The Hydroamination Problem in Cobalt-based Catalytic Hydroaminomethylation

Hans M. de Bruijn, Célia Fonseca Guerra, Elisabeth Bouwman, and F. Matthias Bickelhaupt

The hydroamination (HAM) reaction converts alkenes into N-alkylated amines and has been well studied for rhodium- and ruthenium-based catalytic systems. Cobalt-based catalytic systems are able to perform the essential hydroformylation reaction, but are also known to form very active hydrogenation catalysts, therefore we examined such a system for its potential use in the HAM reaction. Thus, we have quantum-chemically explored the hydrogenation activity of [HCo(CO)]$_3$ in model reactions with ethene, methyleamine, formaldehyde, and vinylamine using dispersion-corrected relativistic density functional theory at ZORA-BLYP-D3(BJ)/TZ2P. Our computations reveal essentially identical overall barriers for the catalytic hydrogenation of ethene, formaldehyde, and vinylamine. This strongly suggests that a cobalt-based catalytic system will lack hydrogenation selectivity in experimental HAM reactions. Our HAM experiments with a cobalt-based catalytic system (consisting of Co$_3$(CO)$_8$ as cobalt source and P(n-Bu)$_3$ as ligand) resulted in the formation of the desired N-alkylated amine. However, significant amounts of hydrogenated starting material as well as alcohol (hydrogenated aldehyde) were always formed. The use of cobalt-based catalysts in the HAM reaction to selectively form N-alkylated amines seems therefore not feasible. This confirms our computational prediction and highlights the usefulness of state-of-the-art DFT computations for guiding future experiments.

Introduction

The hydroaminomethylation (HAM) reaction is an atom-economical transformation of an alkene, amine, CO, and H$_2$ into an N-alkylated amine by consecutive hydroformylation (HF), condensation (comprising a nucleophile addition of the amine to the aldehyde and elimination of water), and hydrogenation reactions (Scheme 1). One of the first reports of the HAM reaction was described in 1950, in which ethene, ammonia, CO, and H$_2$ in the presence of a large amount of metallic cobalt were converted into primary and secondary propylamines under very harsh conditions (170–262°C, 470–755 atmospheres).[1–5] Since then, the HAM reaction has been studied extensively using rhodium[2–7] and ruthenium-based homogeneous catalysts.[8–15]

In general, rhodium and ruthenium form poor isomerization catalysts, and in most cases a terminal alkene is used as substrate to form the linear N-alkylated amine.[6–15] A secondary amine is used in these HAM reactions to prevent overalkylation of the amine. However, some rhodium-based catalytic systems have been reported which can be used to convert internal alkenes to the desired linear N-alkylated amine with 80–90% selectivity.[3–5] A ruthenium-based catalyst has been shown to convert 2-octene to the desired linear N-alkylated amine with 60% selectivity.[15]

Studies using cobalt-based catalysts are less common and the last reports on homogeneously-catalyzed HAM with cobalt-based systems appeared in 1997.[16–20] In all cases, the reaction conditions are forcing: temperatures upwards of 180°C and pressures of at least 100 bar were necessary to reach acceptable conversion. The HAM of propene with morpholine or piperidine under water-gas shift conditions resulted in moderate to high yields of the N-butylamine, albeit using a system comprising 20 mol% of Co and 10 mol% of 1,2-bis(diphenylphosphanyl)ethane (dppe).[16] HAM of 1-hexene with ammonia and syngas, using a catalytic system comprising Co$_3$(CO)$_8$ and either PPh$_3$ or P(n-Bu)$_3$, yielded 57% total selectivity for N-alkylated amines.[17] The addition of dppe as the ligand under the same reaction conditions (up to eight P atoms per Co atom) resulted in complete inhibition of catalytic activity.[20] A selectivity of 57% for the N-alkylated amines is relatively high, but the selectivity was divided over both the primary and secondary amines. The primary amine is more nucleophilic than ammonia,[21] and can also attack the aldehyde present in...
The reaction mixture, leading to the formation of the secondary amine. The tertiary amine can also be formed, but the nucleophilicity of amines decreases going from primary to secondary to tertiary amines,\textsuperscript{22,23} thus preventing the formation of the tertiary amine at low concentrations of the secondary amine.

