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Accelerating lead discovery via advanced screening methodologies

Jens Klein[a,*], Wolfram Stichert[a], Wolfgang Strehlau[a], Armin Brenner[a],
Dirk Demuth[a], Stephan Andreas Schunk[a], Hartmut Hibst[b,1], Sebastian Storck[b,1]

[a] hte Aktiengesellschaft, Kurpfalzring 104, 69123 Heidelberg, Germany
[b] BASF Aktiengesellschaft, 67056 Ludwigshafen, Germany

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Abstract

Sufficient data quality, screening speed and sample throughput are often discussed as the three controversial factors in primary screening attempts within HTE (high throughput experimentation). Hence, one of the most exciting challenges for stage-I-screening attempts is the fast access to performance data with high quality. Apart from the development of new analytical tools, we demonstrate here that an intelligent combination of different analytical techniques which complement each other can lead to substantial acceleration of the screening process while achieving a high data quality. In the given example the direct combination of IR thermography and, e.g. one additional sampling method (e.g. mass spectrometry or GC/MS) via a movable “sniffing capillary” results in a powerful combination utilizing the strength of each method: fast screening for catalyst’s activity by IR thermography and exact determination of relevant reaction selectivities for active candidates only by, e.g. fast GC, GC/MS or MS. In a demonstration example for a partial oxidation reaction in the gas phase with solid catalyst libraries we present the validation data, including the key factors of a new reactor design with ensured homogeneous temperature- and fluid distribution developed by hte Aktiengesellschaft. This advanced primary screening approach is presented in the context of the HTE solution for gas phase oxidation reactions.

Keywords: High throughput experimentation; Stage 1; Primary screening; IR thermography; GC/MS; Combination; Analytics; Reactor design; hte; 96-fold reactor

1. Introduction

The development of new high throughput methods has been a center of interest of research in the field of materials research and catalysis for the last few years. Using the methods of HTE (high throughput experimentation), a great number of different materials can be investigated for their performance properties in a given catalytic target reaction. Regarding catalytic properties, IR-thermographic techniques [1–4] and mass spectrometric or fast-GC methods [5–7] are broadly described and discussed in scientific publications and the relevant patent literature. These analytical methodologies have complementary intrinsic drawbacks for the observation of active components in gas phase catalysis:

(i) IR-thermography as a truly parallel technique can only be used to observe thermal effects on a material and therefore this optical method gives a very fast indication (within microseconds range) about the activity of each member of a materials library

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[*] Corresponding author. Tel.: +49-6221-74970;
fax: +49-6221-7497-134.
E-mail address: info@hte-company.de (J. Klein).
URL: http://www.hte-company.de.

[1] Tel.: +49-621-60-56136; fax: +49-621-60-8606371.

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[4,8]. Providing an optimal experimentation design even small temperature changes of partial oxidation reactions with close to thermo-neutral heat balances can be resolved directly “on” the catalyst with a high spatial resolution [4]. But so far the information content is restricted solely on the activity of a given material: no information is obtained with regards to the reaction selectivities resulting from the chemical reaction.

(ii) On the other hand, MS- or GC methods are the most common sequential methods offering the possibility of a detailed determination of the product spectrum in the exhaust steam of a reactor (also with a determination of conversion, selectivity and finally product yield for catalysis applications), but have the major drawback of being non-parallel and more time consuming. For a product spectrum as it occurs in gas phase partial oxidation reactions like light alkanes, alkenes and oxygenates mixtures (aldehydes, ketones, acids, etc.) chromatographic separation times in the minute range are commonly achieved and also applied for applications outside the field of HTE. For a high number of samples, as generally screened in stage-I-applications within HTE, the necessary time framework is hardly acceptable, unless only a selected number of potentially prospective candidates are measured with the more time consuming methods.

The design of conventionally used screening reactor systems is not useful for the simultaneous application of an optical method to determine the activity together with the sampling to determine the selectivity. Therefore, a novel reactor design is a prerequisite to match these simultaneous analytic requirements. Furthermore, the fluid flow management and the equal temperature distribution are additional key design factors for this new screening concept developed by hte AG [9].

