Acidity effect in the regiochemical control of the alkylation of phenol with alkenes

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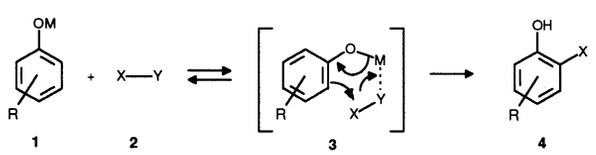
Treatment of 1:1 mixtures of phenol and linear alkenes in the presence of an acidic promoter in $CHCl_3$ at room temperature results in *ortho*-regioselective monoalkylation producing *sec*-alkylphenols in 48–60% yield. In similar reactions, branched alkenes lead exclusively to the corresponding *para*-*tert*-alkylphenols in 80–85% yield. Addition of increasing amounts of potassium phenolate to the reacting system reduces the protic acidity and promotes *ortho*-regioselective *tert*-alkylation. These results are tentatively explained in terms of competition of 'H-bond-template' and 'charge-controlled' mechanisms.

The regiochemical control of the electrophilic alkylation of aromatic substrates has been the subject of intensive synthetic and theoretical investigations.[1] Traditionally, alkyl halides, alcohols, ethers, esters and alkenes have been utilized as alkylating agents and protic or Lewis acids have been utilized to promote the reaction.[2] In the particular case of the protic acid-promoted alkylation of phenol with alkenes, it is well established that the reaction leads initially to predominantly 4-substituted products when the *para* position is available for reaction, *ortho* derivatives being formed only when the *para* position is already occupied or by further substitution to give 2,4- and 2,4,6-trialkylphenols. However the *ortho*-directing effect of the OH group has been utilized in the aluminium phenolate catalyzed *tert*-alkylation of phenol affording *ortho*-*tert*-butylphenol in preference to the *para* isomer.[3]

In previous studies we have reported a series of metal-driven *ortho*-regioselective electrophilic substitutions on metal phenolates with different electrophilic reagents such as aldehydes,[4] ketones,[5] acyl chlorides[6] and nitriles.[7]



Scheme 1

The results showed that the oriented complex **3**, formed between the phenolate **1** and the electrophilic reagent **2**, activates both reagents and promotes complete *ortho*-regioselective control.

We undertook the present study to obtain information about the role played by the acidity of the reacting system on the regiochemical control of the alkylation of phenol with alkenes.

Results and discussion

First we examined the influence of different acid promoters in the model reaction between phenol and hex-1-ene in dry chloroform purged from ethanol (see Experimental section) at 25 °C for 10 h. The experimental conditions for carrying out the reaction were quite simple. The chloroform solution of phenol was added to a stirred mixture of the selected acid in chloroform in a closed reaction flask and this was followed by slow addition of **6** in the same solvent. Results are reported in Table 1.

It is apparent from Table 1 that the reactivity of the system is quite sensitive to the acid utilized, $AlCl_3$ being the best promoter of the process in agreement with previous reports from the literature concerning the alkylation of arenes with alkenes.[3]

In all cases 2-*sec*-hexylphenol **7** was obtained accompanied by minor amounts of 2,6-di-*sec*-hexylphenol **9**.† The exceptional activation effect toward *ortho*-regioselective alkylation of the present system was further showed by some additional experiments. Thus, compound **9** was obtained in 82% yield by carrying out the reaction with an excess of hex-1-ene. In addition to mono- and di-alkylation products, variable quantities of 2-chlorohexane **10**, were detected in all experiments. Compound **10** was recovered as the major product (65% yield) when HCl (molar ratio PhOH : HCl = 1 : 1) was utilized as the protic acid promoter (entry c). 2-Chlorohexane is not an alkylating agent, since its reaction with phenol and $AlCl_3$ under the same conditions resulted in complete recovery of unchanged starting materials. Moreover, the use of CF_3SO_3H as the catalyst resulted in the production of a mixture of *ortho*- and *para*-*sec*-hexylphenols.

As expected, by allowing dichloroaluminium phenolate (which is not a potential proton source) to react with hex-1-ene all the starting phenol was recovered unchanged (entry e). By contrast, addition of phenol to the unreactive dichloroaluminium phenolate (molar ratio 1 : 1) resulted in promotion of the exclusive *ortho*-alkylation in moderate yield (16%) (entry b).

