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# Long-chain (polyfluoroalkyl)oxacarbenes

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**Abstract**

3-Chloro-3-(1*H*,1*H*)-pentadecafluorooctoxy)diazirine (**7a**) and 3,3-bis(1*H*,1*H*-pentadecafluorooctoxy)diazirine (**8**) have been prepared via several steps from 1*H*,1*H*-pentadecafluorooctanol (**3**). Photolysis or thermolysis of these diazirines generated the corresponding carbenes (**1** or **2**), which underwent intermolecular reactions with HCl, alcohol **3** and acrylonitrile.

*Keywords:* (Polyfluoroalkyl)oxacarbenes; Diazirines; Photolysis; Thermolysis; NMR spectroscopy

## 1. Introduction

Fluoroalkylcarbenes are of interest as affinity probes and hydrophobic membrane reagents in biochemistry [1,2]. Usually, fluorine atoms appear in these carbenes as trifluoromethyl groups, difluoromethylene units within alkyl chains or directly substituted on the carbenic centers [1–3]. Extensively fluorinated or long-chain perfluorinated alkylcarbenes appear not to have been investigated as affinity reagents, although their pronounced hydrophobicity might endow them with unusual properties.

Bargamova et al. have reported the generation and reactions of hexafluoroisopropylpentafluoroethylcarbene [4], and Bevan and Haszeldine have prepared fluoromethylfluorocarbene [5]. However, these reactive intermediates readily underwent intramolecular reactions that could reduce their intermolecular utility. A similar drawback afflicted the 1,1-difluorohexylcarbenes examined by Erni and Khorana [3].

Our recent studies of a family of trifluoroethoxycarbenes have revealed that these species are reactive oxacarbenes, capable of a variety of intermolecular reactions [6]. As an extension of this study, we became interested in the preparation and reactions of long-chain (polyfluoroalkyl)oxacarbenes. Although these oxacarbenes should readily exhibit intermolecular chemistry, they lack the self-destructive intramolecular reaction channels available to the fluoroalkylcarbenes.

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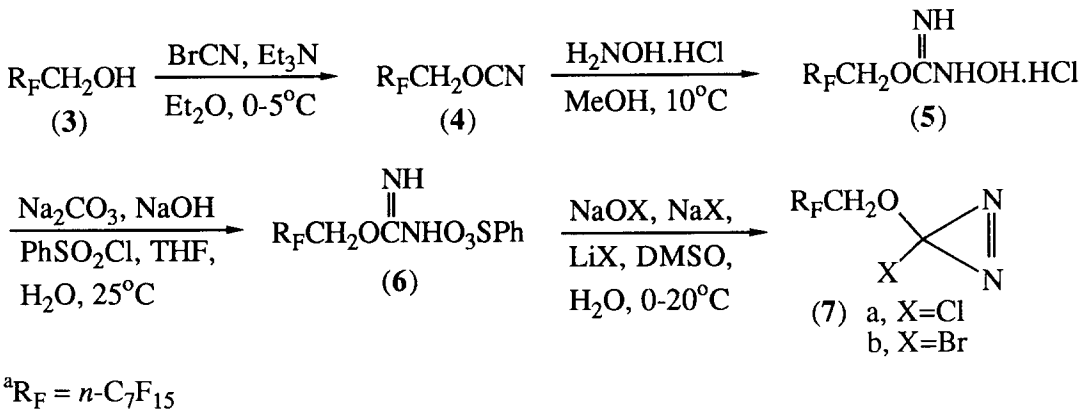
## 2. Results and discussion

Our carbene targets were chloro(1*H*,1*H*-pentadecafluorooctoxy)carbene (**1**) and bis-(1*H*,1*H*-pentadecafluorooctoxy)carbene (**2**). Carbene **1** was generated from the corresponding

