \binom{n}{n} = 2^n - 1$ design points.

To reduce the number of experiments, the sum in the formula above is truncated after the first terms (i. e. taking only few components at once into account). The resulting design points are situated in the centroid position of simplexes in the corresponding lower dimensional subspaces. In other words, these are the center-points of the hyperplanes spanned by the corresponding number of components, confining the original starting point. In successive experiments the dimensionality is increased, but taking only the more prospective components into account and leading the optimization in the high dimensional search space to certain regions of interest. Our approach is motivated by the hypothesis that: a) structurally or chemically related solid state materials do in many cases have similar catalytic properties in catalysis, b) a reduction in structurally or chemical complexity of solid state materials does not necessarily involve a loss in catalytic properties, c) complex reactions like the ammonoxidation involve more than one crucial reaction barrier on the reaction path from the educt to the desired product. Therefore a catalyst needs qualitatively different reactive sites for selective acceleration of intermediate reaction steps in order to be a useful material. In this respect a complex mixed metal oxide catalyst is very similar to a library of organic molecules as it is used in pharmacological screening: In this field mixtures of molecules are tested in order to increase the screening throughput and the library performance is determined. If such a library appears to be prospective, the actually active molecular species has to be identified by systematic screening of sub-libraries (i.e. deconvolution [17]). For catalyst development, the deconvolution technique can be applied to identify performance critical reaction steps and materials providing the proper active sites to establish structure-reactivity relationships based on cause-effect-chains.

The advantage of the deconvolution approach lies in the fact that the parameter space is screened in a systematic way leading to "high quality" data sets: The input parameters are still uncorrelated as in a classical statistical design and can be used for modelling (in contrast to e.g. genetic algorithm type strategies which usually result in unbalanced coverage of the search space leading to statistical bias). A disadvantage of the deconvolution approach is of course the fact that prior knowledge is required to determine a proper starting point. This disadvantage can of course also be interpreted as a strength looking at catalytic problems similar to the one sketched out in the current article: the scientist can go back to related chemical reactions and employ existing knowledge

and solid state materials well characterised and established in research as starting points. In a sense the challenge of ill defined solid state materials versus well defined molecular compound may in that case become less pronounced. However it is evident that there are differences compared to methods employed in medicinal chemistry where compound mixtures are screened versus their useful properties like in [18] or [19]. For solid state materials such approaches would also be viable nevertheless: the inherent complexity would be much higher than for compound mixtures, as the possibility of solid state reactions and the formation of new or mixed phases cannot be ruled out. Therefore our approach for the choice of complex mixed metal oxides was restricted to materials described in the patent or scientific literature.

It is evident that the outcome of such an experimental plan will be largely dependent on the boundary conditions and therefore rely on the scientific intuition of the scientist. In addition, the approach requires to collect and interpret a variety of performance indicators (e.g. yields of side products) and relate the data to a model of the reaction mechanism. This distinguishes our approach from the way deconvolution is applied in the field of biochemistry/pharmacology where usually a single figure of merit is sufficient. In the following we will try and illustrate that in some cases, especially when tackling complex compounds, a simplification *via* retrospective lead deconvolution may help in identifying active compounds in mixed metal oxide catalyst systems.

HTE-APPROACH AND EXPERIMENTAL LAYOUT

All catalytic tests in the project were carried out with "Stage II" catalyst testing equipment at a catalyst volume of 1 ml. The equipment is described in detail elsewhere [20]. For the preparation of the bulk mixed metal oxides mostly the freeze drying approach described in [21] was applied starting from both homogeneous solutions or oxide or hydroxide slurries. The obtained mixed metal oxides were then calcined under controlled atmosphere up to temperatures of 500°C and fractionated to a particle size of 150-300 µm which was used for the catalytic test. Selected samples were characterised by X-Ray diffraction on a Bruker GADDs. Generally all samples were first exposed to n-hexane as hydrocarbon feedstock with a feed-ratio of n-hexane/ammonia/oxygen of 1-5%/2-10%/8-15% with N₂ as balance at GHSV between 500 and 3000 h⁻¹, the hydrocarbon feed was then switched to cyclohexane and subsequently benzene, typical temperature ranges in the parameter screening were between 350 and 550°C. GHSV and temperature were both adjusted so to obtain data at hydrocarbon conversions between 5 and 50%. Samples were allowed to equilibrate under reaction conditions for 6 hours at minimum, measurements giving best results in a run at certain conditions were repeated at the end of each run.

