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Reaction pathway in the vapour-phase synthesis of indole and alkylindoles

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Abstract

The vapour-phase synthesis of indole and its derivatives from aniline or alkylanilines and ethylene glycol or other diols was investigated with the use of a novel ZrO_2/SiO_2 (5:95 w/w) catalyst to check the applicability of this synthesis to a wide number of alkylindoles. During feeding with alkylaniline, the above catalyst showed catalytic results better than those reported in the literature, and a very good regenerability. In particular, with ethylene glycol, the best yields in the corresponding indoles were obtained when a C_2–C_3 alkyl chain was located in the ortho position to the amino group. The differences in reactivity between aniline and alkylaniline were significantly reduced when the length of the diol chain was increased and eliminated with 2,3-butanediol. On the basis of the above data and those collected sharing the synthesis in single steps, a possible overall reaction pathway was proposed to design a better tailor-made catalyst. It was also indicated that the formation of heavy compounds, which are able to deactivate the catalyst, were not derived from the reagents or the following reactions on the indole formed, but might be mainly attributed to the polycondensation of an aldehyde intermediate.

Keywords: Vapour-phase synthesis; Reaction pathway; ZrO_2/SiO_2 catalyst; Indole; Alkylindoles; Aniline; Aromatic ammines; Ethylene glycol; Diols

1. Introduction

Indole or alkylindoles are of considerable industrial interest, and are applied as intermediates in the production of pharmaceuticals, herbicides, fungicides, dyes, etc. [1–3]. Usually they are recovered from the biphenyl-indole fraction obtained by coal tar distillation, although this source no longer seems to be able to cover the increasing market demand. Alternatively, they can be obtained in high yields from well-known liquid-phase reactions, which, however, present many drawbacks [4–8]. Thus, increasing interest has been focused on the vapour-phase synthesis of these molecules [9–16] (Fig. 1), since it exhibits many advantages in comparison with the liquid-phase synthesis.

Although there is a patent literature rich in data regarding the nature and composition of catalysts and the operating conditions for the synthesis of indole, few data have been reported for the synthesis of alkylindoles. Basically, two different technologies may be identified: (i) high-temperature (773–973 K) dehydrocyclisation of dialkylanilines over oxides or chromites, followed by partial hydrogenation of the raw product [9], and (ii) lower temperature (453–623 K) reaction of anilines and glycols, operating at low liquid hourly space velocity (LHSV) [10–16]. In this latter case, many different catalysts have been claimed, making it difficult to identify the reaction requirements and optimum catalyst properties. In particular, it was reported that with copper chromites (the most widely claimed catalysts in the patent literature for the synthesis of indole) a large molar excess

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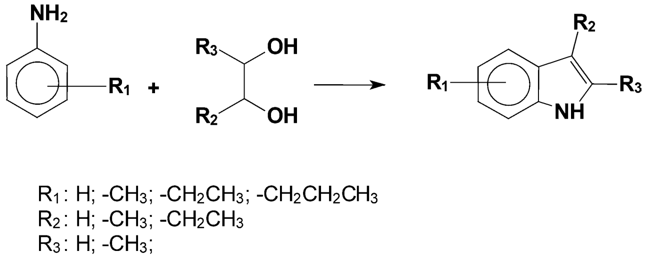


Fig. 1. General reaction scheme of the vapour-phase synthesis of indole and its derivatives.

($\geqslant$10.0) of aromatic amine has to be used to avoid the formation of useless polyalkylated indoles. Thus a high amount of aniline derivatives has to be recycled, with significant economic and environmental drawbacks. In a previous paper [17], some of us reported that the best results can be obtained with a commercial copper chromite containing only promoters, improving the physical properties and permitting operation at low temperature and LHSV values [17]. Furthermore, with a mixture of a commercial SiO_2 and this catalyst, it was possible to operate at higher LHSV values, thus improving the yield in alkylindoles [17].

The excess of aromatic amine and carrier gas (required to operate at low contact times) has been avoided with the use of a new family of ZrO_2/SiO_2 catalysts able to operate with almost stoichiometric feeds and water as the main carrier gas [18–20]. These catalysts showed better performances than those reported in the literature and very good regenerability. Finally, innovative Si/Zr mesoporous catalysts, with a MCM41-type structure, have also been investigated, although they demonstrate poorer catalytic performances [21].

However, it must be noted that almost no data are available in the literature on either the possible reaction pathway in the vapour-phase synthesis of indole and, mainly, alkylindoles or the reactivity in these conditions of different aromatic amines or diols. The aim of this study was to shed light on these two key points to check the applicability of the vapour-phase synthesis to a wider number of alkylindoles and to design tailor-made catalysts.

2. Experimental

Catalytic tests were carried out with 4.0 ml (ca. 2.5 g, 425–850 µm particle size) of ZrO_2/SiO_2 (5:95 w/w) supported catalysts, prepared by incipient wetness impregnation of a commercial SiO_2 (Si-1803 T 1/8″; Engelhard) with a solution of Zr(IV) acetylacetonate in acetic acid and following calcination at 723 K for 5 h. The catalyst had previously been activated in situ, with a progressive increase in the temperature up to 603 K and a 6 l/h flow of a H_2/N_2 (1:9 v/v) gas mixture. Aniline (AN), 2-methylaniline (2-METAN), 3-methylaniline (3-METAN), 4-methylaniline (4-METAN), 2-ethylaniline (2-ETAN), 3-ethylaniline (3-ETAN), 4-ethylaniline (4-ETAN), 2-propylaniline (2-PRAN), ethylene glycol (EG), 1,2-propylene glycol (1,2-PDIOL), 1,2-butanediol (1,2-BDIOL), 2,3-butanediol (2,3-BDIOL), 1,2-hexanediol (1,2-HEXDIOL), Zr(IV) acetylacetonate, and CH_3COOH were purchased from Aldrich Chemicals (purity $\geqslant$ 98.0%) and used as received without any further purification.