$C_7F_{15}CH_2O\text{-}\ddot{C}\text{-}Cl$ (**1**)  $(C_7F_{15}CH_2O)_2C:$ (**2**)

diazirine, which was itself prepared by a sequence of reactions analogous to that utilized in the synthesis of 3-chloro-3-(trifluoroethyoxy)diazirine [6]; see Scheme 1. Thus, 1*H*,1*H*-pentadecafluorooctanol (**3**) was converted [7] to cyanate **4** with cyanogen bromide and triethylamine. Due to its anticipated instability [8], the crude cyanate was immediately treated with hydroxylamine hydrochloride in methanol [9], affording the isourea hydrochloride **5**. Reaction of the latter with sodium carbonate, followed by sodium hydroxide and benzenesulfonyl chloride in aqueous THF, gave *O*-benzenesulfonyl isourea (**6**), m.p. 89–90.5 °C, in 38.5% overall yield from **3**. The structure of **6** was established by $^1H$ and $^{19}F$ NMR spectroscopy, and by elemental analysis.

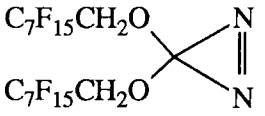
Graham oxidation [10] of **6** with aqueous NaOCl gave 3-chloro-3-(1*H*,1*H*-pentadecafluorooctoxy)diazirine (**7a**) in ca. 40% yield. After chromatography on silica gel, a pentane solution of **7a** exhibited UV maxima at 344 and 358 nm, as anticipated for this chlorodiazirine [6,10]. The analogous oxidation of **6** with freshly prepared NaOBr in aqueous DMSO [10] gave 3-bromo-3-(1*H*,1*H*-pentadecafluorooctoxy)diazirine (**7b**),




[a] $R_F = n\text{-}C_7F_{15}$

Scheme 1 [a].

$\lambda_{max}$=344, 360 nm (pentane). A diazirine exchange reaction [11] of **7b** with the sodium salt of alcohol **3** (NaH, DMF, 0 °C, 1 h) then gave ~70% of 3,3-bis(1*H*,1*H*-pentadecafluorooctoxy)diazirine (**8**), $\lambda_{max}$=344, 358 nm (pentane).



(**8**)

$C_7F_{15}CH_2OCHCl_2$

(**9**)

Photolysis of diazirine **7a** in ethereal pentane containing HCl ($\lambda > 300$ nm, 25 °C, 1 h) gave dichloride **9** in 28% isolated yield (based on isourea **6**). The structure of **9** was verified by $^1H$ and $^{19}F$ NMR spectroscopy, GC–MS and elemental analysis. Photolytic generation of carbene **1** from diazirine **7a**, followed by HCl capture of the carbene, readily accounts for this transformation.

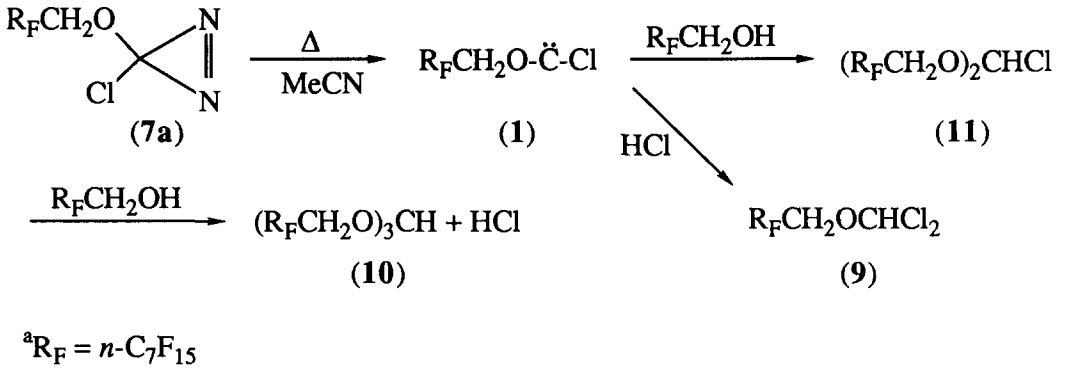
Thermolysis of **7a** (50 °C, 6 h) in acetonitrile containing excess polyfluorooctanol (**3**) also gave **9**, accompanied by a new product, identified (see below) as orthoformate **10**, in a 1:1 distribution and a total yield of 8% (again based on **6**). These reactions most likely involve the initial generation of carbene **1**, followed by proton abstraction ion pair recombination [12] at the OH group of alcohol **3**, leading to the (unobserved) intermediate **11**; see Scheme 2. Reaction of **11** with additional polyfluorooctanol (**3**) affords orthoformate **10** and HCl. The latter diverts a substantial portion of carbene **1** to dichloride **9**.