GENERAL MECHANISTIC CONSIDERATIONS FOR THE AMMOXIDATION REACTION

The reaction of n-hexane and ammonia to muconitrile involves the cleavage of 16 C-H/N-H (14 for cyclohexane) bonds and can be expected to be rather complex. A potential reaction mechanism that is in line with our experimental findings has been reported by Simon *et al.* [7] (see Fig. 1

schematic representation). Accordingly, the first reaction step is the oxidation of cyclohexane to benzene, which is highly exothermic. Benzene is then activated to an intermediate diimine potentially *via* phenol/chinone species. The 1,2-activated chinonediiimine can then be further oxidized to form muconitrile. The 1,4-activated species will decompose and form C4-nitriles. According to density functional calculations in our lab, both chinonediiimines have similar stabilities.

According to the reaction mechanism described above, the reaction starting from a cyclic substrate has only one stereochemically critical step, the activation of the benzene ring. This may result in a 1,2 or a 1,4 activated intermediate (due to the +M effect of the substituent).

If on the other hand n-hexane is used, the situation is different. Any C-H-bond can be activated with a similar statistical probability. The oxidation at both terminal C-atoms is rather unlikely. According to quantum chemical calculations performed in our lab, C-H bond cleavage in the 2- and 3-position is even favoured by 15 kJ/mol over the C-H-activation in the 1-position (UB3LYP/6-31g**). As a consequence, a quite divergent set of reaction paths can be expected leading to fragmentation of the substrate into C1 and C2 units in the course of the oxidation.

LIBRARY PLANNING

The library planning for this ammoxidation reaction was influenced by a number of factors. The main two incentives that drove the planning for the first libraries were a) the wish to reproduce a number of potential lead candidates that were already discussed in the open literature and if successful generate first hits at a very early stage of the project and b) a wish for detailed understanding material reactivity based on defined oxides of different complexity, mostly binary and ternary oxides. Both these two questions were taken as target topics for the first two screening campaigns. Others following are of minor interest in the scope of this publication.

The first library of approximately 300 materials consisted of 1) a number of lead compounds that were found in the open literature concerning the target reaction, 2) other cata-

lysts known to be useful in ammoxidation reactions of olefins and aromatic compounds and 3) other catalysts known to be useful in paraffin partial oxidation in general. For logistical, availability and other reasons it was decided that these 300 materials were the first ones which should be tested in the screening campaign. This initial library proved successful as it delivered a first multicomponent mixed metal oxide lead within the first six weeks of screening.

n-HEXANE AS HYDROCARBON FEEDSTOCK

For classical mixed metal oxide catalyst of redox active metals in this study no ammoxidation products with more than two carbon atoms could be obtained when n-hexane was used as hydrocarbon educt, the dominating products were HCN and CO_x. Nevertheless, rather high yields of 1,4-dimethyltetrahydrofuran could be obtained over oxides with basic character like MgO, CaO, Mg-silicates, and Mg-aluminates. HCN, CO_x and acetonitrile were the side products (2,3- and 1,3- dimethyltetrahydrofuran were also obtained in smaller fractions). 1,4-dimethyltetrahydrofuran is known to be formed as a product of the homogeneous gas phase oxidation of n-hexane over Pt-Rh gauzes as discovered by O'Connor and Schmidt [22], evidently this product can also be obtained under ammoxidation conditions with oxides of basic character. As an important mechanistic conclusion the occurrence of this product clearly illustrates that the thermodynamically favoured H-abstraction takes place for methylene groups, apparently leading to a large extent to a ring closure of a five membered ring after oxygenation of the β-carbon atom. The product distributions obtained gives evidence for an autoxidative pathway of the reaction *via* peroxides. The chances of selectively functionalising the α-carbon atom of n-hexane under the conditions named above are rather low, if not zero.