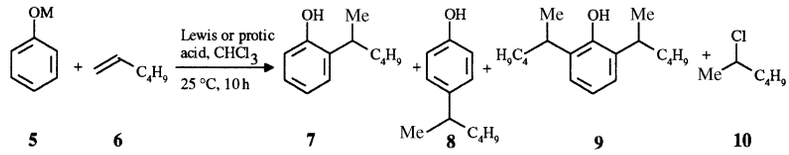
In a series of further experiments, different alkenes were treated with phenol under the same experimental conditions. Results are listed in Table 2. It clearly appears that all linear alkenes react exclusively at the *ortho*-position of the phenol ring in good yield (entries a–e). In contrast, the reaction with branched alkenes resulted in the exclusive production of *para*-alkylphenols in higher yield (entries f–h). The essential mechanisms of the reactions with both linear and branched alkenes are depicted in Scheme 2.

As earlier reported in the literature, the phenol reacts with $AlCl_3$ in non-polar solvents giving the donor–acceptor complex **15** which is a strong Brönsted acid.‡ Compound **15** can equilibrate with dichloroaluminium phenolate **16** by loss of HCl; it is reasonable to suppose that hydrogen bonding between **15** and

† Isomerization of the double bond of the alkene would be expected to occur under acidic conditions producing all possible 2-hydroxyphenylhexanes; however, due to the mild experimental conditions, only products **7** and **9** were recovered.

‡ It was demonstrated that aluminium alkoxides and phenoxides can coordinate a molecule of alcohol or phenol to form acid solutions. Although the acid $HAl(OR)_4$ could not be isolated, a similar complex has been isolated and characterized with titanium phenoxide: G. W. Svetich and A. A. Voge, *Acta Crystallogr., Sect. B*, 1972, **28**, 1760.

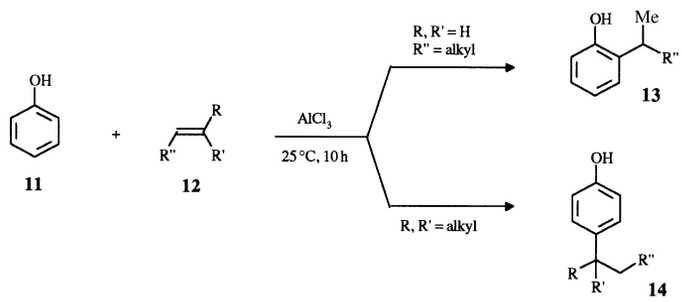
Table 1 Reaction of phenol with hex-1-ene in the presence of different acidic promoters[a]



Entry	M	Acidic promoter	Recovered **5** (%)	**7** Yield (%)	**8** Yield (%)	**9** Yield (%)	**10** Yield (%)
a	H	$AlCl_3$	33	62	—	4	Ne[b]
b	H	$PhOAlCl_2$	82	16	—	1	Ne
c	H	HCl[c]	90	5	—	—	65
d	H	CF_3SO_3H[d]	40	20	18	5	Ne
e	$AlCl_2$	—	99	—	—	—	Ne

[a] All reactions were carried out in a closed vessel and the reagent **6** was added dropwise during 2 h; the molar ratio $PhOH:MX_n:$**6** was 1:1:1. [b] Not estimated. [c] Molar ratio PhOH:HCl:**6** = 1:1:1. [d] 15% of a mixture of isomerized hexylphenols was detected by gas-mass analysis.

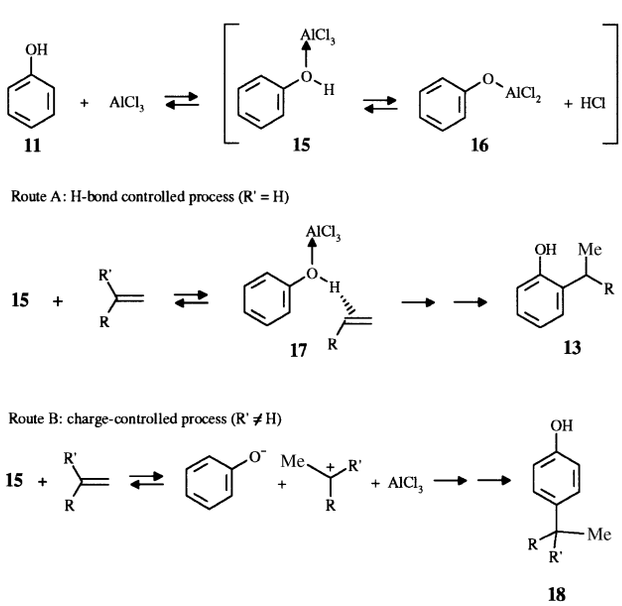
Table 2 Reaction of phenol with different alkenes in the presence of $AlCl_3$