We present here the first integrated 96-fold reactor system [10] for the parallel IR-thermography and subsequent use of MS- (or GC/MS) analytics, which offers the intelligent opportunity to automatically pre-select and analyze only active and therefore interesting materials with regards to time consuming but highly accurate techniques like mass spectrometry or GC/MS. The optimized combinations of analysis techniques can accelerate the overall workflow and therefore more valuable information can be gathered during the time frame of a single experiment. Neglecting of inactive or too active materials under a given set of reaction conditions can save valuable experimental time which can be used for the detailed analysis of the active and prospective candidate materials only.

2. Experimental part

2.1. Catalyst preparation

Catalysts have been synthesized by classical wet impregnation methods on γ-Al_2O_3 multi-hole ceramic bodies (miniliths, CONDEA). As catalyst precursors, aqueous metal nitrate solutions have been used. Classical impregnation procedures have been performed by the aid of a robotic solution dispenser (Multiprobe IIEX, PACKARD), additionally equipped with a Titramax 100 shaker (HEIDOLPH). After the impregnation, materials have been dried for 16 h at 80 °C and calcined for 2 h at 550 °C.

2.2. Characterization

The elemental analysis has been performed by X-ray fluorescence analysis on an EAGLE II μProbe (ROENTGENANALYTIK) with Rh Kα radiation. The X-ray beam is focussed by a multi-capillary system to a spot size of 50 μm. To determine sample homogeneity and element distributions, XRF elemental mappings can be performed automatically with a predefined $a \times b$ matrix of measurement positions on the sample surface by the aid of an automated *xyz*-stage.

2.3. Catalyst screening

After transferring all catalyst samples into our 96-fold screening reactor system, the exhaust stream of each reactor position can be individually analyzed by a conventional mass spectrometer (QMS 300, PFEIFFER), equipped with a heated sampling capillary. In order to avoid cross-talking between neighboring library members and ensure equal temperature distribution for all reactor positions special engineering means are employed [10]. The catalyst volume in each of the 96 reactor positions is approximately 0.1 ml, the gas hourly space velocity (GHSV) is in the range of 3000 h^{-1}, and the temperature range is between 300 and 400 °C. All gaseous reactants have technical purity.

3. Results and discussion

As described in Section 1, the crucial aspect implementing a new screening concept is the central reactor system. The need for the simultaneous application of an optical method to determine the materials' activity in a parallel manner through thermographic visualization of heat release and a sampling capillary connected with a second analytical technique as, e.g. MS or GC for selectivity measurement has two key impacts on the reactor design. Firstly, each candidate material has to be accessible separately and independently through an IR-transparent window for the optical method in a way, that the measurement of, e.g. artifacts by variation of reactor materials emissivities or organic gas phase reflections and a potential cross-talk of neighbored reaction channels can be avoided. Secondly, each catalyst product flow has to be fed without any cross-talking to a sampling capillary connected to the second analytical technique (e.g. GC, GC/MS, MS, etc.). Furthermore, the reaction conditions, e.g. the fluid distribution (concentration, composition and space velocity) and temperature conditions have to be held constant and equal for each material in the separated reaction channels.

The implementation of the above described new screening principle requires three main parts: a thermosensitive IR camera above the reactor system, the reactor as central part and an *xyz*-positionable sampling capillary, connected to the second analytical tool (MS or GC, etc.). The scheme is shown in Fig. 1. To simplify matters, a reactor with a 4 × 4 matrix of reaction channels is shown here, the real 96-fold reactor has an 8 × 12-MTP (micro-titerplate) matrix.

Through an IR-transparent window on top of the reactor, the IR camera can detect temperature changes (exemplary shown in Fig. 1 by two black shadowed spots) of all catalysts in a catalytic gas phase reaction at the same time. The *xyz*-robotic system directs a sampling capillary to the active candidates, indicated by the black effluent streams in Fig. 1, whereas the positional information of active candidates is automatically determined by pattern recognition from the IR-thermogram during the experiment. All parts of the system are fully integrated and automated.

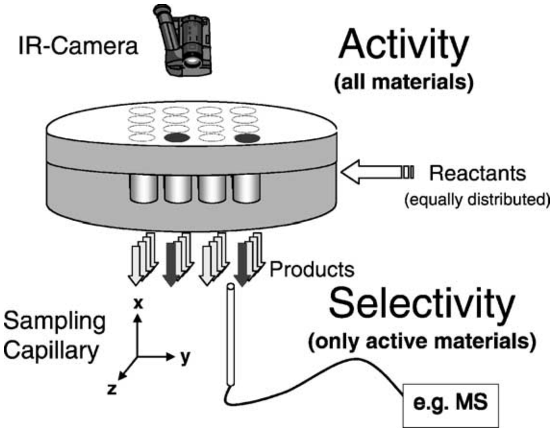


Fig. 1. Scheme of an integrated system IR-thermography-MS.