CYCLOHEXANE AS HYDROCARBON FEEDSTOCK

With both cyclohexane and benzene the conjugated unsaturated analogue of adipodinitrile namely muconitrile and both unsaturated C₄-dinitriles, maleo- and fumarodinitrile could be obtained with the leads produced in the initial library. Other side products of the reaction were acetonitrile

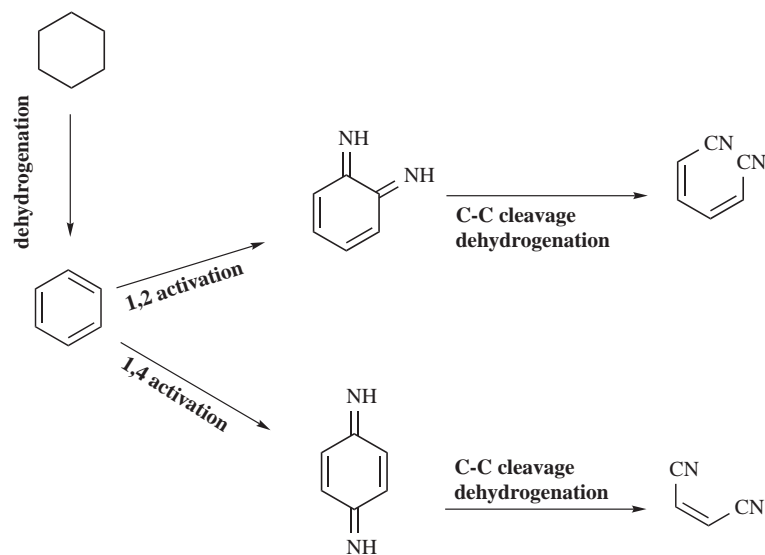


Fig. (1). Illustration of the potential reaction pathways of cyclohexane and benzene activation. Please see also reference [7].

and HCN and CO_x. If the ammonia to hydrocarbon ratio was adjusted at a level of unity mostly maleine-imide was obtained as product. The following observations were made concerning cyclohexane as hydrocarbon feedstock: 1) if cyclohexane was used as hydrocarbon feedstock, conversion of the paraffin to benzene always took place; 2) at similar reaction conditions the use of benzene always led to higher yields for the unsaturated C₆-dinitrile (all 3 conformers were observed in the GC in equal fractions) and the C₄-dinitriles (maleo and fumaro dinitrile in equal fractions); 3) if cyclohexane was used generally higher temperatures or lower GHSV's had to be applied to a) lower the amount of benzene as side product and to obtain the unsaturated C₆-dinitrile and the C₄-dinitriles. In combination with the work of Simon *et al.* [7] it is therefore assumed that the reaction mechanism of the unsaturated C₆-dinitrile and the C₄-dinitrile formation from cyclohexane proceeds through benzene as intermediate. According to our data the direct use of benzene is beneficial for higher product yields, speaking from a more general perspective this fact could at a later stage also contribute to the economy of a later process with benzene being the cheaper and more abundant feedstock compared to cyclohexane.