We prepared N-(2-hydroxyethyl)-2-ethylaniline (NEE) in liquid phase by adding 60 ml of chloroethanol to 150 ml of 2-ETAN, performing the reaction for 3 h at 403 K under a N_2 atmosphere with energetic stirring, and adding at the end 10 g of K_2CO_3 dissolved in 10 ml of H_2O to neutralise the HCl formed. Then we distilled the reaction mixture at 323 K under vacuum (395 Pa), obtaining NEE with a purity of 98%. We prepared N-(2-ethylphenyl)-2-aminoacetaldehyde (NEPA) in liquid phase by adding 50 ml of chloroacetaldehyde dimethylacetal to 75 ml of 2-ETAN, performing the reaction for 3 h at 403 K under a N_2 atmosphere with energetic stirring, and adding at the end 10 ml of a K_2CO_3 solution (50 wt%) to neutralise the HCl formed. The reaction mixture was extracted with toluene, and the product was recovered by solvent distillation at 323 K under vacuum (395 Pa). The NEPA dimethylacetal obtained was then treated with a H_2SO_4 solution (6 wt%) to obtain the corresponding aldehyde (purity $\geqslant$ 98%).

X-ray diffraction (XRD) analyses were carried out with a Philips PW 1050/81 diffractometer (40 kV, 25 mA), equipped with a PW 1710 unit, and Cu-K_α radiation ($\lambda = 0.154118$ nm). A 2θ range from 10° to 80° was investigated at a scanning rate of 0.10°/s. BET surface area and porosity values were determined by physical adsorption of N_2 at 77 K, with a Micromeritics Asap 2020. FT-IR spectra were collected in the range of 4000–400 cm^{-1} with a Perkin–Elmer 1750 spectrometer, with the use of samples diluted in KBr (0.2:99.8 wt/wt). The catalyst surface acidity was determined with a ThermoQuest TPD/R/O 1100 equipped with TCD. The samples were pretreated under a 100 ml/min He flow at 673 K for 60 min, then at 433 K 10 pulses of NH_3 were added, and the samples were maintained at this temperature for 60 min, to favour the elimination of the physically adsorbed NH_3. Finally, under the same He flow, the samples were heated from 433 to 823 K (heating rate 10 K/min) and maintained at the latter temperature for 60 min.

The catalytic tests ($T = 583$ K, GHSV (gas hourly space velocity) $= 2900\ h^{-1}$; $H_2/H_2O = 20{:}80$ v/v; LHSV $= 1.6\ h^{-1}$; amine/diol $= 1{:}1$ mol/mol) were carried out in a fixed-bed glass micro-reactor (i.d. 7 mm, length 400 mm) placed in an electronically controlled oven and operating at atmospheric pressure. The isothermal axial temperature profile of the catalytic bed during the tests was determined with a 0.5-mm J-type thermocouple, sliding in a glass capillary tube. The organic feed and H_2O were introduced by two Infors Precidor model 5003 infusion pumps, and the gas composition and flow were controlled with Brook mass flow meters. After 1 h of time on-stream to reach stationary conditions, the products were condensed in two traps cooled at 268 K and collected in methanol, with tridecane as an internal standard. The analyses were carried out with a Perkin–Elmer AutoSystem XL gas chromatograph, equipped with FID and a wide-bore SE 54 column (length 30 m, i.d. 0.53 mm, film width 0.8 µm). The products were tentatively identified by GC-MS with a Hewlett–Packard GCD 1800 system equipped with a HP5 column (lenght 25 m, i.d. 0.25 mm, film width 1.5 µm); the identifications were subsequently confirmed by a comparison of the experimental GC and GC-MS patterns with those obtained for pure reference compounds.

3. Results and discussion

3.1. Catalyst characterisation

In previous papers [17–21], the vapour-phase synthesis of indole and 7-ethylindole (7-ETI) from AN or 2-ETAN and EG was investigated in depth. These studies produced very interesting results for ZrO_2 impregnated on commercial SiO_2 [18,20]. ZrO_2, because of its hydro-dehydrogenating properties [22–24], should favour the transformation of EG to 2-hydroxyacetaldehyde, whereas the acid sites of SiO_2 should catalyse either the attack of the latter compound on AN or 2-ETAN or the subsequent formation of the corresponding indole. It is worth noting that the acidity of the SiO_2 [25] was not strong enough to catalyse the transformation of EG to crotonaldehyde and, consequently, the alternative synthesis of 2-methyl-8-ethylquinoline from ETAN and EG, as already reported for an acid-treated commercial clay [26]. The best data were obtained for the ZrO_2/SiO_2 (5:95 w/w) catalyst, for which an optimum interdispersion of both hydro-dehydrogenating and acid sites occurred [18,20]. The XRD powder pattern of this catalyst did not show any difference with that of the support (Fig. 2), thus indicating the good dispersion of ZrO_2 on the catalyst surface, which was also maintained after the catalytic tests or the regeneration by calcination at 773 K, followed by a new activation step with a H_2/N_2 (1:9 v/v) mixture [18,20]. Residual carbon from the preparation was not detected, in agreement with the similar values of surface area, porosity, and acidity (Table 1), and the pore size distributions (Fig. 3) of the ZrO_2/SiO_2 (5:95 w/w) catalyst and the starting SiO_2 support. The surface area of the former decreased dramatically after long-time catalytic tests (Table 1), but it was fully recovered after regeneration, indicating that the deactivation was due to the adsorption of heavy products (tar) on the catalyst surface (see below) and not to sintering phenomena, in agreement with XRD findings.

