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Novel rearrangement of secondary alkoxyalkyl radicals during addition to a double bond. Steric shielding in the formation of tertiary alkoxyethyl radicals

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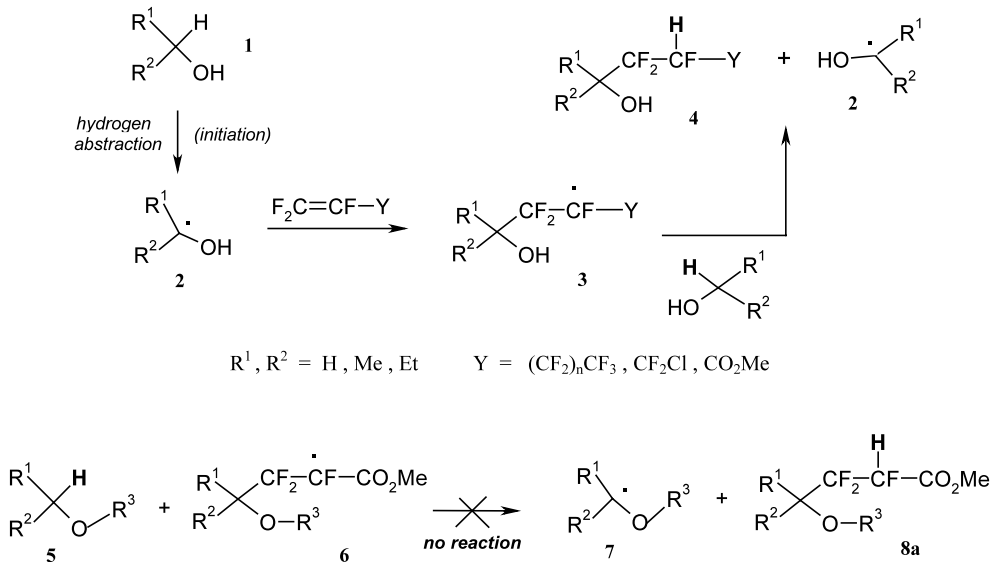
Abstract—The participation of a 1,3-hydrogen shift in initially formed secondary alkoxyethyl radicals $R^1R^2CH\text{-}O\text{-}CH^{\bullet}\text{-}CH_3$ during their free-radical chain additions to methyl 2,3,3-trifluoroacrylate has been confirmed using a deuterium marked additive. Indirect evidence has been obtained for a partial 1,3-hydrogen shift in secondary radicals $CH_3(CH_2)_n\text{-}CH^{\bullet}\text{-}O\text{-}CH_3$ to primary radicals $CH_3(CH_2)_n\text{-}CH_2\text{-}O\text{-}CH_2^{\bullet}$. Initial formation of tertiary alkoxyethyl radicals $R^1R^2C^{\bullet}\text{-}O\text{-}CHR^3R^4$ in the propagation step was not observed due to steric factors.

1. Introduction

In radical additions, intermediate free radicals are formed by the energetically most convenient path. They can be thermodynamically stable under the reaction conditions, but they can also be unstable and rearrange before a subsequent reaction step. The reasons for the formation of unstable intermediate radicals in solution are usually chemical, e.g. homolytic cleavage of unstable bonds or abstraction of more weakly bounded atoms. Unstable radicals can also be formed for stereochemical reasons, when e.g. hydrogen abstraction at an energetically favourable site is sterically shielded resulting in a higher activation energy than the cleavage of a C–H bond with higher bond energy.



Scheme 1.

Keywords: alkoxyalkyl radicals; radical rearrangement; radical addition.