HITS FOUND IN THE INITIAL LIBRARY

For the discussion in this paper we will focus on the prime lead catalyst that was identified as a hit in the initial library. The composition of the mixed metal oxide found to be useful in the conversion was Mo₁₂Sb₃Co₁V₁Nb₁Ta₁Ti₁O_x, this catalyst derived from a set of candidate materials that render themselves useful in the partial oxidation of propylene to acrylonitrile (see for instance [23]). In the initial tests the catalyst delivered a maximum muconitrile productivity of 22,5 μmol/ml_{catalyst}h at conditions of 2% benzene/4% am-

monia/14% oxygen (nitrogen as balance), a GHSV of 1000 h⁻¹ and a temperature of 420 °C. All three conformers of muconitrile were found in the GC. C₄-dinitriles are also produced as side fraction of the product mix, at half the productivity of muconitrile (mix of maleo- and fumarodinitrile). The catalyst itself shows a stable performance under reaction conditions with no performance loss within 36 hours of testing at the same condition. The structural analysis of the catalyst sample revealed a largely amorphous oxide content with crystalline portions of the well known bronze structures of Mo₅O₁₄-type oxides in mixture with β-Co molybdate and traces of MoO₃ [24, 25].

In a first step a variation of the element content in the complex mixed metal oxide was performed. An increase in cobalt and vanadium content leading to higher activity, but a massive loss in selectivity towards unsaturated dinitriles. Increasing the antimony, niobium, tantalum or titanium content led to a loss in activity and selectivity. From the initial library it was already clear that an exchange of nickel against cobalt was detrimental, similar counter productive results were obtained for an exchange of cobalt against iron, chromium or copper. Also exchanges of titanium against zirconium, tin against antimony or bismuth against antimony did not lead to improved performance. Additional experiments in which the catalyst sample was doped with low levels of alkali metals, alkaline earths, phosphorous or tellurium generally lead to loss in activity and selectivity of the samples.

RETROSPECTIVE DECONVOLUTION OF THE LEAD CANDIDATE

The first efforts to improve the hit were not successful as described above, the structural indications that were obtained also left an obscure picture of what the potential "lead struc-

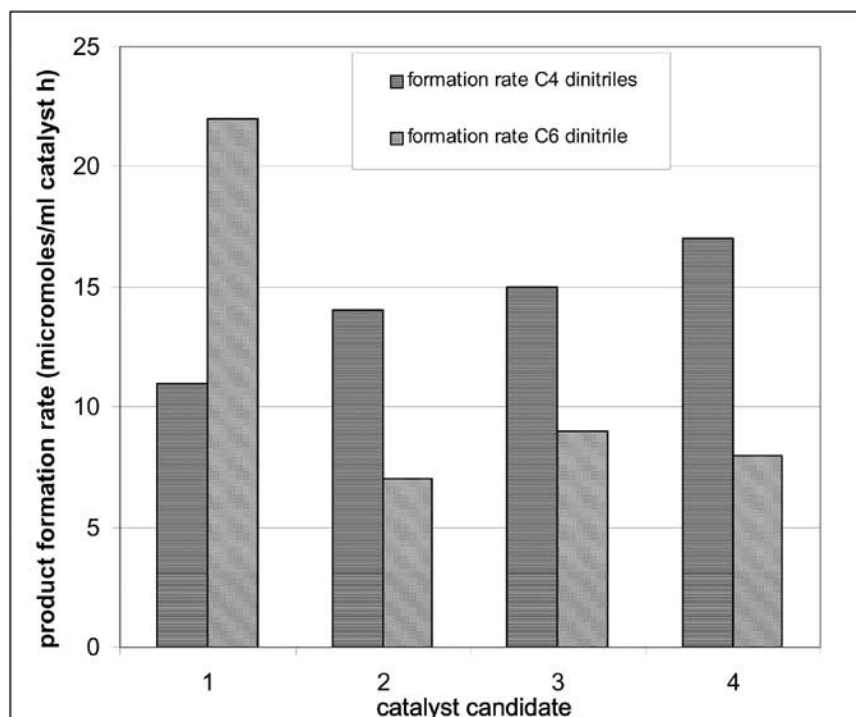


Fig. (2). Comparison of the maximum product formation rates over a the lead compound and related mixed metal oxides expressed in μmol/ml_{catalyst}h. Catalyst candidates: 1) Mo₁₂Sb₃Co₁V₁Nb₁Ta₁Ti₁O_x, 2) Mo₁Sb₁O_x, 3) Mo₁₂Sb₃Ti₁O_x and 4) Mo₁₂Sb₃V₁Ti₁O_x. Reaction conditions 2% benzene, 4% ammonia, 14% oxygen, balance nitrogen, GHSV 1000 h⁻¹, temperature range 420-440°C.

