Asymmetric Amplification

Physical and Chemical Rationalization for Asymmetric Amplification in Autocatalytic Reactions**

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The origin of biological homochirality has intrigued scientists for some time. Discussions of possible mechanisms through which high optical activity was achieved from a racemic or prochiral prebiotic environment[1,2] have implicated both physical processes such as crystallization[3] and chemical processes such as autocatalysis.[4] Kondepudi[2] first reported spontaneous chiral symmetry breaking in crystallization little more than 10 years ago. In the last decade, Soai and co-workers[5] demonstrated the chemical phenomenon of asymmetric autocatalysis in remarkable reactions involving pyrimidyl alcohols that serve as both the catalyst and the product in the alkylation of pyrimidyl aldehydes. When alcohol **2** is used in very low enantiomeric excess as a catalyst in the

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[**] The work reported herein was carried out at the University of Hull, Hull HU6 7RX U.K. Funding from the EPSRC and Merck Co., Inc. is gratefully acknowledged. We also thank J. M. Brown and I. D. Gridnev for stimulating discussions.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

DOI: 10.1002/anie.200353086

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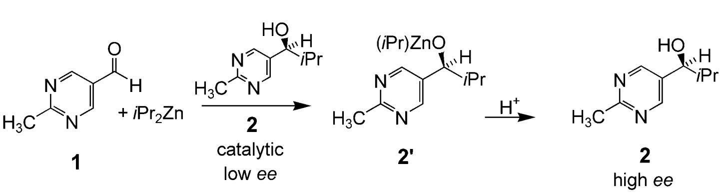
alkylation of the corresponding aldehyde **1** with $i\mathrm{Pr_2Zn}$, **2** may be produced with high enantiomeric excess (Scheme 1).



Scheme 1. The Soai autocatalytic reaction.

We[6] recently elucidated a mechanistic framework for the Soai reaction shown in Scheme 1 based on an autocatalytic version of the Kagan $\mathrm{ML_2}$ model[7] describing a nonlinear relationship between the catalyst and the product *ee* in asymmetric reactions (Scheme 2). We showed that the alkoxide product species **2′** is strongly driven toward the formation of a dimeric species **3**, implicating these dimers as the active catalytic species. Heterochiral ($\mathbf{3}_{RS}$) and homochiral ($\mathbf{3}_{RR}$ and $\mathbf{3}_{SS}$) dimers are formed in a statistical distribution, and the observed amplification in *ee* is due solely to the higher activity of the homochiral dimer. Further kinetic studies have recently implicated a tetrameric transition state in this autocatalytic reaction.[6c]

$$\mathbf{2}'_R + \mathbf{2}'_R \overset{K_\text{homo}}{\rightleftarrows} \mathbf{3}_{RR} \qquad \mathbf{3}_{RR} + \mathbf{3}_{SS} \overset{K_\text{ML2}}{\rightleftarrows} 2\cdot\mathbf{3}_{RS} \qquad ee_\text{cat, active} = \frac{\mathbf{3}_{RR} - \mathbf{3}_{SS}}{\mathbf{3}_{RR} + \mathbf{3}_{SS}}$$

$$\mathbf{2}'_S + \mathbf{2}'_S \overset{K_\text{homo}}{\rightleftarrows} \mathbf{3}_{SS} \qquad K_\text{ML2} = \left(\frac{K_\text{hetero}}{K_\text{homo}}\right)^2 = \frac{[\mathbf{3}_{RS}]^2}{[\mathbf{3}_{RR}][\mathbf{3}_{SS}]}$$

$$\mathbf{2}'_R + \mathbf{2}'_S \overset{K_\text{hetero}}{\rightleftarrows} \mathbf{3}_{RS} \qquad \begin{array}{c}\text{statistical}\\ \text{distribution}\end{array} \Rightarrow K_\text{hetero} = 2\cdot K_\text{homo} \Rightarrow K_\text{ML2} = 4$$

Scheme 2. Formation of dimer species **3** from the monomeric alkoxides **2′**. The relationship between the equilibrium constant in Kagan's $\mathrm{ML_2}$ model (K_ML2) and the equilibrium constants for homochiral (K_homo) and heterochiral (K_hetero) dimer formation is shown. The dimers are formed with a statistical distribution and only the homochiral dimers are active as catalysts.