It is attractive to use homogeneous cobalt-based catalysts since cobalt is a more abundant and less toxic metal than rhodium and ruthenium, and, in contrast to rhodium-based catalysts, cobalt-based catalysts generally have a very high isomerization activity.\textsuperscript{24} This high isomerization activity opens up the possibility of the use of internal alkenes as the substrate, which prevents the arduous separation of the terminal alkene from the industrial mixture of isomeric internal alkenes.\textsuperscript{25} Furthermore, cobalt forms very active hydrogenation catalysts in combination with phosphine ligands, even in the presence of carbon monoxide.\textsuperscript{24,26,27} Steering the hydrogenation selectivity of the catalytic system is therefore of paramount importance: hydrogenation of the intermediate enamine is necessary to yield the desired amine, but the alkene as well as the intermediate aldehyde may also be hydrogenated to yield the undesired alkane and alcohol (Scheme 2).

To better understand the cobalt-catalyzed hydrogenation of the alkene, aldehyde, imine (formed if a primary amine is used in the HAM reaction), and enamine (formed with secondary amines) under HAM conditions, we have conducted a combined quantum-chemical and experimental exploration into the feasibility of such a process. Thus, we have quantum chemically studied the use of \([\text{HCo(CO)}_3]\) as a model catalyst for the hydrogenation of ethene, formaldehyde, methyleneamine,
and vinylamine as model compounds using dispersion-corrected relativistic density functional theory at ZORA-BLYP-D3(BJ)/TZ2P. These computations suggest potentially insufficient selectivity for the N-alkylated amine in the HAM reaction. In order to endorse this outcome, we have carried out experiments with a cobalt-based catalytic system comprising Co₂(CO)₈ and P(n-Bu)₃ for the HAM of 1-octene and pyrrolidine under a range of conditions. The motivation for this effort is the attractiveness of a cobalt alternative for the HAM reaction in combination with the fact that our computational exploration is based on a simplified model system, leaving room for the assumption that an in-vitro catalyst might have more favorable behavior.

Results and discussion

DFT study of hydrogenation

For a successful catalyst in the HAM reaction hydrogenation selectivity to the formation of the desired N-alkylated amine is crucial. We computationally studied the hydrogenation according to the mechanism in Scheme 3 with [HCo(CO)₃] as the active catalytic species for four substrates: ethene (X = CH₂), formaldehyde (X = O), methyleneamine (X = NH), and vinylamine (X = CHNH₂). These are model substrates for the alkene, aldehyde, imine, and enamine which are present during the HAM reaction. The use of a primary amine as a nucleophile in the reaction can result in the formation of both the imine and enamine species, while the use of a secondary amine can only result in the formation of the enamine. For each of the substrates, with exception of the symmetrical ethene, we studied the hydride transfer (step b to c) to either atom of the double bond: the carbon or the nitrogen or oxygen atom for methyleneamine and formaldehyde respectively, and the α- or β-atom for vinylamine. For formaldehyde and methyleneamine, we also studied the coordination of the substrate to the cobalt center with the π-bond (b_pi) or with the lone pair (b_X) present on the nitrogen or oxygen atom. All our calculations were performed in the gas phase and in aqueous solution using the CONductor-like Screening Model (COSMO). The gas phase is very close in polarity to n-hexane, which was used as solvent in our catalytic experiments. In the case of in vitro experiments, water would participate as reactant, leading to undesired side reactions. This makes water, in practice, unsuitable as a solvent for the HAM reaction. Note, however, that aqueous solution was chosen solely to simulate, in a generic manner, extremely strong solvation and how this situation would affect the hydrogenation of our model substrates. The undesirable participation of the model solvent is prevented in our approach by the use of a continuum solvation model, i.e., COSMO.

The Gibbs free energies for the stationary points in the gas phase and water are plotted in Figures 1 to 7. We defined the total overall barrier (TOB) as the energy difference between the

Scheme 3. The catalytic cycle for the hydrogenation of ethene, methyleneamine, formaldehyde, and vinylamine using [HCo(CO)₃] as the catalyst. Only the pathway for the hydride transfer (b to c) to the carbon atom is shown for clarity.
The TOB determines the rate of the catalytic reaction\(^{(44)}\) and therefore is related to the selectivity for the specific reaction. The TOB for these substrates is very similar: 19.0, 18.7, and 18.7 kcal mol\(^{-1}\) respectively for ethene (E), formaldehyde (hydride transfer to the oxygen atom, \(F_O\)), and vinylamine (hydride transfer to the \(\beta\)-carbon atom, \(V_\beta\)), thus essentially suggesting the absence of selectivity for the hydrogenation reaction (Table 1).