ture" might be. A reduction in complexity of the problem seemed useful at that point in order to a) reduce the number of degrees of freedom from a point of view of the constituents of the candidate material and b) arrive at a clearer structure property relationship especially concerning the structure of the active phase of the material. In order to deconvolute the nature of the active phase and to get to an understanding of the structure property relationships it was decided to go for an approach similar to the one described in the second library and synthesizing the binary, ternary, quaternary and higher oxides that can be obtained by permutatively combining the elements of the hit on each level of complexity and exposing them to the range of reaction conditions described above for obtaining the multidimensional library (Fig. 3a,b). The example given for the variation of the target compound focussed around defined crystalline compounds is to be seen as an illustrative example. For the lead variation a variation of the stoichiometric amounts of the different elements was also performed as well for stoichiometries that do not result in defined crystal structures within this library. Nevertheless for element combinations where different oxide structures with identical stoichiometries could be obtained, these were tested as separate catalyst candidate samples. The total library contained 190 different materials based on the principles explained above. Table 1 shows a number of the binary, ternary and higher oxides that were tested in this library and a led a) to ammoxidation products with a carbon backbone larger than C₂ and b) give a conclusive picture of the potential roles of the elements in the lead compound. For clarity the results were restricted for the use of benzene as hydrocarbon feedstock. From the table it can be seen that most of the oxides have the ability of transforming benzene to unsaturated nitriles with a carbon backbone of C₄. Evidently rutile based materials like V-Sb-O or V-Sb-Ti-O produce preferentially unsaturated C₄-dinitriles from benzene, not even traces of muconitrile were found using these oxides as catalysts. A lowering in the ammonia content shifts the product spectrum to maleine-imide which is obtained at a lower yield than the sum of unsaturated C₄-dinitriles. Muconitrile is only obtained with Mo-Sb-O, Mo-Sb-Ti-O and Mo-V-Sb-Ti-O type oxides which structurally display mainly an amorphous to semi-crystalline character similar to oxides of the type Mo₅O₁₄, still contain fractions of MoO₃ and Sb₂O₅ [24]. Generally samples of this type showed some loss in activity and selectivity if exposed to feed conditions for 36 hours, leading to inferior performance than the original lead candidate. This performance loss was usually accompanied

by antimony oxide deposits in the guard bed of the catalyst sample which were produced by gas phase deposition: a feature not uncommon for antimony containing catalysts of partially crystalline nature. Another interesting feature of the Mo-Sb-O type oxides is the fact that also here the main product are also the unsaturated C₄-dinitriles. Similar to the rutile type V-Sb-O or V-Sb-Ti-O oxides, a lowering in ammonia content in the feed shifts the product spectrum towards maleine imide, muconitrile no longer observable as product.

STRUCTURE PROPERTY RELATIONSHIPS DEDUCTABLE FROM THE STUDY

Apparently rutile type oxides like V-Sb-O, V-Sb-Ti-O, Mo-Sb-O and Mo-Sb-Ti-O type oxides of partially crystalline nature have the capability of activating benzene in the above described chinone like manner. From a thermodynamic viewpoint both activations 1,2-chinoide and 1,4-chinoide should be on a similar energetic level, still it appears that the unsaturated C₄-dinitriles are to be the preferential products with the above named rutile type oxides and still make a large fraction of the Mo-Sb-O oxides. An essential feature of both Mo-Sb-O, Mo-Sb-Ti-O and Mo-Sb-V-Ti-O is the semicrystalline nature, which also leads to a partial instability of the oxide.