Entry	R	R′	R″	Recovered **11** (%)	**13** Yield (%)	**14** Yield (%)
a	H	Et	H	59	45	—
b	H	Bu	H	36	60	—
c	H	C_6H_{13}	H	36	59	—
d	H	$C_{10}H_{21}$	H	44	52	—
e	H	$-C_4H_8-$		49	48	—
f	Me	Me	H	13	—	85
g	Me	Me	Me	16	—	82
h	Me	$-C_4H_8-$		17	—	80

the alkene gives rise to the complex **17**.§ This interaction has two effects: the simultaneous activation of both the alkene (by H-bonding) and the phenol (by loosening the O–H bond) and the association of the partners in a complex with a favourable geometry for concerted *ortho*-specific alkylation (Route A).[3] The observation that *para*-alkylation mainly occurs when alkylating agents such as isobutene, 2-methylbut-2-ene and 1-methylcyclohexene were used, leads us to the suggestion that *para*-alkylation is diagnostic of the intermediacy of carbonium ions¶ which reacts with phenol by a process involving reversible *O*- and *C*-attack followed by the predominant formation of the thermodynamically more stable 4-*tert*-alkylphenol at equilibrium (Route B).[8] In connection with this study we have recently demonstrated that under controlled conditions 2,4-di-*tert*-butylphenol undergoes selective and exclusive $AlCl_3$-promoted *ortho*-de-*tert*-butylation.[9]

If such are the mechanisms of the activation of both reagents, one may expect a different regiochemical behaviour in the *tert*-alkylation process, by reducing the Brönsted acidity of the complex **15** and disfavouring the charge-controlled mechanism.

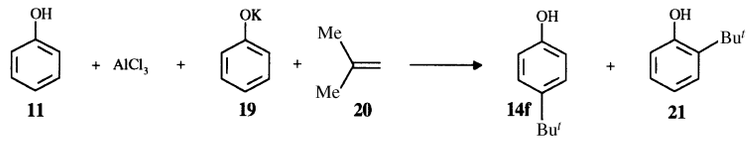


Scheme 2

§ Previous IR spectroscopy studies suggested that π electrons of double and triple bonds are comparable acceptors of hydrogen bonds: S. A. McDonald, G. L. Johnson, B. W. Keelan and L. Andrews, *J. Am. Chem. Soc.*, 1980, **102**, 2892; L. W. Buxton, P. D. Aldrich, J. A. Shea, A. L. Legon and W. H. Flygare, *J. Chem. Phys.*, 1981, **75**, 2651.

¶ *tert*-Butyl cations were recognized in both the solid state and the gas phase: (*a*) S. Hollestein and T. Laube, *J. Am. Chem. Soc.*, 1993, **115**, 7240; (*b*) M. E. Crestoni and S. Fornarini, *J. Am. Chem. Soc.*, 1994, **116**, 7240.

Table 3 Reaction of phenol with isobutene in the presence of $AlCl_3$* and different amounts of potassium phenolate



Entry	**19**/**11**	Recovered phenol (%)	**14f** Yield (%)	**21** Yield (%)	(**21**–**14f**)/(**21** + **14f**) × 100
a	0.000	19	78	—	−100
b	0.100	23	71	1	−97
c	0.200	28	60	8	−76
d	0.225	31	42	24	−27
e	0.250	36	29	31	3
f	0.275	39	19	38	33
g	0.300	45	7	43	72
h	0.400	52	1	43	95
i	0.500	57	—	40	100
j	0.750	60	—	38	100
k	1.000	61	—	36	100

* Molar ratio **11**/$AlCl_3$ = 1.