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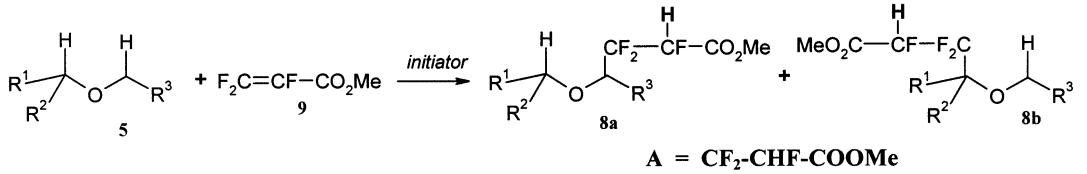
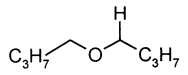
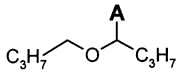
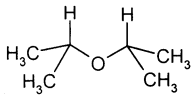
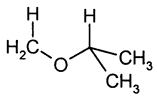
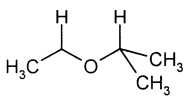
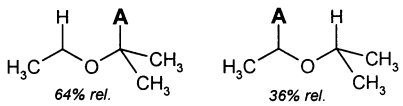
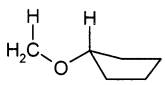
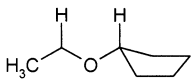
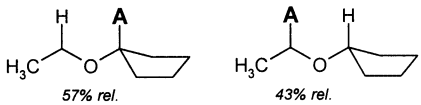
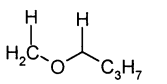
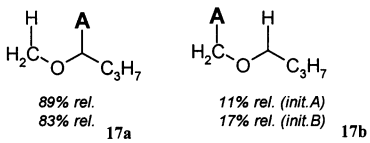
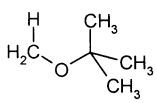
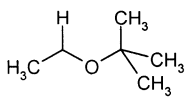
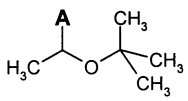
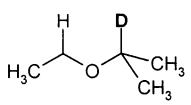
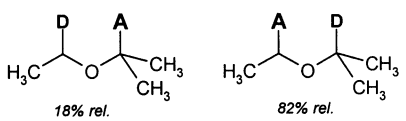
Table 1. Products of radical additions of ethers to methyl 2,3,3-trifluoroacrylate (**6**)