Table 1
Surface area, porosity and acidity for the catalyst ZrO_2/SiO_2 (5:95 w/w) and the corresponding commercial SiO_2 support

Catalyst	Surface area (m^2/g)			Porosity	Surface acidity
	a	b	c	(cm^3/g)	(µmoles of NH_3/g_{cat})
SiO_2	300	n.d.	n.d.	0.5368[a]	250
ZrO_2/SiO_2	283	12	290	0.4169[a]	246

[a] Before reaction.
[b] After 11 h of time-on-stream.
[c] After regeneration.

3.2. Reactivity of the different amines or diols

The very interesting results obtained by feeding of EG and AN or 2-ETAN onto the ZrO_2/SiO_2 (5:95 w/w) catalyst [18,20] suggested the extension of the study to different aromatic amines and/or diols. In the first step, a comparison was made between AN and the three ethylanilines (ETAN). With 2-ETAN in the feed, we had observed a yield in 7-ETI about twice that obtained with an indole feed AN (Fig. 4), and this difference was not modified by an increase in the temperature or the AN/EG molar ratio. This result is not triv-

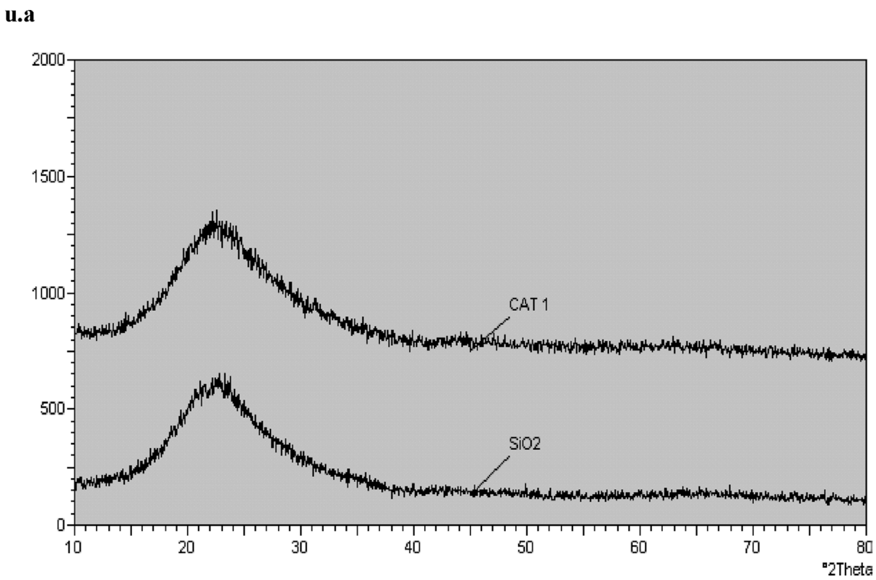


Fig. 2. XRD powder patterns of the ZrO_2/SiO_2 (5:95 w/w) catalyst and the corresponding commercial SiO_2 support.

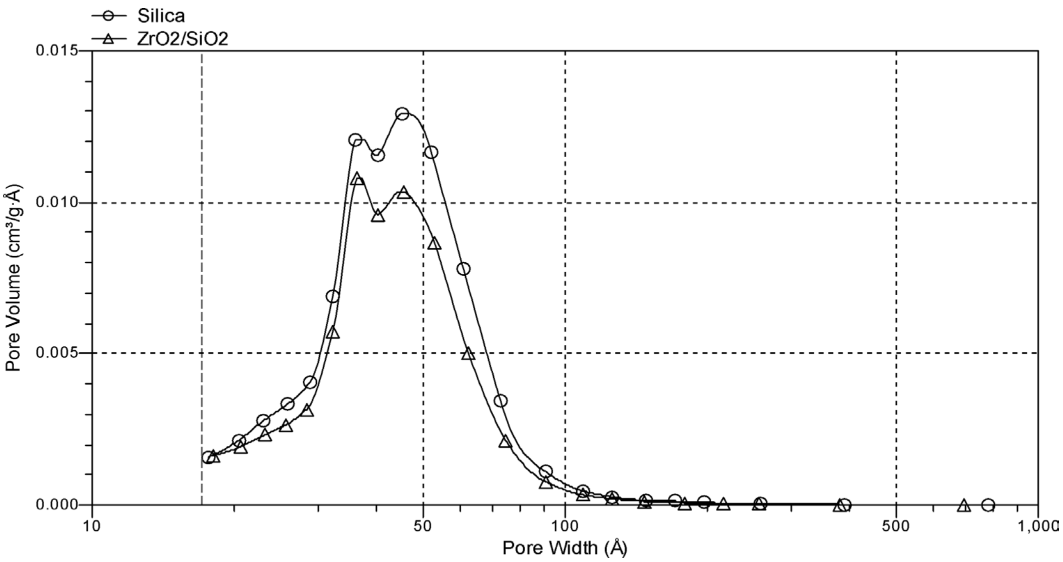


Fig. 3. Pore size distribution for the ZrO_2/SiO_2 (5:95 w/w) catalyst and the corresponding commercial SiO_2 support.