Thermolysis of diazirine **8** in alcohol **3** (25 °C, 24 h) led directly to orthoformate **10** in 16% isolated yield, a conversion most reasonably formulated as a reaction of carbene **2** with the alcoholic OH group. The identity of **10** followed from $^1H$ and $^{19}F$ NMR spectroscopy and elemental analysis.

Carbenes **1** and **2** also gave intermolecular addition products with acrylonitrile: thermolysis of diazirine **7a** in acrylonitrile (50 °C, $N_2$ atmosphere, 6 h) gave 26% of a 1:2.1 mixture of isomeric cyclopropanes **12**, after chromatography on silica gel. Analogously, gentle decomposition of diazirine **8** in acrylonitrile (25 °C, 24 h) furnished 10% of purified cyclopropane **13**, via the addition of bis(pentadecafluorooctoxy)carbene (**2**). In both cases, the isolated yields of the purified cyclopropanes are based on isourea **6**, so that yields referred to the proximate precursor diazirines are probably 2–3-times higher. The isolated yields are also lowered by the poor solubility characteristics of the starting materials and products in the usual organic solvents.

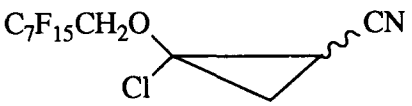
Laser flash photolysis [13,14] of diazirine **7a** (351 nm, 14 ns pulse, ~70 mJ) in the presence of pyridine (in either pentane or acetonitrile solvents) gave rise to ylide **14**, as indicated by its UV absorption at 400 nm [15,16]. From the apparent rate constants for the formation of **14** as a function of pyridine concentration [15], linear correlations were derived whose slopes gave the second-order rate constants for the reactions of carbene **1** with pyridine. These were $1.6\times10^8$ $M^{-1}$ $s^{-1}$ in pentane and $2.3\times10^7$ $M^{-1}$ $s^{-1}$ in acetonitrile.

The latter rate constant is similar to that observed for the analogous reaction of $CF_3CH_2OCCl$ with pyridine ($2.8\times10^7$ $M^{-1}$ $s^{-1}$) [16], and is an order of magnitude greater than the rate constant for the comparable reaction of MeOCCl ($9.0\times10^5$ $M^{-1}$ $s^{-1}$) [13]. (Data for the two latter reactions were unavailable in pentane solvent.) The electron-attracting inductive effect of fluorine substitution destabilizes the fluoroalkyloxacarbenes and renders them more reactive than an alkyloxacarbene. This effect, however, may not extend further than the first carbon atom of the alkoxy group because replacement of the $CF_3$ group of chlorotrifluoroethoxycarbene with a perfluoroheptyl moiety (affording **1**) does not further enhance the reactivity. Unfortunately, attempts to use the absorbance of **14** to monitor the rates of reaction of carbene **1** with methanol, trifluoroethanol or alcohol **3** were unsuccessful because of the rapid decay of the ylide absorbance in the presence of these alcohols. Presumably, **14** is very readily protonated at carbon.