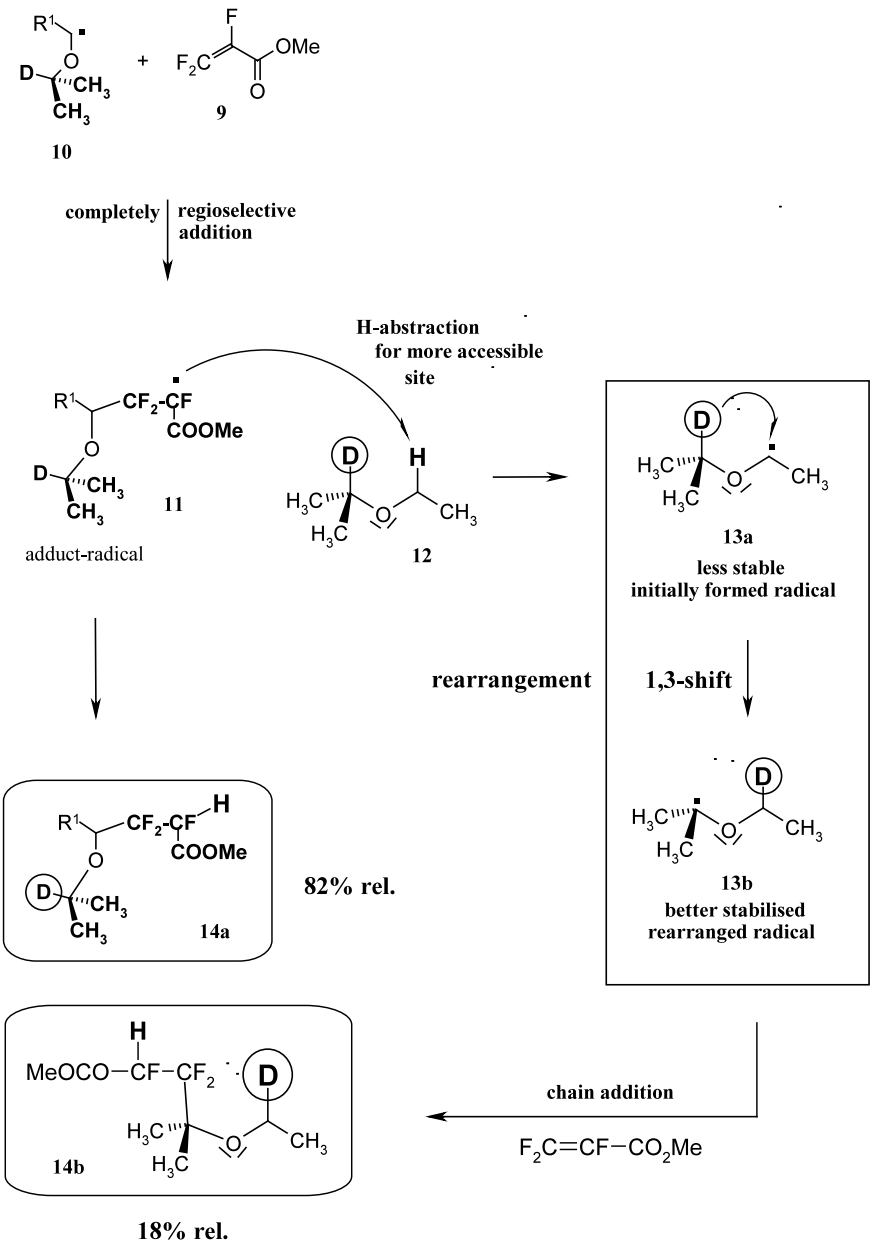
A = CF_2-CHF-COOMe

	Additive	Initiator[a]	Yield[b] (%)	Products (Yields)
/1/		B	71	
/2/		A B	-	no reaction observed
/3/		A B	-	no reaction observed
/4/		A	76	 64% rel. 36% rel.
/5/		A B	-	no reaction observed
/6/		B	69	 57% rel. 43% rel.
/7/		A B	66 82	 89% rel. 83% rel. **17a** 11% rel. (init.A) 17% rel. (init.B) **17b**
/8/		A B	-	no reaction observed
/9/		B	75	
/10/		A	64	 18% rel. 82% rel.

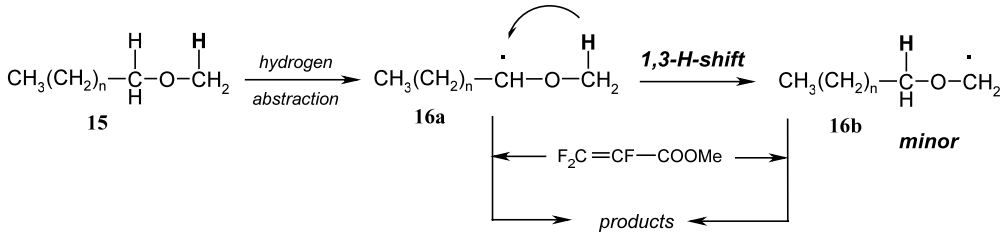
[a] Initiation: A – UV light; B – mixture AIBN/DBP; [b] isolated yield.

One of the general processes of radical stabilisation has been a 1, *n*-hydrogen shift. Rearrangements of radicals in solutions have been thoroughly reviewed.[1] Quantum chemical calculations of activation enthalpies for 1, *n*-hydrogen migrations in alkyl radicals[2] revealed that the 1,5- and 1,6-hydrogen shifts are energetically more favourable than the 1,4-, 1,3- or 1,2- shifts. Nevertheless, 1,3-hydrogen shifts in radicals in solution have been observed. The first type of 1,3-shift included rearrangements of initially formed radicals, e.g. shifts in the carbon chain of alkyl radicals,[3] a 3,3-dichloropropyl radical,[4] (2-methylphenyl) radicals,[5] and carboxylic ester radicals.[6] The second type of 1,3-shift included rearrangements of adduct radicals, e.g. in additions of benzyl radicals to unsaturated carboxylic esters,[7] of 1,3-dioxolane or hydroxy radicals to but-2-ynedioic acid,[8] and telomerization of unsaturated esters.[9] Rearrangements of alkoxyethyl radicals in solution, to our knowledge, have not been reported so far.

We have observed unusual reactivity of dialkyl and alkyl cyclopentyl ethers in the free-radical chain addition reaction to methyl 2,3,3-trifluoroacrylate. The observed reactivity is different to that of alkanols. Secondary alkanols add easily under radical initiation to olefins possessing the trifluorovinyl grouping as in alkenes[10,11] or unsaturated carboxylic esters.[12] In the additions of secondary alkanols **1** (Scheme 1), hydrogen is abstracted via external attack and tertiary hydroxy radicals **2** are generated that add to fluoroolefins to form secondary adduct-radicals **3**. These relatively bulky radicals abstract hydrogen from alkanols **1** with the formation of adducts **4** and generation of the tertiary hydroxy radicals **2**. In contrast to this



Scheme 2.