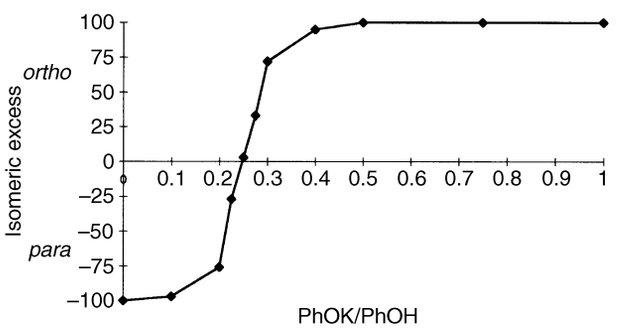


Fig. 1 Diagram of the *ortho/para* isomeric excess (%) in the reaction of phenol with isobutene in the presence of increasing amounts of potassium phenolate

Thus phenol, $AlCl_3$ and isobutene (molar ratio 1:1:1) were allowed to react under the same conditions as those described for the preceding experiments but in the presence of increasing amounts of potassium phenolate (PhOK) which could react replacing HCl with phenol. Results of these experiments are reported in Table 3 and Fig. 1

In the absence of PhOK the reaction proceeds with 81% conversion and a 78% yield of *para-tert*-butylphenol **14f**, while in the presence of PhOK, mixtures of *para*- and *ortho-tert*-butylphenols **14f** and **21** were produced. The composition of these mixtures depends on the PhOK/PhOH ratio. Two interesting trends are apparent from the experimental data reported. First, the reactivity of the present system seems to be governed by the protic acidity effect: as the PhOK/PhOH molar ratio becomes higher, the phenol conversion decreases. Second, an increase in the *ortho/para tert*-butylation ratio resulted upon addition of increasing amounts of PhOK to the reaction mixture. *ortho-tert*-Butylphenol **21** was obtained as the sole product in 40% yield by using a 0.5 PhOK/PhOH ratio. The regioselectivity variation as a function of the PhOK/PhOH ratio is shown in Fig. 1. The S-shaped curve obtained shows an inflection point when the PhOK/PhOH ratio is 0.25. This is in contrast with a typical salt effect; in fact, addition of a salt to the reaction mixture increases the dielectric constant. This effect would be predicted to increase the rate of *para*- relative to *ortho*-alkylation.[10]

Finally, attempted alkylation by isobutene of a 1:1 mixture of PhOK and $AlCl_3$ resulted in complete recovery of the starting reagents.

These results indicate that the different positional selectivities observed can be explained in terms of the different mechanisms involved: thus, *ortho*- and *para*-alkylation are obtained through 'H-bond template'[11] or 'charged-controlled' mechanisms,‖ respectively. Our results also indicate that it is possible to promote such processes selectively by varying the basicity of the alkene or the protic acidity of the complex involving the phenolic substrate and the Lewis acid.

Experimental

Bps and mps were obtained on a Gallenkamp melting-point apparatus. IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AC 300 spectrometer at 300 MHz and on a Varian EM 360 spectrometer at 60 MHz.

Chemical shifts are expressed in ppm relative to tetramethylsilane as internal standard and *J* values are expressed in Hz. Mass spectra were recorded on a Varian MAT CH 5 spectrometer in EI mode at 70 eV. Microanalyses were carried out by Dipartimento di Chimica Generale ed Inorganica, Chimica Analitica, Chimica Fisica dell'Università di Parma. TLC analyses and chromatography were performed on Merck PF_{254} silica gel using hexane–ethyl acetate (90:10) as eluent. Quantitative analyses were performed on a Dani 3900 gaschromatograph equipped with SE 52 capillary column. All reagents were of commercial quality from freshly opened containers. Chloroform was washed 15 times with water, dried (Na_2SO_4), distilled twice and kept over molecular sieves before use.