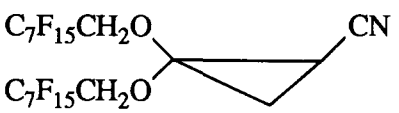



[a]$R_F = n\text{-}C_7F_{15}$

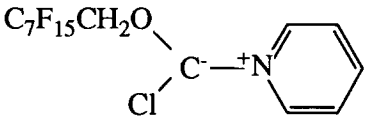
Scheme 2 [a].




(12)




(13)




(14)

In summary, we have shown that preparations of long-chain (polyfluoroalky)oxadiazirines are practical; that the corresponding carbenes can be generated from these precursors either thermally or photochemically; and that the carbenes react intermolecularly with HCl, an alcohol or acrylonitrile to give appropriate products. The utility of these reagents as affinity probes can now be explored.

## 3. Experimental details

Melting points are uncorrected. $^1H$ and $^{19}F$ NMR spectra were obtained on a Varian VXR-200 spectrometer. $^{19}F$ spectra were obtained at 188.22 MHz. Chemical shifts are reported as ppm ($\delta$) relative to internal $Me_4S$ ($^1H$) or $Cl_3CF$($^{19}F$). UV spectra were acquired on a HP Model 8451 instrument; GC–MS data were obtained with a HP Model 5890 unit equipped with a HP 5971 mass selective detector. For details concerning the laser flash photolysis system, see Ref. [14]. Methodology pertaining to the measurement of rate constants for carbene/pyridine reactions is described in Refs. [15] and [16]. Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ.

### 3.1. Preparation of N-benzenesulfonyl-O-(1H,1H-pentadecafluorooctyl)isourea (6)

To 30.6 g (75 mmol) of 98% 1*H*,1*H*-pentadecafluorooctanol (Fluorochem Ltd., Old Glossop, Derbyshire, UK) and 8.57 g (81 mmol) of BrCN in 100 ml of anhydrous ether at 0–5 °C, was added 7.60 g (75 mmol) of triethylamine in 50 ml of dry ether, with stirring under a nitrogen atmosphere. Stirring was continued for 5 min after the addition, triethylamine hydrobromide was removed by vacuum filtration and the filtrate concentrated by rotary evaporation.

The yellow oily residue (mostly cyanate **4**) was added under nitrogen to a solution consisting of 5.12 g (74 mmol) of hydroxylamine hydrochloride in 40 ml of methanol, with the temperature kept below 20 °C. Stirring was continued for an additional 1.5 h at 10 °C. The solvent was removed by rotary evaporation; the residual solid was washed with acetone and air-dried to give 33.5 g (68 mmol, 91%) of the crude amidine hydrochloride **5**. (This material is unstable upon heating; no melting point was determined.)

Amidine **5** was dissolved in 50 ml of water and 100 ml of THF, and treated with 8.0 g (75 mmol) of $Na_2CO_3$ in 50 ml of water and 3.0 g (75 mmol) of NaOH in 20 ml of water, while keeping the reaction temperature below 10 °C. Then, 15.0 g (84 mmol) of benzenesulfonyl chloride was added with stirring at 20 °C, and stirring was continued for 2 h at 25 °C. The reaction solution was concentrated by rotary evaporation, affording crude solid **6** that was filtered, washed with water, air-dried and recrystallized from hexane/ether to give 17.3 g (28.9 mmol, 38.5% overall yield) of isourea **6**, m.p. 89–90.5 °C. $^1H$ NMR (DMSO-$d_6$) $\delta$: 4.61 (t, $J$=14 Hz, 2H, $CH_2CF_2$); 7.13 (s, 2H, NH); 7.53–7.94 (m, 5H, Ph) ppm. $^{19}F$ NMR (DMSO-$d_6$) $\delta$: −80.8 (t, $J$=9.6 Hz, 3F, $CF_3CF_2$); −119.5 (m, 2F); −122.1 (m, 4F); −122.8 (m, 2F); −123.1 [m, 2F, $(CF_2)_5$]; −126.1 (crude t, 2F, $CH_2CF_2$) ppm. Analysis: Calc. for $C_{15}H_9F_{15}N_2O_4S$: C,

30.1; H, 1.52; N, 4.68; F, 47.6%. Found: C, 29.7; H, 1.58; N, 4.72; F, 47.0%.