Scheme 3.

behaviour of secondary alkanols, we have evidence that dialkyl ethers **5** having a secondary α-carbon do not form tertiary alkoxy radicals **7** by direct hydrogen abstraction by the adduct-radicals **6** (Scheme 1).

2. Results and discussion

In this study of rearrangements of secondary alkoxy radicals, methyl 2,3,3-trifluoroacrylate (**9**) was used as the olefinic compound because additions of nucleophilic radicals to this substrate are known to be easy and completely regioselective.[12a] UV light and/or AIBN/DBP were applied as initiators. The results are summarised in Table 1.

Dibutyl ether possessing a primary α-carbon added[13] to **9** affording one 1:1 addition product (entry /1/). In contrast, diisopropyl ether did not react using both kinds of initiation (entry /2/), which meant that hydrogen abstraction at the tertiary α-carbon did not occur. Analogous negative results were obtained for methyl isopropyl ether (entry /3/), methyl cyclopentyl ether (entry /5/) and methyl *tert*-butyl ether (entry /8/). From these experiments it can be concluded that radicals are not formed by hydrogen abstraction at the tertiary α-carbon or at the methyl group in the ethers.

On the other hand, all ethyl alkyl or cycloalkyl ethers afforded addition products. A positive result in the case of ethyl *tert*-butyl ether (entry /9/) confirms that an α-radical species is formed at the ethyl group. However, how can the predominant formation of products (type **8b**, Table 1) formed by the addition of tertiary alkoxy radicals in entries /4/ and /6/ be explained? The hypothesis could be as follows: the radicals are primarily formed at the ethyl groups, the tertiary α-radicals **7** being formed by a rearrangement, a 1,3-hydrogen shift. To verify this hypothesis, we used deuterated ethyl isopropyl ether (entry /10/). The results confirmed the hypothesis—no deuterium was detected in the fluorinated part in the adducts, i.e. no deuterium abstraction occurred at the isopropyl group of the ether **12**. The novel rearrangement is depicted in Scheme 2: initially formed alkoxyethyl radical **10** adds to the trifluoroacrylate **9** to afford the adduct–radical **11**. The bulky radical **11** is terminated by hydrogen abstraction from the ethyl group of the starting ether **12** to form product **14a** as the C–D bond in the isopropyl group is sterically shielded. The primarily formed secondary radical **13a** rearranges by a 1,3-hydrogen shift to give the tertiary alkoxyethyl radical **13b**, which subsequently adds to trifluoroacrylate **9** to afford the product **14b**. The amount of the product **14b** (18% rel.), formed by the addition of the rearranged radical (Table 1, entry /10/) is much smaller than that in the reaction of the non-deuterated ethyl isopropyl ether (64% rel., entry /4/). This difference can be explained by a primary deuterium isotope effect. We also observed that the reaction of the deuterated ether **12** proceeded at approximately a third of the rate of the non-deuterated compound.

Suprising results were obtained in the addition of butyl methyl ether (Table 1, entry /7/; Scheme 3): the ether **15** afforded products of reactions of both the butyl and methyl groups. As the reaction did not take place at the methyl groups in methyl isopropyl ether (entry /3/), methyl cyclopentyl ether (entry /5/) or methyl *tert*-butyl ether (entry /8/), the explanation must be that an alkoxymethyl radical **16b** was formed by a partial rearrangement of the initially formed secondary radical **16a** at the butyl group (Scheme 3). The study of the rearrangements is being continued.

The structures of the addition products (Table 1) were elucidated on the basis of ^{1}H, ^{19}F, ^{13}C NMR and MS spectra and microanalyses.[13] Diastereoisomeric adducts could be recognised in the NMR spectra.