The use of more polar solvents than \(n\)-hexane probably results in a lower selectivity for the \(N\)-alkylated amine. Our DFT calculations show that in water the selectivity for the hydrogenation of vinylamine is lower compared to the gas phase, since the TOB is higher for vinylamine than for ethene and formaldehyde (Table 1). Therefore, it is likely that the alkene and aldehyde will be hydrogenated faster in water compared to the enamine, resulting in the formation of more of the alkane and alcohol than the \(N\)-alkylated amine.

Solvation of the catalytic system by water in general destabilizes the points along the reaction coordinate slightly for ethene, methyleneamine, and formaldehyde, by up to 3.6 kcal mol\(^{-1}\). For vinylamine as substrate solvation by water destabilizes points \(eTSp\) and \(a+p\) by up to 9.3 kcal mol\(^{-1}\), while the other points are destabilized similarly as for the other substrates. Other notable differences between the hydrogenation in the gas phase and water are that both point \(cTSD\) for the \(M_C\) system and point \(e\) for the \(V_\beta\) system do not exist in the gas phase, but do exist in water (see Figure 2).

Figure 1. Free energy profile (with electronic energies in parenthesis) of the hydrogenation of ethene with the HCo(CO)\(_3\) catalyst in the gas phase (black) and water (grey, using COSMO), computed at ZORA-BLYP-D3(BJ)/TZ2P.
Figure 2. Free energy profile (with electronic energies in parenthesis) of the hydrogenation of methyleneamine (hydride transfer to the carbon atom) with the \( \text{HCo(CO)}_3 \) catalyst in the gas phase (black) and water (grey, using COSMO), computed at ZORA-BLYP-D3(BJ)/TZ2P.

Table 1. Total uphill barrier (TOB) in kcal mol\(^{-1}\) (Gibbs free energy at 423.15 K and 75 bar) and the lowest and highest point during the catalytic cycle for the hydrogenation of the studied systems.\(^{[a]}\)

| System | TOB (gas) | TOB (water) | Lowest point | Highest point |
|--------|-----------|-------------|--------------|---------------|
| E      | 19.0      | 19.1        | b            | etSp          |
| M_C    | 31.6      | 32.7        | c (g), b (aq)\(^{[b]}\) | etSp          |
| M_N    | 27.4      | 27.8        | c            | etSp          |
| F_C    | 28.0      | 28.6        | c            | etSp          |
| F_O    | 18.7      | 20.4        | c            | etSp          |
| V_α    | 24.7      | 28.0        | b            | etSp          |
| V_β    | 18.7      | 28.9        | b            | etSp          |

\(^{[a]}\) Computed at ZORA-BLYP-D3(BJ)/TZ2P using COSMO to estimate the effect of aqueous solution. \(^{[b]}\) Intermediate c is the lowest point in the gas phase, intermediate b is the lowest point in aqueous solution.
In non-polar solvents, the use of a primary amine in the HAM reaction results in the formation of the $N$-alkylated amine via hydrogenation of the enamine species. Both the imine and enamine species would form during catalysis, but in the gas phase the TOB for the hydrogenation of methyleneamine is much higher than for vinylamine: 27.4 and 18.7 kcal mol$^{-1}$, respectively. In very polar solvents the formation of the $N$-alkylated amine can occur via both the imine and enamine species, since in water the TOBs for both methyleneamine and vinylamine are very similar: 27.8 and 28.0 kcal mol$^{-1}$, respectively.

Methyleneamine and formaldehyde were found to preferentially coordinate to the cobalt center with a lone pair present on the nitrogen or oxygen atom. The structures for the coordination with the lone pair ($b_X$) are 8.7 and 1.1 kcal mol$^{-1}$ lower in energy (for methyleneamine and formaldehyde respectively, Table S7) compared to the coordination of the substrate to the Co center with the $\pi$-system. No pathway was found from the $b_X$ structures to the $c$ structures for both substrates. Therefore, the $b_X$ structures in situ convert to the $b_{\pi}$ structures, before the subsequent reaction to $c$ can take place. In our analysis of the TOB for the hydrogenation of methyleneamine and formaldehyde the energies of the $b_X$ structures were taken for the $b$ structures.