### 3.2. Preparation of 3-chloro-3-(1H,1H-pentadecafluorooctoxy)diazirine (7a)

To a solution consisting of 2.0 g of LiCl and 1.2 g (2.0 mmol) of isourea **6** in 70 ml of pentane and 50 ml of DMSO contained in a 250 ml Erlenmeyer flask was slowly added, with stirring, 70 ml of aqueous NaOCl solution ('pool chlorine', 12% Cl) that had been saturated with NaCl. The temperature was maintained below 20 °C during the addition, and stirring was continued for an additional 1 h at 0 °C after the addition.

The reaction solution was quenched with 300 ml of ice water, the pentane layer being separated and combined with a 70 ml pentane extract of the aqueous layer. The combined pentane solution was washed with ice-cold brine (2×100 ml) and dried over $CaCl_2$ at 0 °C for 12 h. The pentane solution containing diazirine **7a** was concentrated to ~40 ml and passed through a short silica column, affording **7a** with $\lambda_{max}$=344, 358 nm, $A \sim 1.4$. This diazirine solution was used without further purification.

### 3.3. Preparation of 3-bromo-3-(1H,1H-pentadecafluorooctoxy)diazirine (7b)

A solution consisting of 1.0 g of LiBr, 6.0 g of NaBr and 1.2 g (2 mmol) of isourea **6** in 70 ml of pentane and 50 ml of DMSO was cooled to 10 °C and an aqueous solution of NaOBr [prepared from 2.0 g of NaOH and 1.0 ml (2.9 g, 18 mmol) of bromine in 15 ml of water] was added dropwise, with stirring, at 20 °C. Stirring was continued for 20 min at 10 °C after the addition.

The reaction mixture containing diazirine **7b** was worked up in an identical manner to that of diazirine **7a** (see above), affording ~40 ml of a pentane solution of bromodiazirine **7b**, $\lambda_{max}$=344, 360 nm, $A \sim 0.5$. The yield of **7b** was ~50%.

### 3.4. Preparation of 3,3-bis-(1H,1H-pentadecafluorooctoxy)diazirine (8)

Under a nitrogen atmosphere, 2.4 g (6.0 mmol) of alcohol **3** in 20 ml of dry DMF was converted to the alkoxide by the addition of 180 mg (6.0 mmol) of NaH (80% dispersion in mineral oil). The mixture was stirred at 0 °C for 30 min, and then bromodiazirine **7b**, prepared from 1.2 g (2.0 mmol) of isourea **6**, was added in 20 ml of dry DMF. The reaction mixture was stirred at 0 °C for 1 h, then quenched with 300 ml of ice water and 70 ml of pentane. The pentane phase was separated and combined with a 50-ml pentane extract of the aqueous phase. The combined pentane solution of diazirine **8** was washed with ice-cold brine and dried over $Na_2SO_4$ at 5 °C for >5 h. The pentane solution was concentrated to ~40 ml by rotary evaporation and chromatographed over a short silica column, affording a final pentane solution of **8** with $\lambda_{max}$=344, 358 nm, $A \sim 0.9$.