We report herein continuing investigations that highlight further complexities in this intriguing system. Our observations led us to conclude that a synergistic combination of chemical and physical processes may result in an amplification of product *ee* and indeed may help serve as a model to rationalize the origin of the high optical activities characteristic of biological systems.

Figure 1 shows reaction rate and enantiomeric excess as a function of time for a reaction sequence carried out by consecutive injection of aliquots of the aldehyde **1** into a toluene solution initially containing the catalyst **2** (46% *ee*) and excess $i\mathrm{Pr_2Zn}$. The rate maximum is seen to increase from the first to the second reaction in the sequence, as expected for an autocatalytic reaction. However, the rate *decreases* upon addition of subsequent aliquots of the substrate, revealing that the further production of catalyst was no longer reflected in increased activity.

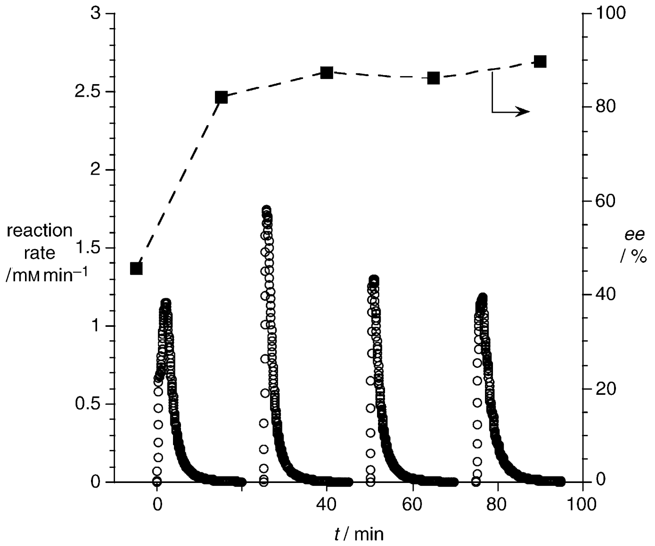


Figure 1. Reaction rate (○) and enantiomeric excess of **2** (■) vs. time in the autocatalytic reaction of consecutive aliquots (0.13–0.17 M) of **1** injected into a solution of $i\mathrm{Pr_2Zn}$ (0.70 M) with an initial catalytic concentration of **2** (0.014 M, 46% *ee*) in toluene at 298 K. The reaction was monitored calorimetrically, as previously described.

Another key observation was the detection of product precipitation during the course of these reactions. The onset of precipitation appears to correlate with a feature at high conversion in the reaction heat flow curves (Figure 2) that has also been observed previously.[6] Separation of the filtrate from the solid white precipitate followed by workup showed that both contain **2** and no other products.[8] It has not yet proved possible to extract crystals from the precipitate.

Whereas optimized conditions for the Soai reaction typically involve the use of solvents such as toluene or

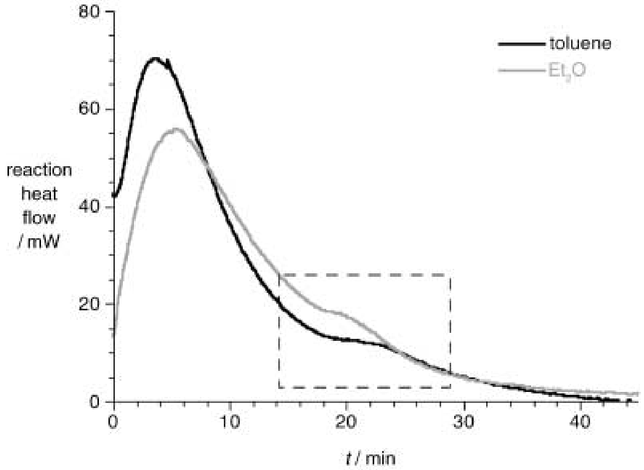


Figure 2. Reaction heat flow vs. time for the reaction shown in Scheme 1 carried out in toluene (——) and in diethyl ether (–•–•) with **1** (0.1 M), $i\mathrm{Pr_2Zn}$ (0.20 M), and **2** at an initial concentration of 0.01 M (6% *ee* in toluene, racemic in diethyl ether) at 298 K. The reaction rate was monitored calorimetrically, as previously described.