The assumption lies near that the unsaturated C₄-dinitriles cannot only be a product of the direct 1,4-chinoide activation but may also be a result of the further oxidation of muconitrile, which is thermodynamically much more labile. Still we lack experimental proof of this assumption. Evidently an excess of ammonia is helpful in reducing the catalyst activity with regard to the chinoide activation and the further oxidation of the desired product with the C₆-backbone.

CONCLUSIONS

With the study described in the above paper we have illustrated that retrospective hit deconvolution of complex lead compounds can be a helpful tool for uncovering structure property relationships. Evidently the catalytic functions of the complex hit could be assigned to more simple mixed metal oxides. For the successful oxidation of cyclohexane and benzene to muconitrile Mo-Sb-O, Mo-Sb-Ti-O and Mo-Sb-V-Ti-O type oxides of partially amorphous character could be identified as most simple lead compounds. We could also show that the reaction pathway on these oxides

Table 1. Results of the Retrospective Hit Deconvolution

Ternary Oxide Systems	Products Found	Quaternary Oxide Systems	Products Found	Pentenary Oxide Systems	Products Found	Hexenary Oxide Systems	Products Found
V-Sb-O	C4-DN	V-Sb-Ti-O	C4-DN	V-Sb-Ti-Nb-O	C4-DN	V-Sb-Ti-Nb-W-O	C4-DN
Mo-V-O	C4-DN MLI	Mo-V-Nb-O Mo-V-Ta-O	C4-DN MLI	Mo-V-Nb-Ta-O	C4-DN MLI		
Mo-Sb-O	C4-DN C6-DN	Mo-Sb-Ti-O	C4-DN C6-DN	Mo-Sb-V-Ti-O	C4-DN C6-DN	Mo-Sb-V-Nb-Ti-O	C4-DN
		Co-Mo-Sb-O	C4-DN	Co-Mo-Sb-Ti-O	C4-DN	Co-Mo-Sb-Nb-Ti-O	C4-DN

The table illustrates the products found for the various mixed metal oxides that were used as catalysts in the reaction. For simplicity, systems where only oxidation products with a carbon backbone < C₄ are found are left out (abbreviations: C4-DN = C₄-dinitriles, C6-DN = C₆-dinitriles, MLI = maleine imide). Reaction conditions 2% benzene, 4% ammonia, 14% oxygen, balance nitrogen, GHSV 1000 h⁻¹, temperature range 420-440°C.