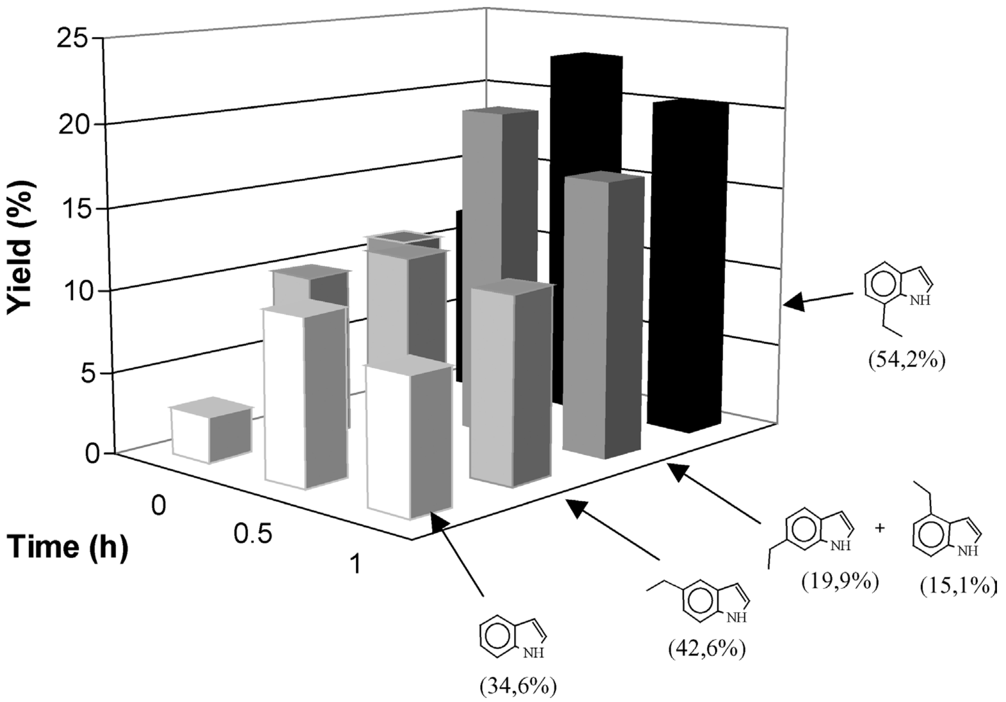


Fig. 4. Yield (%) in indole or in the different ethylindoles as a function of the reaction time (values referred to the aromatic amine fed; between the round brackets are reported the selectivity average values in the different products). (Reaction conditions: ZrO_2/SiO_2 (5:95 w/w) catalyst = 4.0 ml; $T = 583$ K, GHSV = 2900 h^{-1}; H_2/H_2O = 20:80 v/v; LHSV = 1.6 h^{-1}; aromatic amine/diol = 1:1 mol/mol.)

ial, if we take into account the absence of a steric hindrance for AN (unlike 2-ETAN), and it could have been justified by considering the increased electronic availability on the nitrogen atom due to the inductive effect of the ethyl chain.

However, the results obtained with 3-ETAN and 4-ETAN feeds, which give a progressive decrease in yields (always higher, however, than that of simple indole) in the corresponding ethylindoles as the distance between the alkyl chain and the amine group increases, show that the steric hindrance around the nitrogen atom plays a very important role. It is worth noting that if the ethyl chain is in position 3, two ethylindoles are formed, although 6-ETI was obtained in a higher amount (60% excess ca.) than 4-ETI, showing that the closure of the ring occurs preferentially in the less hindered position.

Given the interesting results obtained with the three ETANs, the possibility of extending this synthesis to further alkylindoles was investigated. Surprisingly, with the