Acknowledgements

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13. **Typical procedures**

Procedure A: The reactions were carried out in a round-shaped two-necked (with septa) quartz cell (diameter 5 cm, thickness 1.5 cm, plane-parallel sites) irradiated externally by a medium pressure UV lamp (Tesla, RVK 250 W), placed in a reflecting-metal cylindrical housing, with a round window (diameter 5 cm). The cell was charged with fluoroacrylate **9** (2.13 g, 15.2 mmol) butyl methyl ether (29.1 g, 330 mmol) and the solution was deaerated with nitrogen at −50°C for 15 min. The cell was irradiated until the conversion of **9** was above 95% (check by GC). Unreacted volatile components were distilled off in vacuum, the residue was mixed with methylene chloride (15 mL). The solution was washed with a water solution of $NaHCO_3$ (2×10 mL) and dried over $MgSO_4$. Methylene chloride was removed (rotary evaporator) and the residue distilled in vacuum to afford a mixture of regioisomeric adducts **17a** (89% rel.) and **17b** (11% rel.), yield 2.74 g; (79%), bp 52–54°C/0.3 mmHg. Analysis: found: C, 47.07; H, 6.67. $C_9H_{15}F_3O_3$ requires: C, 47.37; H, 6.63.

Procedure B: A three-necked round-bottom flask equipped with a Dimroth reflux condenser combined with a bubbler was charged with fluoroacrylate **9** (2.10 g, 15. mmol) and butyl methyl ether (30 g, 294 mmol) and the mixture was deaerated with a stream of nitrogen at −20°C for 15 min. A mixture of dibenzoyl peroxide and AIBN (2 and 2 mol%) was added to the flask and the reaction mixture under nitrogen was heated to reflux, which was continued until ca. 95% conversion of **9** (check by GC). The reaction mixture was then treated as above to afford the products **17a** and **17b** in the ratio of 83 and 17% rel.

Methyl 4-methoxy-2,3,3-trifluoroheptanoate (17a):

Content of diastereoisomers: Procedure A, 58 and 42% rel.; *Procedure B*, 62 and 38% rel.

^{1}H NMR ($CDCl_3$): δ 0.95 (t, 3H, CH_3CH$_2$, ds$_1$, $^3J_{HH}$ = 7.2); 0.96 (t, 3H, CH_3CH$_2$, ds$_2$, $^3J_{HH}$ = 7.1); 1.50–1.72 (m, 4H, CH$_3$CH_2CH_2, ds$_1$, ds$_2$); 3.43 (s, 3H, OCH$_3$, ds$_1$); 3.47 (s, 3H, OCH$_3$, ds$_2$); 3.72–3.85 (m, 1H, CHCF$_2$, ds$_1$, ds$_2$); 3.60 (s, 3H, COOCH$_3$, ds$_2$); 3.65 (s, 3H, COOCH$_3$, ds$_1$); 5.08 (ddd, 1H, CHF, ds$_2$, $^2J_{HF}$ = 46.7, $^3J_{HF}$ = 10.4, $^3J_{HF}$ = 9.3); 5.14 (ddd, 1H, CHF, ds$_1$, $^2J_{HF}$ = 46.2, $^3J_{HF}$ = 19.8, $^3J_{HF}$ = 3.3) ppm.

^{13}C NMR ($CDCl_3$): δ 13.93 (s, CH$_3$CH$_2$, ds$_1$, ds$_2$); 18.76 (s, CH$_3$$CH_2$, ds$_1$, ds$_2$); 29.73 (s, CH$_3CH_2$$CH_2$, ds$_2$); 30.16 (s, CH$_3CH_2$$CH_2$, ds$_1$); 52.76 (s, OCH$_3$, ds$_1$, ds$_2$); 59.77 (s, COO$CH_3$, ds$_1$); 59.83 (s, COO$CH_3$, ds$_1$); 78.86 (dd, CHCF$_2$, ds$_1$, $^2J_{CF}$ = 23.5, $^2J_{CF}$ = 2.3); 79.23 (dd, CHCF$_2$, ds$_2$, $^2J_{CF}$ = 24.1, $^2J_{CF}$ = 4.0); 85.06 (ddd, CHF, ds$_1$, $^1J_{CF}$ = 191.8, $^2J_{CF}$ = 30.3, $^2J_{CF}$ = 26.3); 85.51 (ddd, CHF, ds$_2$, $^1J_{CF}$ = 193.6, $^2J_{CF}$ = 30.3, $^2J_{CF}$ = 21.2); 118.88 (dt, CF$_2$, ds$_1$, $^1J_{CF}$ = 256.0, $^2J_{CF}$ = 24.1); 118.93 (ddd, CF$_2$, ds$_2$, $^1J_{CF}$ = 256.2, $^1J_{CF}$ = 256.0, $^2J_{CF}$ = 24.1), 164.51–165.30 (m, CO, ds$_1$, ds$_2$).