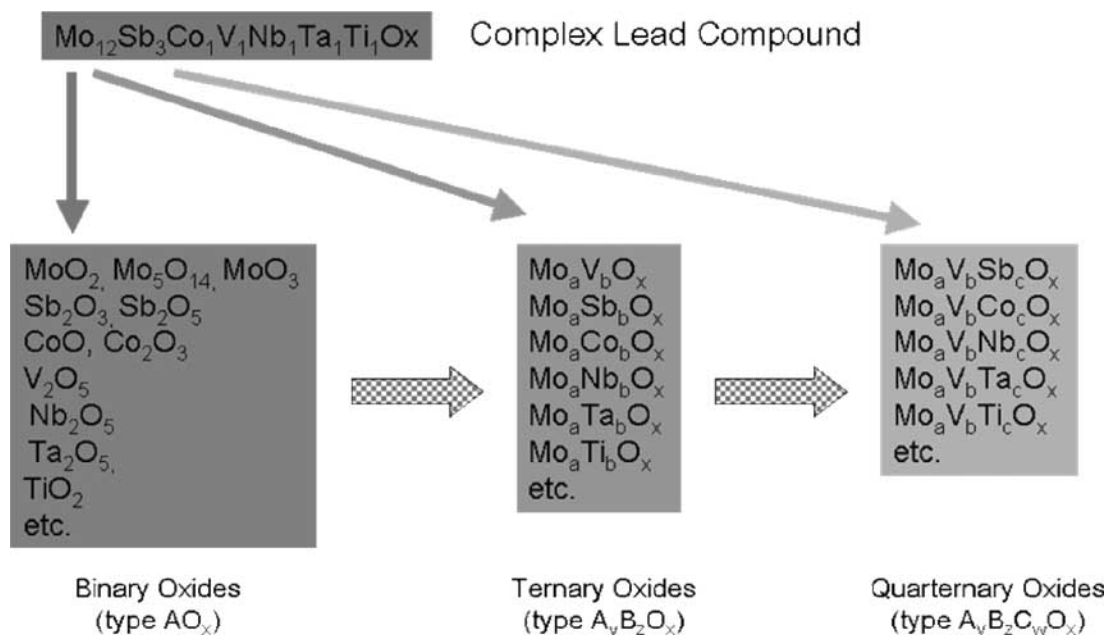


Fig. (3a). Schematic depiction of the hit deconvolution performed on the complex mixed metal oxide lead: Based on the primary complex hit binary, ternary and higher oxides are derived (only exemplary examples shown to illustrate the principle).

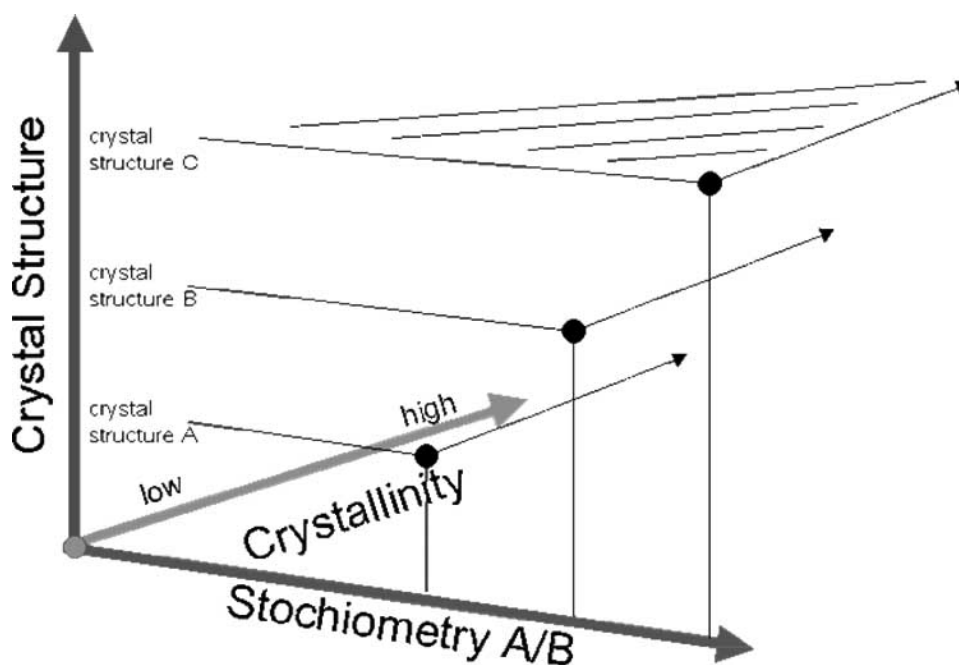


Fig. (3b). Schematic depiction of the hit deconvolution performed on the complex mixed metal oxide lead: Based on the an example of a ternary oxide the potential for the development of a three dimensional development of the solid state material based on variation of the stoichiometry, the crystal structure and the crystallinity is illustrated.

proceeds *via* chinoide activation of the aromatic compound either by 1,4- or 1,2-activation of benzene being the decisive step in the product formation. From the study it can be concluded that the retrospective hit deconvolution is a viable way of generating hits and establishing structure property relationships within reasonably sized libraries and time-frames.

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