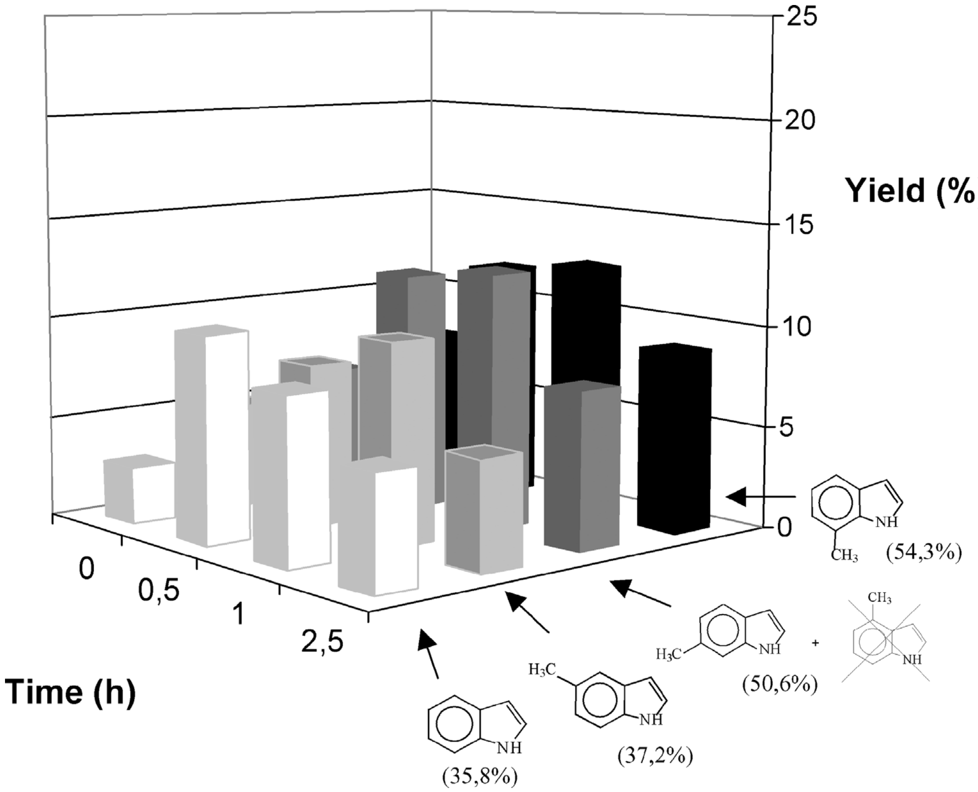


Fig. 5. Yield (%) in indole or the different methylindoles as a function of the reaction time (values referred to the aromatic amine fed; between the round brackets are reported the selectivity average values in the different products). (Reaction condition: ZrO_2/SiO_2 (5:95 w/w) catalyst = 4.0 ml; $T = 583$ K, GHSV = 2900 h^{-1}; H_2/H_2O = 20:80 v/v; LHSV = 1.6 h^{-1}; aromatic amine/diol = 1:1 mol/mol.)

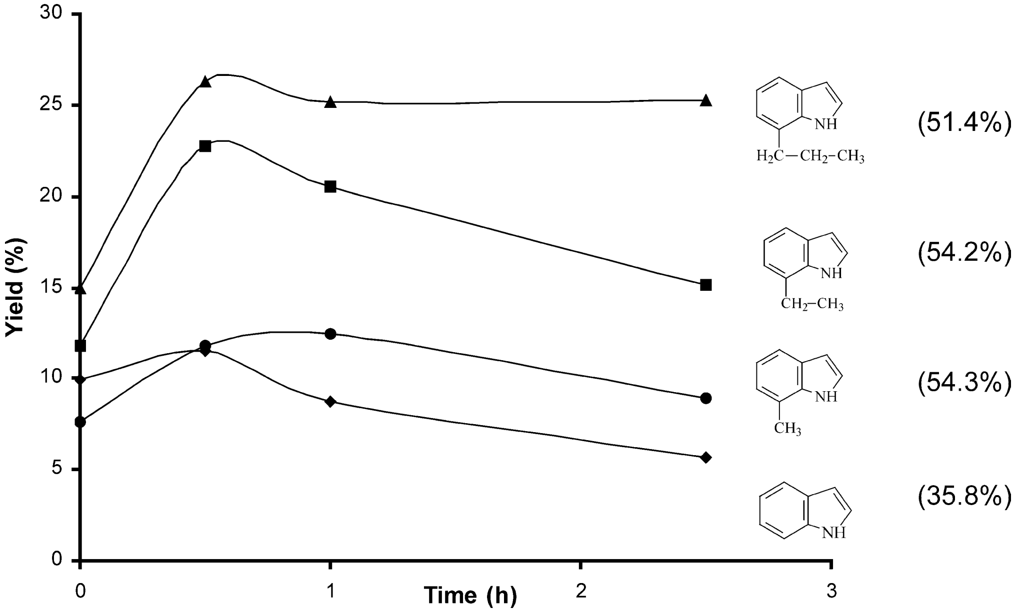
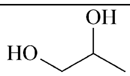
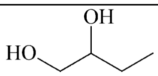
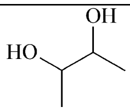
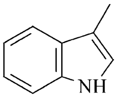
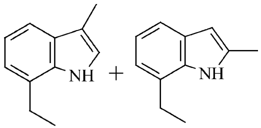
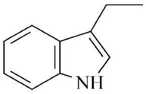
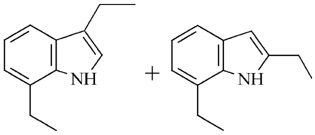
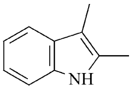
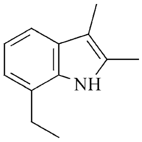


Fig. 6. Yield (%) in indole and the different alkylindoles as a function of the reaction time (values referred to the aromatic amine fed; between the round brackets are reported the selectivity average values in the different products). (Reaction conditions: ZrO_2/SiO_2 (5:95 w/w) catalyst = 4.0 ml; $T = 583$ K, GHSV = 2900 h^{-1}; H_2/H_2O = 20:80 v/v; LHSV = 1.6 h^{-1}; aromatic amine/diol = 1:1 mol/mol.)

methylanilines (METAN or toluidines) in the feed, the yields in the different methylindoles were almost unaffected by the presence and position of the methyl group (Fig. 5), with values more similar to that observed with an AN feed than to those obtained with an ETAN feed. Furthermore, in the case of 3-METAN, only 6-methylindole was detected. These results seem to confirm the conclusion that simple electronic effects play a minor role, if any, in the reaction pathway.