The key hardware for the combined application of, e.g. a parallel optical and a subsequent fast sequential analytical method is the reactor. A photograph of the reactor system is shown in Fig. 2.

Fig. 2 shows the assembled reactor. The reactor design is based on a modular, sandwich-like construction, which eases the exchange or the maintenance of single modules. The reactor top plate comprises an IR-transparent window, in this case a sapphire window

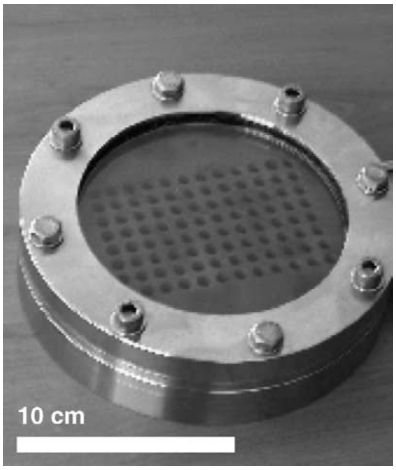


Fig. 2. 96-fold reactor system at hte Aktiengesellschaft.

with a sufficient visible sector. The next modular layer consists of a black ceramic plate with an 8 × 12 matrix of drilled holes, fitting to the positions of the materials matrix. The last module is the main reactor part with gas supply, heating and reaction channels. The resulting "IR camera-"view onto the reactor through the sapphire window and the black ceramic surface ensures, that only materials of interest are in the visual field of the IR camera. The homogeneous emissivity of the black ceramic mask is similar to a black body and allows the above mentioned precise and high temperature resolution [11].

Fig. 3a represents the top view photo of the open reactor module with a symmetrically distributed materials library in the separated and independent reaction chambers for the validation of the 96-fold screening system, while Fig. 3b shows the schematic visualization of the symmetrical distribution of equal materials over the 96 reactor positions.

For an optimal fluid distribution with a minimal pressure drop over the 96 reactor channels we used multi-channel ceramic bodies (miniliths) as supports, which are impregnated with the corresponding catalyst precursor solutions in an automatic manner. Therefore, at each of the 96 reactor positions, a candidate material modified by impregnation is available for further testing. The shadowed scheme of the materials library positions of Fig. 3b will ease the understanding of Figs. 4 and 5. Unimpregnated ceramic bodies are visualized by white color. The validation library (Fig. 3) consists of only three different catalysts and the inert support material, which are distributed in a pattern of diagonals (Fig. 3b) over the 96 reactor positions. Therefore, materials symbolized by the same shading in Fig. 3 are synthesized in the same way, but not in one batch. Homogeneity is proved and ensured by μ-XRF measurements on different samples of the same elemental composition.

The main aspects of the new reactor design are temperature homogeneity and homogeneous gas flow for all 96 reactor positions. In Figs. 4 and 5, homogeneities of temperature and gas distribution are indirectly verified by an IR-thermogram and a product distribution of a partial oxidation reaction, measured over all 96 catalyst samples.

Fig. 4 shows the very good temperature homogeneity of the whole reactor system with a symmetrical distribution of equal materials compositions in an 8 × 12 MTP array (see Fig. 2a and b).

Fig. 4a and b shows the thermographic pictures, taken with the IR camera above the reactor system as shown in Fig. 1 under typical reaction conditions: 1% hydrocarbon in synthetic air, 375 °C and GHSV 3000 h^{-1}. The thermogram is emissivity corrected for these conditions. The very homogeneous temperature distribution of the reactor temperature (375 °C, black surface background in Fig. 4) is evident. Each deviation from a homogeneous temperature distribution