The identical overall barrier for the hydrogenation of the E, F, O, and V systems spurred us to compare the energy profiles of these systems along the reaction coordinate (Figure 8). The energy profile is raised in energy going from E to V.
β, and to F_O, which is caused by differences between the substrates, since the energy difference between the systems is present along the entire reaction coordinate. The π-bond of formaldehyde is stronger than that of ethene (86.7 and 84.0 kcal mol\(^{-1}\), respectively),\(^{45}\) and is broken in bTSc, thus increasing the energy of the hydrogenation pathway of F_O compared to E.

The much lower Gibbs free energy for the hydrogenation of ethene compared to formaldehyde and vinylamine (−20.1, −10.8, and −9.6 kcal mol\(^{-1}\) respectively) can be explained by the more exothermic hydrogenation of ethene compared to formaldehyde. Our calculations show that the hydrogenation of ethene is 11.8 and 9.5 kcal mol\(^{-1}\) more exothermic than for formaldehyde and vinylamine. The same trend is present in the experimental enthalpy of hydrogenation of ethene, which is 4.2 kcal mol\(^{-1}\) more exothermic than the hydrogenation of formaldehyde (calculated with tabulated bond dissociation energy (BDE) values).\(^{45}\) For vinylamine the enthalpy of hydrogenation and the strength of the π-bond could not be calculated, since tabulated BDE values are unavailable for this substrate.

Our DFT calculations show that the hydrogenation of ethene, formaldehyde, and vinylamine with [HCo(CO)]\(_3\) as catalyst is essentially unselective due to very similar overall barriers. This suggests it is unlikely that selective formation of the N-alkylated amine can be achieved in the HAM reaction with a Co-based catalytic system. However, our DFT calculations employ a simplified catalytic system, simplified sub-

Figure 4. Free energy profile (with electronic energies in parenthesis) of the hydrogenation of formaldehyde (hydride transfer to the carbon atom) with the HCo(CO)\(_3\) catalyst in the gas phase (black) and water (grey, using COSMO), computed at ZORA-BLYP-D3(BJ)/TZ2P.
strates, and do not take into account the complicated kinetics of the multiple reactions that occur subsequently in the HAM reaction. These reasons, and the fact that a Co-based catalytic system which forms the N-alkylated amine would be an important scientific discovery, motivated us to perform HAM experiments with a Co-based catalytic system.

**Hydroaminomethylation of 1-octene and pyrrolidine**

The formation of the N-alkylated amine from the HAM reaction of 1-octene and pyrrolidine was studied with a catalytic system comprising Co$_2$(CO)$_8$ and P(n-Bu)$_3$ in $n$-hexane, under 75 bar of H$_2$:CO (2:1 ratio) at 150 °C for 12 h. In the experiments we varied the amount of ligand and pyrrolidine, the solvent, and the H$_2$:CO ratio in an attempt to increase the selectivity for the N-alkylated amine. The variation of temperature in the HAM reaction was not investigated, but in preliminary HF reactions a temperature of 150 °C was found to result in the highest selectivity for the aldehyde, which in HAM reactions is converted to the N-alkylated amine (Table S1). Therefore, a temperature of 150 °C was used in all subsequent experiments.

The use of 1 or 0 eq (eq = molar equivalent) of ligand was not investigated, since the use of 2 eq of a phosphine ligand in HF reactions resulted in a higher selectivity for the aldehyde than 1 eq of phosphine ligand. The use of 5 eq of P(n-Bu)$_3$ in HAM experiments resulted in a lower conversion and similar selectivity for the N-alkylated amine compared to the use of 2 eq of P(n-Bu)$_3$ (Table 2). Reactions without ligand were not

![Free energy profile (with electronic energies in parenthesis) of the hydrogenation of formaldehyde (hydride transfer to the oxygen atom) with the HCo(CO)$_3$ catalyst in the gas phase (black) and water (grey, using COSMO), computed at ZORA-BLYP-D3(BJ)/TZ2P.](image-url)
performed since unmodified Co complexes need high (partial) CO pressures to remain stable during catalysis,\textsuperscript{[47,48]} which are not reachable in our experimental setup. Therefore 2 eq of P(\textit{n}-Bu)\textsubscript{3} were used in all following experiments.