cumene, Soai et al. recently reported interesting results for spontaneous asymmetric synthesis (reaction in the absence of added alcohol catalyst) in a 1:3 toluene/diethyl ether solvent mixture.[9] We find that the reaction shown in Scheme 1 proceeds smoothly in toluene, in diethyl ether, and in toluene/diethyl ether solvent mixtures, exhibiting similar autocatalytic rate profiles (Figure 2) and similar amplification of product enantiomeric excess (Figure 3) for reactions carried out under similar conditions. In contrast, the reaction in THF is extremely sluggish. No amplification of product *ee* is observed, suggesting that the reaction proceeds differently in this solvent. Product precipitation may be observed during reactions in all solvents under some conditions, accompanied by the feature in the heat flow curve noted above at high conversions, as shown in Figure 2 for reactions using racemic catalyst **2** in diethyl ether and 6% *ee* **2** in toluene.

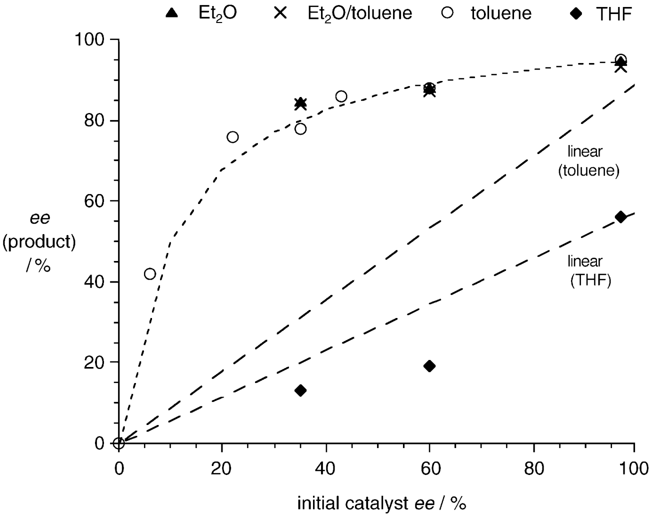


Figure 3. Product enantiomeric excess vs. initial catalyst enantiomeric excess for the autocatalytic reaction shown in Scheme 1 under conditions of Figure 2 carried out in toluene (○), diethyl ether (●), Et_2O/toluene (×), and THF (◆). The calculation for the linear relationship with *ee* for an autocatalytic reaction is described in reference [6b] and Equation (3) in reference [10].

Table 1: Enantiomeric excess and% product in solution and in the precipitate for the reaction shown in Scheme 1.[a]

Entry	Solvent	% *ee* (cat.)	% *ee* (solution)	% *ee* (precipitate)	% *ee* (total)	% product in solution
1	toluene	60	95.8	88.3	88.5	42
2	toluene	60	94.3	78.9	85.6	59
3	toluene	60	96.6	69.5	87.2	68
4	toluene	60	96.7	66.2	83.9	46
5	toluene	35	93.2	64.3	79.9	45
6	toluene	35	93.0	61.2	77.3	50
7	toluene	35	94.9	73.1	78.8	24
8	toluene	35	91.4	63.0	78.4	42
9	toluene	35	90.4	64.0	75.1	40
10	Et_2O	60	63.7	94.4	88.8	16
11	Et_2O	60	41.8	92.6	90.5	14
12	Et_2O	60	35.7	91.3	84.8	17
13	Et_2O	60	51.4	89.4	88.5	14
14	Et_2O	60	49.5	92.3	88.1	14
15	Et_2O	35	37.9	88.7	80.3	18
16	Et_2O	35	54.0	86.3	85.5	7
17	Et_2O	35	57.3	86.1	86.9	5
18	Et_2O	35	56.1	86.4	83.3	8
19	Et_2O/toluene	60	73.3	91.5	89.0	7.5
20	Et_2O/toluene	60	57.6	91.6	86.5	10.5
21	Et_2O/toluene	60	58.3	93.5	90.7	12
22	Et_2O/toluene	60	68.4	90.5	86.4	8.5
23	Et_2O/toluene	60	58.1	90.9	86.1	20
24	Et_2O/toluene	60	72.7	90.3	86.7	12
25	Et_2O/toluene	60	69.3	90.0	87.5	24
26	Et_2O/toluene	60	72.8	90.2	86.3	14
27	Et_2O/toluene	35	81.8	85.5	83.8	10
28	Et_2O/toluene	35	80.3	84.5	83.2	5
29	Et_2O/toluene	35	82.4	85.8	83.6	10
30	Et_2O/toluene	35	76.4	85.1	85.1	7
31	Et_2O/toluene	35	81.9	85.3	83.4	12
32	Et_2O/toluene	35	81.6	82.5	81.8	19
33	Et_2O/toluene	35	81.9	83.8	83.7	20
34[b]	THF	96	56	n.d.	56	98
35[b]	THF	60	19	n.d.	19	n.d.
36[b]	THF	35	13	14	13	96
37[b]	THF	10	0	3	1	55