Table 2
Yield (%) in alkylindoles as a function of the reaction time, feeding (A, C, E) aniline or (B, D, F) 2-ethylaniline and 1,2-propylene glycol, 1,2-butanediol or 2,3-butanediol (between the round brackets are reported the selectivity average values in the different products). (Reaction conditions: ZrO_2/SiO_2 (5:95 w/w) catalyst = 4.0 ml; $T = 583$ K, GHSV = 2900 h^{-1}; H_2/H_2O = 20:80 v/v; LHSV = 1.6 h^{-1}; aromatic amine/diol = 1:1 mol/mol)

Time (h)	Yield (%)					
	Feed: 		Feed: 		Feed: 	
	A	B	C	D	E	F
	 (48.5%)	 (25.3%) (6.4%)	 (46.9%)	 (31.8%) (8.6%)	 (52.0%)	 (54.6%)
0	6.5	4.0	19.2	20.2	18.8	23.3
0.5	11.1	13.4	20.0	22.1	19.0	23.7
1.0	12.0	18.8	20.4	24.2	20.5	24.4

This study was finally extended to 2-propylaniline (2-PRAN). Fig. 6, which summarises the results obtained with aniline and different 2-alkylanilines in the feed, points out that the differences observed cannot be explained by electronic effects. Therefore, we believe that a stabilisation of a reaction intermediate, due to the presence of a C_2–C_3 alkyl chain located ortho to the nitrogen atom, may be important. It must be emphasised that, in all cases, the main by-products detected were the N-(2-hydroxyethyl)-anilines, N-vinyl- or N-alkylanilines, together with smaller amounts of N-alkyl-indole derivatives. Furthermore, heavy products (tar) adsorbed to the catalyst surface were also formed, indicated by FTIR bands at 1590, 1456, and 1384 cm^{-1} [27]; these were responsible for the progressive deactivation with time on-stream. However, as previously reported [18,20], the ZrO_2/SiO_2 catalyst almost completely recovered the initial activity by calcination at 773 K, followed by a new reducing activation step.

The interpretation of the results seems still more difficult if we analyse the results obtained for the reaction of AN and alkylanilines with other diols. In fact, with a 1,2-propylene glycol (1,2-PDIOL) feed, the differences deriving from the nature of the amine remain apparent: with AN only the 3-methylindole (3-METI) was formed, whereas with 2-ETAN both 2-methyl-7-ethylindole and 3-methyl-7-ethylindole were obtained, with an overall yield 25–30% higher than that observed with AN (Table 2, A and B). In contrast, with a feed of 1,2-butanediol (1,2-BDIOL) or 2,3-butanediol (2,3-BDIOL), the differences in yield between the two amines were significantly reduced, with a general increase in the values observed (Table 2, C and D, E and F, respectively). Furthermore, with both diols almost no deactivation was detected with time on-stream (deactivation was completely absent with a feed of 2,3-BDIOL), thus suggesting that the increase in stabilisation of an intermediate depends also on the alkyl chain length of the diol. However, a significant worsening in the yield was found when the alkyl chain of the diol became longer, as in the case of 1,2-hexanediol [20]. Type and amount of the detected by-products (i.e., excluding tar), on the other hand, were almost unaffected by the diol structure.

3.3. Single-step reactions

To collect further information on the reaction mechanism, first the synthesis of 7-ETI in the single reaction steps was shared, by a feed of the 2-ETAN/EG mixture on ZrO_2 alone, to determine the role of hydro-dehydrogenating sites [22–24]. A high yield ($\geqslant$ 18%) in N-(2-hydroxyethyl)-2-ethylaniline (NEE) was obtained, with selectivity higher than 85% and only a slight deactivation with time on-stream, thus suggesting NEE as a possible key intermediate, formed according to the scheme in Fig. 7. Surprisingly, with SiO_2 as a catalyst and a feed of NEE in the usual reaction conditions, a very low formation of 7-ETI was observed (yield 2.2%; selectivity 6.2%), with mainly the NEE self-condensation to heavy products or the NEE decomposition. These results remained almost unchanged with increasing numbers of Lewis sites, resulting from impregnation of SiO_2 with $ZnCl_2$ [28] or the catalyst acidity, for a H-β commercial zeolite (this latter gave a slight decrease in the formation of the main by-products and a higher NEE decomposition).

When the 2-ETAN/EG mixture was fed onto a dual catalytic bed (a layer of ZrO_2 followed by a layer of SiO_2, maintaining the same ratio of the ZrO_2/SiO_2 catalyst investigated), only low amounts of 7-ETI were formed, whereas the yield in NEE was comparable to the value obtained when only ZrO_2 was used, showing that the high boiling point of NEE did not affect the previous results. On the other hand, operating in liquid phase at 573 K with the ZrO_2/SiO_2 (5:95 w/w) catalyst, we observed the cyclisation of the corresponding aldehyde [N-(2-ethylphenyl)-2-