Synthesis of the alkylphenols 13 and 14: general procedure

A solution of phenol (0.94 g, 10 mmol) in dry $CHCl_3$ (30 ml) was added dropwise, under nitrogen, to a stirred suspension of $AlCl_3$ (1.33 g, 10 mmol) in dry $CHCl_3$ (30 ml). After 30 min a solution of the selected alkene (10 mmol) in dry $CHCl_3$ (30 ml) was added to the mixture over 30 min. The stirring was continued at room temperature for 10 h after which the reaction was quenched by addition of 10% aqueous HCl (100 ml) to the mixture which was then extracted with diethyl ether (3 × 100 ml). The combined extracts were dried (Na_2SO_4) and evaporated and the residue was subjected to preparative TLC with hexane–ethyl acetate (90:10) to give the products.

Reaction of isobutene with phenol in the presence of potassium phenolate: general procedure

A solution of phenol (0.94 g, 10 mmol) in dry $CHCl_3$ (30 ml) and potassium phenolate were successively added, under nitro-

‖ Control in the relative electrophilicity of alkylating agents by variation of the Lewis acid concentration has been previously reported: H. Mayr, C. Schade, M. Rulbow and R. Schneider, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 1029.

gen, to a stirred suspension of $AlCl_3$ (1.33 g, 10 mmol) in dry $CHCl_3$ (30 ml). After 30 min a titred solution of isobutene (10 mmol) in dry $CHCl_3$ (30 ml) was added to the mixture over 30 min. The stirring was continued for 10 h at room temperature after which the reaction was quenched by the addition of saturated aqueous NH_4Cl (100 ml) to the mixture which was then extracted with diethyl ether (3 × 100 ml). The combined extracts were dried (Na_2SO_4) and evaporated and the residue was subjected to preparative TLC with hexane–ethyl acetate (90 : 10) to give the products.

2-(1-Methylpentyl)phenol 7. Pale yellow oil, bp 82–84 °C/0.1 mmHg (lit.,[12] bp 60 °C/0.01 mmHg).

2,6-Bis(1-Methylpentyl)phenol 9. Pale yellow oil (Found: C, 82.3; H, 11.3. $C_{18}H_{30}O$ requires C, 82.4; H, 11.5%); ν_{max}(NaCl)/cm^{-1} 3420; δ_H (60 MHz; $CDCl_3$) 0.7–1.0 (6 H, m, 2 CH_2CH_3), 1.0–1.8 (18 H, m, 2 CH_3 and 6 CH_2), 2.85 (2 H, m, *J* 7.0, 2 CH), 4.62 (1 H, s, OH) and 6.7–7.1 (3 H, m, H-arom); *m/z* 262 (M^+, 10%), 205 (100) and 191 (14).

4-(1-Methylpentyl)phenol 8. Pale yellow oil, bp 92–94 °C/0.1 mmHg (lit.,[12] bp 80 °C/0.05 mmHg).

2-(1-Methylpropyl)phenol 13a. Pale yellow oil, bp 224–226 °C (bp of an authentic sample 226–228 °C).

2-(1-Methylheptyl)phenol 13c. Pale yellow oil, bp 72–75 °C/0.05 mmHg (lit.,[13] bp 129–132 °C/2 mmHg).

2-(1-Methylundecyl)phenol 13d. Pale yellow oil, bp 150–153 °C/0.05 mmHg (Found: C, 82.6; H, 11.7. $C_{18}H_{30}O$ requires C, 82.4; H, 11.5%); ν_{max}(NaCl)/cm^{-1} 3420; δ_H (300 MHz; $CDCl_3$) 0.83 (3 H, t, *J* 7.1, CH_2CH_3), 1.1–1.7 (21 H, m, CH_3CH and 9 CH_2), 3.00 (1 H, m, *J* 7.0, CH), 4.69 (1 H, s, OH), 6.67 (1 H, d, *J* 7.5, H-arom), 6.84 (1 H, t, *J* 7.5, H-arom), 6.99 (1 H, t, *J* 7.5, H-arom), 7.10 (1 H, d, *J* 7.5, H-arom); *m/z* 262 (M^+, 31%), 135 (29), 121 (100) and 107 (70).

2-Cyclohexylphenol 13e. Pale yellow solid, mp 55–57 °C (lit.,[14] mp 56–57 °C).

4-*tert*-Butylphenol 14f. White solid, mp 96–98 °C (mp of an authentic sample 98–99 °C).

4-(1,1-Dimethylpropyl)phenol 14g. White solid, mp 90–93 °C (mp of an authentic sample 91–94 °C).