[a] The reactions were carried out in different solvents under conditions similar to those of the reactions shown in Figure 2. Reactions were sampled after 1 hour, except where noted. All reactions exhibited 100% conversion, except where noted. [b] Sampled after 24 h; reaction products other than **2** were observed. Total conversion of aldehyde **1** in reactions in THF after 24 h was < 50%.

Extensive further studies were carried out to compare the precipitation phenomenon for reactions carried out in these different solvents with catalysts of different *ee*. The enantiomeric excess of the reaction product **2** was determined separately for the filtrate and the solid in each case. An internal standard allowed independent calculation of the fraction of product present in the solid and in the filtrate. The results are given in Table 1 and are highlighted in Figure 4.

A striking conclusion to be drawn from Table 1 and Figure 4 is that precipitation in this asymmetric autocatalytic reaction is selective, with enrichment versus depletion of the solution enantiomeric excess being solvent-dependent. In toluene, the *ee* of the precipitate is *lower* than that of the solution. In diethyl ether, this trend is reversed, with the solid precipitate giving *higher ee* than the solution. Reactions in the 3:1 diethyl ether/toluene mixture follow the trend found for the major component, diethyl ether, but the difference between solution and precipitate *ee* is less pronounced than in the case of pure diethyl ether as solvent. These results suggest that the physical properties of these diastereomers $\mathbf{3}_{RR}$, $\mathbf{3}_{SS}$, and $\mathbf{3}_{RS}$ include complex, solvent-dependent solubility behavior.[8] The heterochiral dimer species $\mathbf{3}_{RS}$ is *less* soluble than the homochiral dimers $\mathbf{3}_{RR}$ and $\mathbf{3}_{SS}$ in toluene solution. In diethyl ether, $\mathbf{3}_{RS}$ is *more* soluble than $\mathbf{3}_{RR}$ and $\mathbf{3}_{SS}$.

In studies of the asymmetric catalytic alkylation of aldehydes employing chiral aminoalcohols as catalysts, Bolm et al.[11] observed selective precipitation of a species of lower enantiomeric excess. They recognized the role that this phenomenon may play in enhancing nonlinear effects on product enantiomeric excess by altering the *ee* of the active

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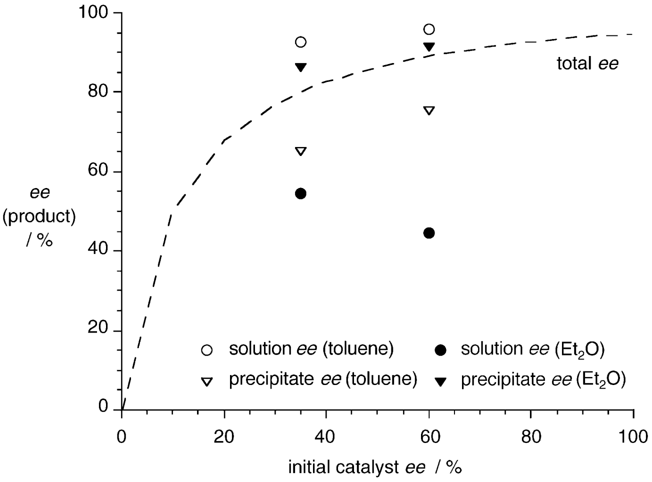