Amines are known to coordinate to the cobalt center during catalysis resulting in less active catalytic systems.\textsuperscript{[20]} Therefore, the amount of pyrrolidine in the reaction mixture was varied. Again, this did not result in an increased selectivity for the \textit{N}-alkylated amine (Figure 9). The use of 1 eq of pyrrolidine (relative to 1-octene) in the reaction resulted in a 1-octene conversion of 64 % and a selectivity for the amine of 13 %. Addition of less than 1 eq of pyrrolidine resulted in a

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**Figure 6.** Free energy profile (with electronic energies in parenthesis) of the hydrogenation of vinylamine (hydride transfer to the \textit{\alpha}-carbon atom) with the HCo(CO)\textsubscript{3} catalyst in the gas phase (black) and water (grey, using COSMO), computed at ZORA-BLYP-D3(BJ)/TZ2P.

**Table 2.** The effect of the P(\textit{n}-Bu)\textsubscript{3} concentration on the conversion and product distribution of the HAM of 1-octene and pyrrolidine (\textit{Y} = yield).\textsuperscript{[a]}

| Entry | Eq | Conv. (%) | Y alkane (%) | Y aldehyde (%) | Y alcohol (%) | Y enamine (%) | Y amine (%) |
|-------|----|-----------|-------------|---------------|--------------|--------------|-------------|
| 1     | 2  | 68        | 15          | 1             | 6            | 0            | 15          |
| 2     | 5  | 63        | 18          | 8             | 1            | 17           |             |

\textsuperscript{[a]} Conditions: \textit{T} = 150 °C, \textit{P} = 75 bar, \textit{H}\textsubscript{2}: CO = 2:1, \textit{t} = 12 h, 1 mol\% Co, x equivalent P(\textit{n}-Bu)\textsubscript{3} to Co, 10.8 mmol 1-octene, 1 eq pyrrolidine to 1-octene, \textit{V}_{\text{tot}} = 17.0 mL, solvent = \textit{n}-hexane.
higher conversion and higher yield of the alcohol than for the reaction with 1 eq of pyrrolidine, while the yields for the alkane and amine were similar. At 0.25 eq of pyrrolidine 7% of the aldehyde was detected due to the low concentration of amine present, which prevented full conversion of the aldehyde to the enamine or amine products.

Addition of 2 or 5 eq of pyrrolidine resulted in a lower catalytic activity than for 1 eq of pyrrolidine (17% conversion at 5 eq of pyrrolidine). The lower catalytic activity is probably due to coordination of pyrrolidine to the cobalt center, as reported before for the use of ammonia in combination with Co$_2$(CO)$_8$ and P(n-Bu)$_3$ in the HAM of 1-hexene. The rather basic pyrrolidine could also deprotonate the hydride species, forming an inactive complex [H$_2$NR][Co(CO)$_3$P(n-Bu)].

The effect of the variation of the solvent on the conversion of 1-octene and the product distribution was studied. Changing the solvent from n-hexane to toluene, THF or diglyme resulted in a less active catalytic system and in very low yields for the N-alkylated amine (\(<5\%\)), regardless of the H$_2$:CO ratio used (Figure 10). The low activity of cobalt-based catalytic systems in polar solvents, such as THF, MeCN, and t-amylalcohol, has been reported before in HF reactions, either without a ligand or with the use of monodentate ligands.

Assuming that the hydrogenation reactions are positive order in the hydrogen concentration, a decrease in the hydrogen concentration in solution could result in a decrease in the rate of the hydrogenation reactions. Any differences between the hydrogenation kinetics of the alkene, aldehyde, and enamine would then be amplified possibly resulting in a higher