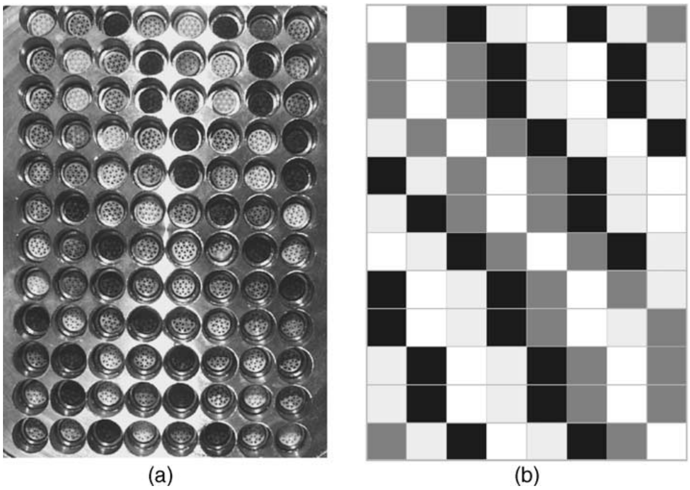
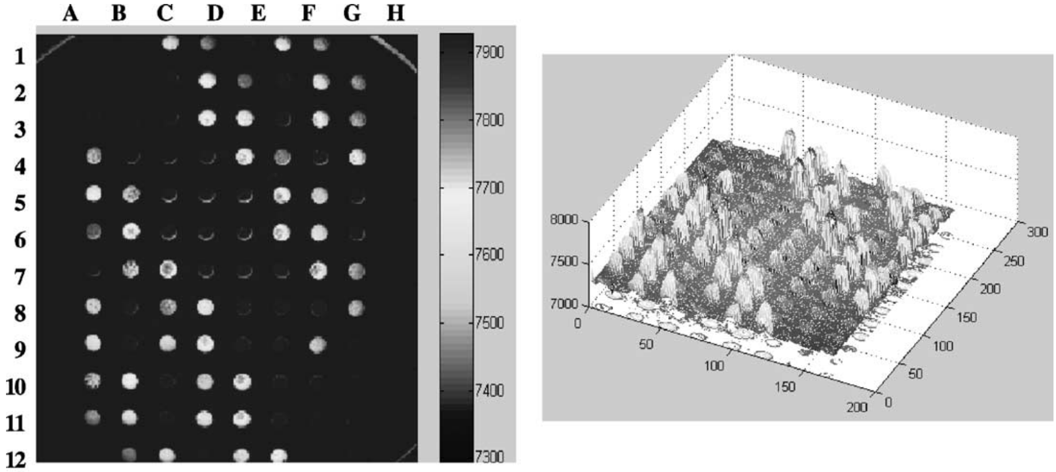


Fig. 3. Top view of the open reactor (a) and schematic representation of the symmetrically arranged materials (b) as validation library.



(a) (b)

Fig. 4. Temperature distribution of a symmetrical materials library in a 96-fold reactor (Fig. 3) as IR thermogram (a) and 3D view (b). A–H: reactor columns, 1–12: reactor rows (temperature in arbitrary units).

would result in color gradients in Fig. 4. The result of several thermocouples around the catalyst positions of the reactor system support the finding on the reactor surface. The maximal temperature deviation in the reactor system applied here is minimized below 2 °C and therefore allows a subtle differentiation of catalyst samples. The activity pattern in Fig. 4 matches perfectly with the library pattern in Fig. 3b: the black-colored catalyst is the most active one, followed by the light gray-colored one. The material encoded with dark gray-codes shows very low activity and the white encoded materials (unimpregnated ceramic supports) are inactive. The equal thermal behavior amongst catalyst samples of one kind over the