4-(1-Methylcyclohexyl)phenol 14h. White solid, mp 111–113 °C (lit.,[15] mp 112.5 °C).

2-*tert*-Butylphenol 21. Colourless oil, bp 218–220 °C (bp of an authentic sample 221 °C).

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References

1 (*a*) G. A. Olah, *Angew. Chem., Int. Ed. Engl.*, 1973, **12**, 173; (*b*) R. M. Roberts and A. A. Khalaf, *Friedel-Crafts Alkylation Chemistry*, M. Dekker Inc., New York, 1984; (*c*) A. Iraqi, R. Gallo and R. Phan Tan Luu, *Bull. Soc. Chim. Fr.*, 1988, 548; (*d*) R. Taylor, *Electrophilic Aromatic Substitution*, Wiley, New York, 1990.

2 (*a*) G. Sartori, F. Bigi, G. Casiraghi, G. Casnati, L. Chiesi and A. Arduini, *Chem. Ind.* (*London*), 1985, 762; (*b*) G. A. Olah, R. Krishnamurti and G. K. Surya Prakash, Friedel-Crafts Alkylations, in *Comprehensive Organic Synthesis*, B. M. Trost, I. Fleming eds, Pergamon Press, Oxford, 1991, vol. 3, pp. 292–339; (*c*) J. Tateiwa, T. Nishimura, H. Horiuchi and S. Uemura, *J. Chem. Soc., Perkin Trans. 1*, 1994, 3367; (*d*) P. E. Gheorhiou and M. Ashram, *J. Org. Chem.*, 1995, **60**, 2909; (*e*) M. Yamaguchi, A. Hayashi and M. Hirama, *J. Am. Chem. Soc.*, 1995, **117**, 1151; (*f*) T. Kondo, S. Kajiya, S. Tantayanon and Y. Watanabe, *J. Organomet. Chem.*, 1995, **489**, 83.

3 (*a*) A. J. Kolka, J. P. Napolitano, A. H. Filbey and G. G. Ecke, *J. Org. Chem.*, 1957, **22**, 462; (*b*) Ya. B. Kozlekovskii, V. A. Koshchii and T. F. Ovsiyuk, *Zh. Org. Khim*, 1989, **25**, 55; (*c*) J. A. M. Laan, F. L. L. Giesen and J. P. Ward, *Chem. Ind* (*London*), 1989, 354.

4 G. Casnati, G. Casiraghi, A. Pochini, G. Sartori and R. Ungaro, *Pure Appl. Chem.*, 1983, **55**, 1677.

5 G. Casiraghi, G. Casnati, G. Sartori and L. Bolzoni, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2027.

6 G. Sartori, G. Casnati, F. Bigi and G. Predieri, *J. Org. Chem.*, 1990, **55**, 4371.

7 F. Bigi, R. Maggi, G. Sartori, G. Casnati and G. Bocelli, *Gazz. Chim. Ital.*, 1992, **122**, 283.

8 (*a*) N. B. Nevrekar, S. R. Sawardekar, T. S. Paudit and N. A. Kudav, *Chem. Ind.*, 1983, 206; (*b*) M. Bataille and J. Landais, *C.R. Acad. Sci.* (*Paris*), 1973, **276**, 1305.

9 G. Sartori, F. Bigi, R. Maggi and C. Porta, *Tetrahedron Lett.*, 1994, **35**, 7073.

10 P. G. Duggan and W. S. Murphy, *J. Chem. Soc., Perkin Trans. 2*, 1975, 1291.

11 (*a*) D. V. Banthorpe, *Chem. Rev.*, 1970, **70**, 295; (*b*) K. Norrman and T. B. McMahon, *J. Am. Chem. Soc.*, 1996, **118**, 2449.

12 G. G. S. Dutton, M. E. D. Hillman and J. G. Moffatt, *Can. J. Chem.*, 1964, **42**, 482.

13 Röhm & Hass Co., U.S.P. 2098203, 1937 (*Chemisches Zentralblatt*, 1938, **I**, 1457).

14 S. Skraup and W. Beifuss, *Chem. Ber.*, 1927, **60**, 1070.

15 W. Schrauth and K. Quasebarth, *Chem. Ber.*, 1924, **57**, 857.

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