^{19}F NMR ($CDCl_3$): δ −112.13 (ddt, 1F, CF$_2$, ds$_1$, $^2J_{FF}$ = 271.6, $^3J_{FH}$ = 10.7, $^3J_{FF}$ = $^3J_{FH}$ = 7.6); −116.49 (dddd, 1F, CF$_2$, ds$_2$, $^2J_{FF}$ = 271.6, $^3J_{FH}$ = 18.3, $^3J_{FF}$ = 12.2, $^3J_{FH}$ = 4.6); −121.17 (dddd, 1F, CF$_2$, ds$_2$, $^2J_{FF}$ = 271.6, $^3J_{FH}$ = 18.3, $^3J_{FF}$ = 7.6, $^3J_{FH}$ = 3.1); −121.33 (ddt, 1F, CF$_2$, ds$_1$, $^2J_{FF}$ = 271.6, $^3J_{FH}$ = 15.3, $^3J_{FF}$ = $^3J_{FH}$ = 9.2); −202.43 (dddd, 1F, CHF, ds$_2$, $^2J_{FH}$ = 45.8, $^3J_{FF}$ = 13.7, $^3J_{FF}$ = 7.6, $^4J_{FH}$ = 3.1); −205.18 (ddd, 1F, CHF, ds$_1$, $^2J_{FH}$ = 45.8, $^3J_{FF}$ = 11.2, $^3J_{FF}$ = 9.2) ppm.

GCMS (EI): 215 (0.25, M$^+$), 208 (0.5), 185 (8.0), 157 (1.5), 149 (5.5), 129 (3.5), 107 (5.0), 87 (72.5), 77 (5.0), 59 (24.0), 45 (100).

Methyl 4-butoxy-2,3,3,-trifluorobutanoate (17b)

^{1}H NMR ($CDCl_3$): δ 1.96 (t, 3H, CH_3CH$_2$, $^3J_{HF}$ = 6.6); 1.32–1.48 (m, 4H, CH$_3$CH_2CH_2); 3.48–3.60 (m, 2H, CH$_2$CF$_2$); 3.48 (t, 2H, CH$_2$O, $^3J_{HH}$ = 7.0); 3.85 (s, 3H, OCH$_3$); 5.14 (ddd, 1H, CHF, $^2J_{HF}$ = 46.2, $^3J_{HF}$ = 12.6, $^3J_{HF}$ = 7.7) ppm.

^{13}C NMR ($CDCl_3$): δ 13.657 (s, CH$_3$CH$_2$); 18.95 (s, CH$_3$$CH_2$); 31.39 (s, CH$_3CH_2$$CH_2$); 68.16 (t, CHCF$_2$, $^2J_{CF}$ = 29.8), 72.26 (s, CH$_2$$CH_2$O), 84.80 (ddd, CHF, $^1J_{CF}$ = 193.6, $^2J_{CF}$ = 32.1, $^2J_{CF}$ = 29.2), 117.85 (dt, CF$_2$, $^1J_{CF}$ = 250.2, $^2J_{CF}$ = 25.2) ppm.

^{19}F NMR ($CDCl_3$): δ −114.757 (dtt, 1F, CF$_2$, $^2J_{FF}$ = 270.1, $^3J_{FH}$ = 13.7, $^3J_{FF}$ = $^3J_{FH}$ = 7.6), −117.16 (dtt, 1F, CF$_2$, $^2J_{FF}$ = 270.1, $^3J_{FF}$ = $^3J_{HF}$ = 13.7, $^3J_{HF}$ = 10.7); −205.31 (dtt, 1F, CHF, $^2J_{HF}$ = 47.6, $^3J_{FF}$ = 10.7, $^4J_{HF}$ = 3.1) ppm.

GCMS (EI): 215 (0.25, M$^+$), 208 (2.0), 185 (0.5), 171 (0.5), 155 (44.5), 133 (6.0), 120 (2.5), 87 (13.0), 77 (7.0), 57 (100), 41 (40.5)