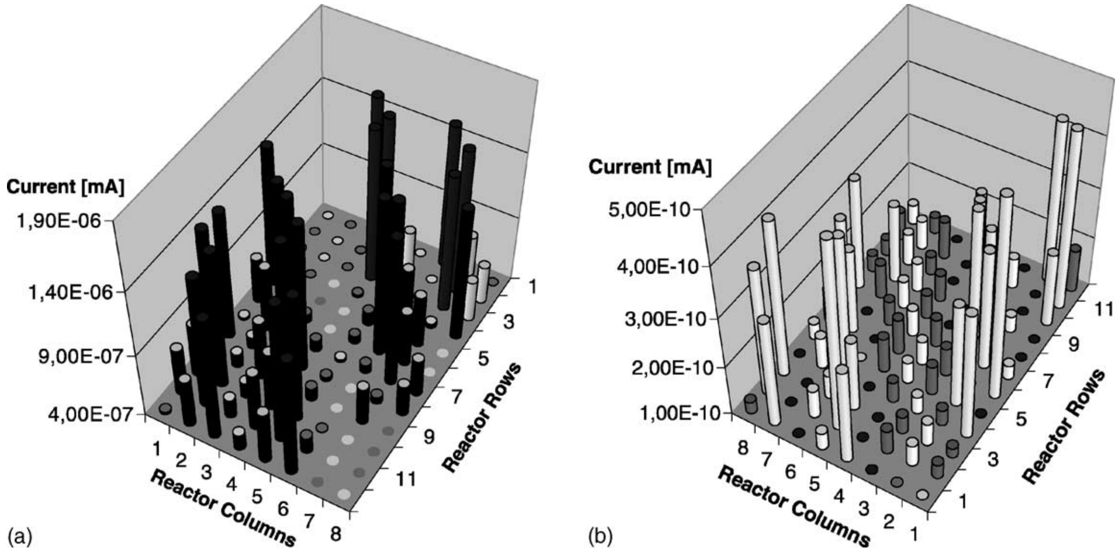


Fig. 5. Product distribution of two different products (a) and (b) determined by MS-sampling.

whole reactor system can be taken directly as proof for homogeneous temperature distribution as well as for the perfect fluid distribution: equal heat release on equal catalysts indicates obviously identical reaction conditions. The diagonal pattern can be detected perfectly in the IR thermogram (Fig. 4); library pattern (Fig. 3) and IR results (Fig. 4) show a very good conformity.

The subsequent sequential analytic via a commercially available MS is shown in Fig. 5. For reference purposes the result of the MS-sampling of all 96 reactor positions is provided.

The MS intensities for two different oxidation products correlate with the evolved heats of reaction, observed by an IR camera in Fig. 4, and reproduce very well the library pattern from Fig. 3b. Product 1 (Fig. 5a) is produced mainly by the black-colored material. Only minor quantities of product 1 can be found over the light gray-colored catalyst. The dark gray encoded catalyst samples show nearly no activity as the unimpregnated support materials (white-colored). For another partial oxidation product (Fig. 5b) the light gray-colored catalysts show high selectivities, whereas the black-colored materials are totally inactive under the given set of reaction parameters. The unimpregnated support ceramics (white) and the dark gray-colored catalyst show a minor selectivity to product 2. Finding this regular pattern of product distribution in accordance with the validation library (Fig. 3) manifests at least two main features of the screening reactor setup: (1) in accordance with the XRF analysis, sample synthesis fulfills all requirements of high throughput capable synthesis method. Materials synthesized under the same conditions show very similar, not to say identical results in the validation reaction. (2) Reaction conditions as fluid and temperature distribution are the same for all 96 reactor positions. The same materials produce exactly the same results.

The key statement from Figs. 4 and 5 is, that the main principle of our intelligent screening concept is proved by the above demonstration data: the test of just the 48 black- and light gray-colored materials from the overall 96-membered library would have led to potentially active and selective candidates. In a real screening program testing the dark gray- and white-colored materials would have been an unproductive use of valuable experimentation time, but for the purpose of this demonstration paper the detailed measurement of all 96 positions provided experimental evidence for the homogeneity of fluid and temperature distribution. The general procedure at hte Aktiengesellschaft to apply cross-checks of suitability of the applied analytical techniques and optimization of the equipment to the application of interest prior to entering the final screening program to all reaction types included our R&D programs has proven to be very valuable.

4. Conclusion

We presented the first time-saving and advanced screening tool for gas phase reactions capable of operation under realistic process conditions: by using the reaction heat as (pre-) selection tool for activity and selecting the active or interesting candidates of a materials library to determine product selectivities in more detail. The reactor design is expandable and not restricted to the described system of 96 reaction channels. Also the MTP-adapted format is just one possible example, which eases the complexity of handling material libraries.

In combination with a smart library design and a DOE (design of experiments) this screening tool strongly accelerates R&D times for new materials and processes. Besides the time-saving aspect there is an additional economical aspect to be considered: the reactor utilization is much more efficient, the deterioration of analytical modules (GC columns, MS filaments, valves, pumps, etc.) are minimized by only measuring a smaller selected part of the whole materials library.

The integration of this new screening philosophy in a typical HTE workflow R&D efficiency (i) provides a powerful scientific tool for well considered and planed HTE and (ii) enables the significant increase of experimental output with respect to time and money.

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