Figure 4. Product enantiomeric excess for the solution phase (○, ●) and the precipitate (▽, ▼) for the autocatalytic reaction shown in Scheme 1 carried out in the presence of catalyst **2** with initial *ee* values of 35% and 6% in toluene and diethyl ether. The data for each point are averaged from the 3–5 individual experiments given in Table 1. The dashed line gives the average total product *ee* (solution + precipitate) from Figure 3.

catalyst species in these catalytic reactions. The implications of such selective precipitation for asymmetric amplification in *autocatalytic* reactions are even more profound. If homochiral and heterochiral dimer species remain in rapid equilibrium with one another in solution on the reaction timescale, but equilibrium with the solid species is not rapidly established, a redistribution of the concentrations of the remaining dimeric species in solution will occur according to Le Chatelier's principle. How this redistribution affects the product enantiomeric excess in further autocatalytic cycles depends on whether the solution is enriched or depleted in enantiomeric excess.

The results in toluene suggest that with the onset of precipitation, a fraction of solution-phase homochiral dimers will be diverted towards the inactive heterochiral dimer as the system strives to maintain the balance dictated by the equilibrium constant $K_{\mathrm{ML2}} = 4$. Under these conditions, the physical process of selective precipitation will *enhance* the enantioselectivity achievable through the asymmetric autocatalytic reaction. The results for reactions carried out in diethyl ether suggest that selective precipitation of homochiral rather than heterochiral dimers acts to erode the *ee* of the active solution-phase catalyst.

The opposing trends for selectivity in the precipitation of the reaction product in diethyl ether and in toluene may also help to shed light on the intriguing results reported by Soai and co-workers for low-temperature reactions carried out in the absence of added catalyst. Previous observations of absolute asymmetric synthesis in the absence of added catalyst in reactions carried out in toluene were attributed to the ubiquitous presence of chiral impurities.[12] Because the same reactions in toluene/diethyl ether mixtures gave stochastic imbalances, it was proposed that these reactions provide a genuine test for spontaneous asymmetric synthesis. The results reported herein suggest that the effect of any unknown chiral factors may be moderated in the toluene/diethyl ether solvent mixture by virtue of the two opposing trends giving higher and lower *ee* precipitate relative to the solution in pure diethyl ether and toluene, respectively.[13]

Precipitation also rationalizes why reaction rates did not rise monotonically in consecutive reactions converting **1** into **2** (Figure 1). As the solution becomes saturated with catalyst, the active solution concentration of catalyst ceases to increase. Under reaction conditions such as those shown in Figures 2–4, precipitation becomes significant only at the high product concentrations found at the very end of the reaction. That precipitation is not a significant factor is reflected in the fact that amplification of *ee* is similar for reactions in diethyl ether, toluene, and the mixed solvent system. For reactions carried out at lower temperatures or higher concentrations, however, precipitation may play a significant role. Indeed, we observed that precipitation is more significant for reactions carried out at 273 K that for those at 298 K.

Brown and co-workers[14] recently noted that enantiomer enrichment by selective crystallization is the most likely rationalization for biological chirality originating from relatively few nucleation events. Siegel[15] has pointed out that the problem with this explanation of achiral symmetry breaking is that equilibration of crystals by dissolution or degradation is likely to occur, which would inexorably erode the *ee* back towards a racemic world. However, asymmetric autocatalysis *combined* with selective precipitation provides a means of shifting even a minute imbalance decisively and irrevocably towards a homochiral outcome.

The Soai reaction provided the first experimental "proof of concept" of the chemical rationale for the evolution of high optical activity from low *ee* precursors that was first presented theoretically nearly 50 years ago. The investigations reported herein suggest that the amplification of product *ee* observed in the Soai asymmetric autocatalytic reaction may be achieved under some conditions through a synergistic combination of the chemical process of autocatalysis aided by the physical process of selective precipitation, which together can enhance the driving force toward the creation of a homochiral reaction environment.