Figure 7. Free energy profile (with electronic energies in parenthesis) of the hydrogenation of vinylamine (hydride transfer to the $\beta$-carbon atom) with the HCo(CO)$_3$ catalyst in the gas phase (black) and water (grey, using COSMO), computed at ZORA-BLYP-D3(BJ)/TZ2P.
selectivity for the amine. However, a lower $\text{H}_2$/$\text{CO}$ ratio of 1.5:1 or 1:1, compared to the normal 2:1, did not result in a change in product distribution. A decrease of the $\text{H}_2$/$\text{CO}$ ratio to 1.5:1 in $n$-hexane and THF resulted in a lower conversion and a decrease in the amount of amine detected. In toluene the conversion and the product distribution did not change significantly. A further reduction of the $\text{H}_2$/$\text{CO}$ ratio to 1:1 in $n$-hexane did not result in any changes in the product distribution. The decrease in conversion when changing the $\text{H}_2$/$\text{CO}$ ratio from 2:1 to 1.5:1 points to at least a partial positive dependence of the rate of conversion of octene in hydrogen, as has been reported for HF with a cobalt-based catalytic system, both experimentally\cite{52} and computationally.\cite{53}

In all experiments described above (Table 2, Figure 9 and 10) none or very little of the aldehyde was detected, and only relatively small amounts of the alcohol. This is due to the immediate reaction between nonanal and pyrrolidine during catalysis, resulting in a low concentration of the aldehyde during catalysis. $^1$H NMR experiments showed 80% conversion of nonanal to the amine hydrate and enamine immediately after mixing 1 eq of nonanal and 1 eq of pyrrolidine CDCl$_3$ at room temperature (Scheme 4, Table S5, and Figure S2). During catalysis pyrrolidine will always be present in a large excess relative to the intermediate aldehyde. Therefore, most of the aldehyde formed during catalysis will be immediately converted to the enamine during HAM experiments, thus lowering the amount of aldehyde that can be hydrogenated to the alcohol.

The low mass balance in the experiments described above is due to aldol condensation of the formed aldehydes, a reaction which is catalyzed by the basic pyrrolidine (Scheme 4). The formed aldol-condensation products can also undergo condensation with pyrrolidine to yield larger enamines, or undergo further aldol condensation reactions. The resulting high-mass products are difficult to detect with GC, and are therefore absent in our graphs. The formation of high-mass products has been reported regularly for both HAM\cite{2,4,6,7,17,20} and HF reactions.\cite{47,48}

Our experiments thus have shown that Co-catalyzed HAM of 1-octene and pyrrolidine results in the formation of the
desired \(N\)-alkylated amine and a similar amount of octane, as well as alcohol. Variation of the amount of ligand, the amount of pyrrolidine, of the solvent and the \(H_2:CO\) ratio does not result in an increased selectivity for the \(N\)-alkylated amine compared to our standard conditions. As a consequence, the selective formation of the \(N\)-alkylated amine in the HAM reaction with the use of a cobalt-based catalytic system seems
to be challenging, and replacement of rhodium or ruthenium by cobalt in the HAM reaction is probably not feasible.

Conclusions
The HAM reaction with a cobalt-based catalytic system results in the formation of comparable amounts of the desired N-alkylated amine and the undesired alkane. Variation in temperature, solvent, the H₂:CO ratio or the amount of ligand or amine did not result in an increased selectivity for the N-alkylated amine. These experimental results are in line with the results of our DFT computations of the hydrogenation cycle of the model substrates ethene, methyleneamine, formaldehyde, and vinylamine with [HCo(CO)]₃ as the catalyst. The total barriers of hydrogenation for ethene, formaldehyde, and vinylamine were computed to be essentially identical, resulting in an absence of selectivity for the N-alkylated amine with respect to the alkane.

The present study has shown that the HAM reaction with a cobalt-based catalytic system is unsselective towards the desired N-alkylated amine. Our results show that it will be difficult to increase the selectivity for the N-alkylated amine due to the very similar energy barriers for the hydrogenation of the substrate and intermediates. However, we also have shown that state-of-the-art DFT calculations on suitably chosen model systems can be reliably used to guide the planning of expensive and time-consuming experiments.

Supporting Information
The supporting information contains experimental details of the catalytic reactions, results of catalytic experiments, full analytical details of the hydroaminomethylation reactions and NMR experiments for the reaction of nonanal and pyrrolidine. Also included are an example of a representative input file used in the DFT calculations, and the Cartesian coordinates, energies, number of imaginary frequencies, and figures of all computed structures.

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Conflict of Interest
The authors declare no conflict of interest.

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