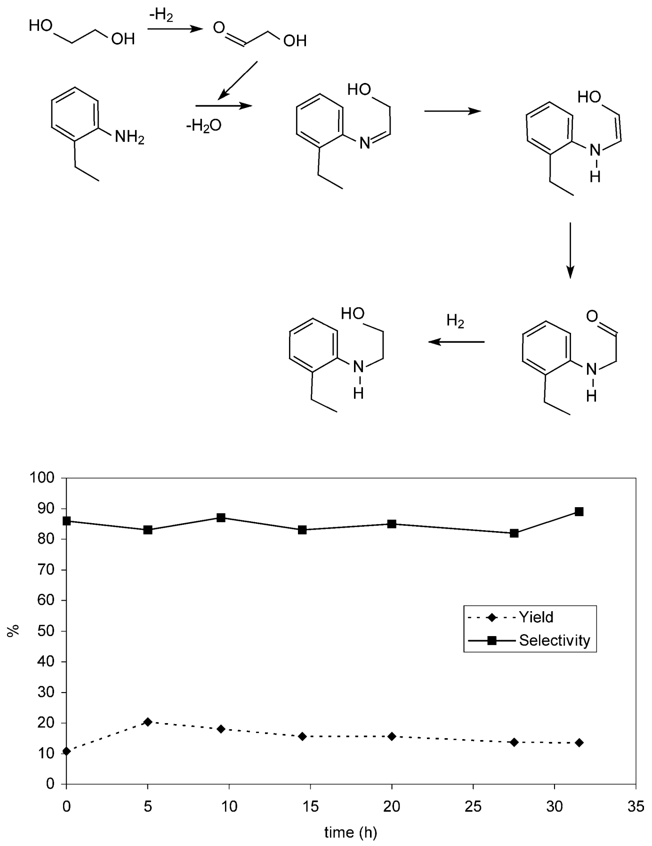


Fig. 7. Yield (%) and selectivity (%) in N-(2-hydroxyethyl)-2-ethylaniline (NEE) and proposed reaction pathway for its synthesis. (Reaction conditions: ZrO_2 catalyst = 4.0 ml; T = 583 K, GHSV = 2900 h^{-1}; H_2/H_2O = 20:80 v/v; LHSV = 1.6 h^{-1}; aromatic amine/diol = 1:1 mol/mol.)

aminoacetaldehyde or NEPA] to 7-ETI (yield 16.0%), together with high amounts of heavy products (tar). Unfortunately, it was not possible to perform the same test in the vapour phase, since NEPA polymerised dramatically already in the vapourisation step, affording heavy products (tar).

We wanted to shed light on the formation of heavy products that are responsible for catalyst deactivation. As a preliminary measure, their possible formation from the reagents was studied, on the ZrO_2/SiO_2 (5:95 w/w) catalyst, first with a feed of 2-ETAN or EG for 2 h and then with the mixture 2-ETAN/EG for another 2 h. In both cases, the results were very similar to those previously obtained with a direct feed of the 2-ETAN/EG mixture, which allowed us to exclude a significant role in catalyst deactivation for both reagents. Thus, it may be hypothesised that the heavy products derive from reaction intermediate(s) or other reaction products. Therefore, a 7-ETI/EG (1:1 mol/mol) mixture was always fed onto the ZrO_2/SiO_2 (5:95 w/w) catalyst; under the usual conditions, the 7-ETI was recovered almost completely, with formation only of traces of N-ethyl-7-ethylindole or N-ethylindole. Thus, it may also be excluded that the heavy compounds, responsible for catalyst deactivation, are formed by consecutive polyalkylation of the indole or alkylindoles formed, in agreement with the specific features of Zr-based catalysts already reported in the literature [18–20].

3.4. *Proposed reaction pathway*

On the basis of the results discussed in previous sections, some relevant suggestions may be made: (i) NEE is not, in our opinion, a reaction intermediate, but a more stable by-product formed by hydrogenation of the true intermediate, that is, the corresponding aldehyde [N-(2-ethylphenyl)-2-aminoacetaldehyde or NEPA]. Thus it may be hypothesised that the reaction intermediates have to contain a carbonyl (aldehyde or ketone) group. (ii) For the vapour-phase synthesis of indole and alkylindoles it is necessary that the hydro-dehydrogenating sites (ZrO_2) and weak acid sites (SiO_2) be very close to each other. (iii) The synthesis is favoured by the presence of a C_2–C_3 alkyl chain in the ortho position of the nitrogen group. This effect is significantly reduced by an increase in the chain length of the diol, and is fully absent for an internal diol such as 2,3-BDIOL (in comparison with 1,2-BDIOL), for which, furthermore, deactivation was not observed. (iv) The heavy products, responsible for catalyst deactivation, are not formed from the reagents or by further alkylation of the indoles formed, but seem to be attributable to a reaction involving the carbonyl intermediate.

On this basis, the following reaction pathway may be proposed for the vapour-phase synthesis of indole or alkylindoles, as it allows us to rationalise the different reactivities and products observed (Fig. 8). Two possible reaction intermediates may be hypothesised, an aldehyde (path A) or a ketone (path B), which form the final indole compounds by cyclisation. As a side reaction, both intermediates give rise by hydrogenation to the corresponding amino alcohol and, by further reaction, to N-substituted anilines and N-alkyl indole derivatives. However, the aldehyde intermediate is more reactive than the ketone intermediate and may easily polycondense to heavy products (tar), with consequent catalyst deactivation. The presence of a C_2–C_3 alkyl chain in the ortho position and the use of diols longer than EG (but not so long as to undergo the steric hindrance effects) seem to reduce the rate of polycondensation of the aldehyde by steric hindrance, thus favouring its cyclisation to alkylindole. On the other hand, the ketone intermediate is more stable and does not give rise to polycondensation to heavy products, completely eliminating the differences between aniline and alkylaniline and avoiding any deactivation (see, for example, the tests with 2,3-BDIOL).