Received: October 14, 2003 [Z53086]

Keywords: asymmetric amplification · asymmetric catalysis · autocatalysis · chirality · kinetics

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[1] M. Calvin, *Chemical Evolution*, Oxford University Press, Oxford, **1969**.
[2] D. K. Kondepudi, *Science* **1990**, *250*, 975.
[3] F. C. Frank, *Biochim. Biophys. Acta* **1953**, *11*, 459.
[4] For recent reviews on spontaneous asymmetric synthesis, see: a) K. Mislow, *Collect. Czech. Chem. Commun.* **2003**, *68*, 849; b) B. L. Feringa, R. A. van Delden, *Angew. Chem.* **1999**, *111*, 3624; *Angew. Chem. Int. Ed.* **1999**, *38*, 3418c) H. Buschmann, R. Thede, D. Heller, *Angew. Chem.* **2000**, *112*, 4197; *Angew. Chem. Int. Ed.* **2000**, *39*, 4033; d) D. K. Kondepudi, K. Asakura, *Acc. Chem. Res.* **2001**, *34*, 946; e) M. Avalos, R. Babiano, P. Cintas, J. L. Jimenez, J. C. Palacios, *Chem. Commun.* **2000**, 887, and references therein.

[5] First publications: a) K. Soai, T. Shibata, H. Morioka, K. Choji, *Nature* **1995**, *378*, 767; b) T. Shibata, K. Choji, T. Hayase, Y. Aizu, K. Soai, *Chem. Commun.* **1996**, 1235; c) T. Shibata, H. Morioka, T. Hayase, K. Choji, K. Soai, *J. Am. Chem. Soc.* **1996**, *118*, 471; for a recent review, see: K. Soai, I. Sato, *Chirality* **2002**, *14*, 548.

[6] a) D. G. Blackmond, C. R. McMillan, S. Ramdeehul, A. Schorm, J. M. Brown, *J. Am. Chem. Soc.* **2001**, *123*, 10103; b) D. G. Blackmond, *Adv. Synth. Catal.* **2002**, *344*, 156; c) F. G. Buono, D. G. Blackmond, *J. Am. Chem. Soc.* **2003**, *125*, 8978.

[7] a) C. Puchot, O. Samuel, E. Duñach, S. Zhao, C. Agami, H. B. Kagan, *J. Am. Chem. Soc.* **1986**, *108*, 2353; b) D. Guillaneux, S. H. Zhao, O. Samuel, D. Rainford, H. B. Kagan, *J. Am. Chem. Soc.* **1994**, *116*, 9430.

[8] Reactions in toluene, diethyl ether, and toluene/diethyl ether mixtures show complete conversion of aldehyde **1** into the alkylation product **2** upon workup. Reactions in THF show significant side reactions, including reduction to the primary pyrimidyl alcohol.

[9] K. Soai, L. Sato, T. Shibata, S. Komiya, M. Hayashi, Y. Matsueda, H. Imamura, T. Hayase, H. Morioka, H. Tabira, J. Yamamoto, Y. Kowata, *Tetrahedron: Asymmetry* **2003**, *14*, 185.

[10] For an asymmetric autocatalytic reaction exhibiting no non-linearity, the enantiomeric excess at the end of the reaction ($ee_{\text{cat,end}}$) is given by Equation (1), in which $ee_{\text{cat,0}}$ is the initial catalyst *ee*, ee_{prod} is the intrinsic enantioselectivity of the reaction, and x_{cat} is the mole fraction of catalyst used in the reaction. See reference [6b] for a derivation.

$$ee_{\text{cat, end}} = ee_{\text{cat, 0}}\left(x_{\text{cat}}\right)^{1-ee_{\text{prod}}} \qquad (1)$$

[11] C. Bolm, G. Schlinghoff, K. Harms, *Chem. Ber.* **1992**, *125*, 1191.

[12] D. A. Singleton, L. K. Vo, *J. Am. Chem. Soc.* **2002**, *124*, 10010.

[13] The similarity in the rate profiles and asymmetric amplification observed for reactions carried out under similar conditions in diethyl ether, toluene, and toluene/diethyl ether mixtures, and their compliance with the model proposed in reference [6c], suggest that the reactive intermediate itself may be similar in different solvents.

[14] I. D. Gridnev, J. M. Serafimov, H. Quiney, J. M. Brown, *Org. Biomol. Chem.* in press.

[15] J. S. Siegel, *Nature* **2002**, *419*, 346.