4. Conclusions

The vapour-phase synthesis of indole and its derivatives with heterogeneous catalysts represents a novel example of an economical and environmentally friendly process, with significant advantages in comparison with known industrial processes. The ZrO_2/SiO_2 catalysts work much better than

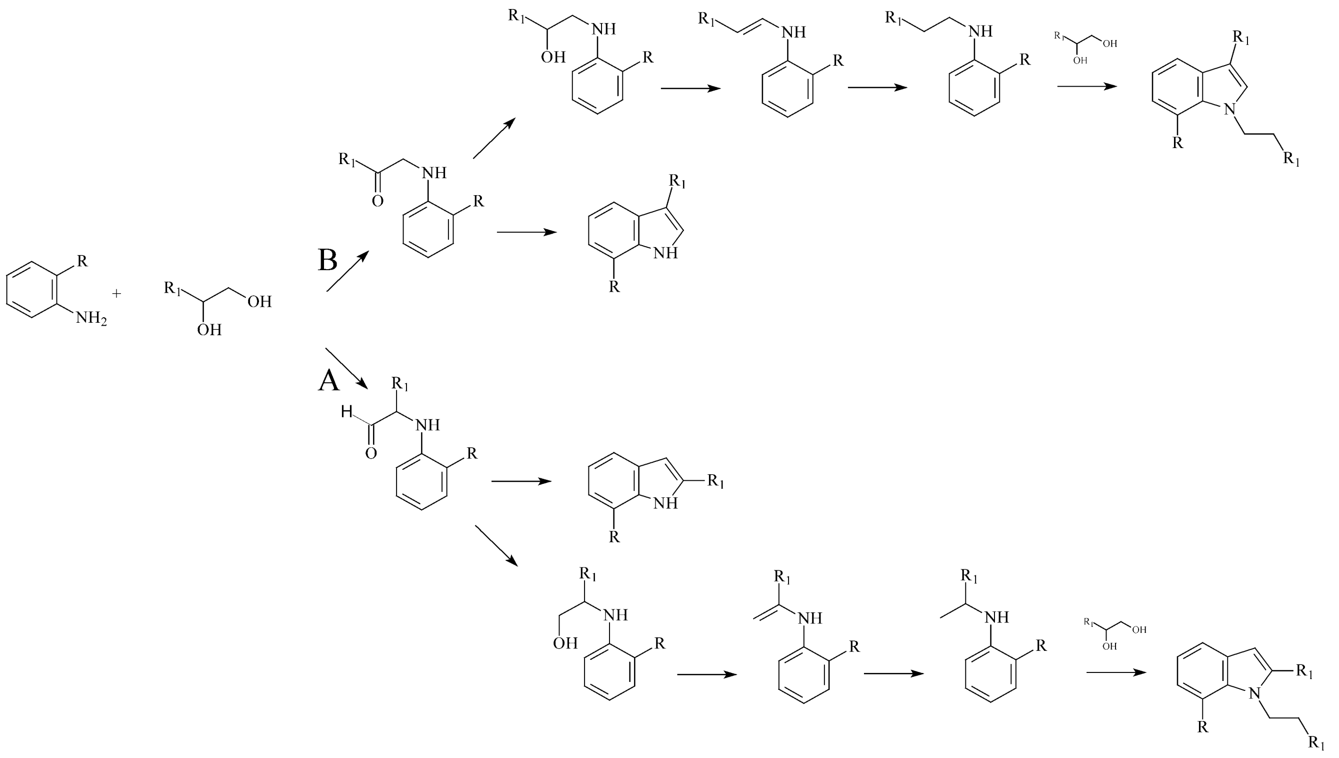


Fig. 8. Proposed reaction pathway for the vapour-phase synthesis of indole and alkylindoles as a function of the aromatic amine and diol fed.

most widely reported copper chromites, and are able to operate with an almost stoichiometric ratio between the aromatic amine and the diol, reducing the costs and risks of high amounts of aromatic amine to be recycled. This catalytic system exhibits good regenerability and recovers the initial activity almost completely by calcination and following reducing activation [18,20]. Last, but not least, this process uses water as the main carrier gas, which can be easily separated by condensation and recycled directly to the reactor, with no purification, thus avoiding any environmental constraints.

This synthesis can be applied to a wide number of substrates (anilines and/or diols), even if a possible industrial use is more interesting for specific derivatives. In particular, when EG was used, the best yields in the corresponding indoles were obtained when an alkyl chain was located in the ortho position to the amino group and the length of the chain was increased. Moreover, the differences in the reactivity between aniline and alkylanilines were significantly reduced by an increase in the length of the diol chain, although with a limit due to steric hindrance of the diol. A possible reaction pathway, including two possible routes with an aldehyde or a ketone as an intermediate, is able, in our opinion, to justify these behaviours, the side products detected, and the different deactivation effects observed, with the different reactivities of the two intermediates taken into consideration.

In conclusion, the proposed vapour-phase synthesis with ZrO_2/SiO_2 catalysts, although unable to compete economically in the synthesis of unsubstituted indole with the high-temperature process [9], is most interesting for the synthesis of alkylindoles, for which a high temperature may favour side reactions (dealkylation, transalkylation, etc.), also with the increase in yield and stability observed taken into account. In any case, it is worth noting that the selectivity values obtained were of the same order as, or, in some cases, higher than the values reported in the patent literature [9–16].

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