### 3.5. Photolysis of diazirine 7a with HCl

A solution consisting of 5 ml of 1.0 M aqueous HCl in diethyl ether was mixed with 40 ml of a pentane solution of diazirine **7a** (see above). The mixture was photolyzed (Rayonet reactor, 350 nm) for 1 h at 25 °C; solvent was removed by rotary evaporation and the residue was purified by chromatography on silica gel (eluent: hexane/ethyl acetate), affording 270 mg (0.56 mmol, 28% yield based on isourea **6**) of dichloromethyl 1*H*,1*H*-pentadecafluorooctyl ether (**9**). $^1$H NMR ($C_6F_6$ solution, external $CD_3CN$) $\delta$: 3.45 (t, $J$=13 Hz, 2H, $CH_2CF_2$); 6.37 (s, 1H, $CHCl_2$) ppm. $^{19}$F NMR ($C_6F_6$ solution, external $CD_3CN$) $\delta$: −83.39 (t, $J$=10 Hz, 3F, $CF_3$); −121.6 (m, 2F); −123.6 (m, 4F); −124.4 (m, 2F); −124.8 [m, 2F, $(CF_2)_5$]; −128.0 (crude t, 2F, $CF_2CH_2$) ppm. Analysis: Calc. for $C_9F_{15}H_2OCl_2$: C, 22.4; H, 0.63; Cl, 14.7; F, 59.0%. Found: C, 22.3; H, 0.41; Cl, 14.9; F, 59.2%.

### 3.6. Thermolysis of diazirine 8 with alcohol 3

To ~40 ml of a pentane solution of diazirine **8** (made from 2.0 mmol of isourea **6**, see above) was added 1.0 g (2.5 mmol) of alcohol **3** in 20 ml of acetonitrile. The pentane was removed by rotary evaporation and the acetonitrile solution of **8** and **3** allowed to decompose at 25 °C in the dark for 24 h. Solvent was then removed and the residue chromatographed over silica gel with hexane/ethyl acetate as eluent to afford 390 mg (0.32 mmol, 16%) of tris-(1*H*,1*H*-pentadecafluorooctoxy)methane (**10**). $^1$H NMR ($C_6F_6$ solution, external $CD_3CN$) $\delta$: 3.28 (t, $J$=13 Hz, 6H, 3×$CH_2CF_2$); 4.71 (s, 1H, CH) ppm. $^{19}$F NMR ($C_6F_6$ solution, external $CD_3CN$): $\delta$: −83.40 (t, $J$=10 Hz, 3F, $CF_3$); −122.0 (m, 2F); −123.6 (m, 4F); −124.4 (m, 2F); −125.0 [m, 2F, $(CF_2)_5$]; −128.1 (m, 2F, $CF_2CH_2$) ppm. Analysis: Calc. for $C_{25}F_{45}H_7O_3$: C, 24.8; H, 0.58; F, 70.6%. Found: C, 24.7; H, 0.48; F, 70.75%.

### 3.7. Thermolysis of diazirine 7a with alcohol 3

The pentane solution of diazirine **7a** (derived from 2 mmol of isourea **6**, see above) was mixed with 10 ml of acetonitrile containing 1.1 g (2.75 mmol) of alcohol **3**. The pentane was removed by rotary evaporation and the acetonitrile solution of **7a** and **3** heated to 50 °C for 6 h. Solvent was stripped and the residue was

chromatographed over silica with hexane/ethyl acetate as eluent to afford 260 mg (20%) of an approximately 1:1 mixture of dichloride **9** and orthoformate **10**. The mixture was identified and quantitated by $^1$H NMR spectroscopy and by capillary GC.

### 3.8. Thermolysis of diazirine 7a with acrylonitrile

To 5 ml of a pentane solution of diazirine **7a**, made from 2 mmol of isourea **6** (see above), was added 5 ml of freshly distilled acrylonitrile. The pentane was removed on the rotary evaporator and the **7a**/acrylonitrile solution was heated at 50 °C for 6 h under a nitrogen atmosphere. Precipitated solid (polymerized acrylonitrile) was filtered, the filtrate was concentrated under reduced pressure and the residue chromatographed over silica gel with hexane/ethyl acetate as eluent to afford 260 mg (0.52 mmol, 26%) of 1-chloro-1-(1*H*,1*H*-pentadecafluorooctoxy)-2-cyanocyclopropane (**12**), m.p. 39–40 °C, as an ~1:2 mixture of isomers. $^1$H NMR ($CDCl_3$, both isomers) $\delta$: 1.8–2.0 (m, 2H, cyclopropyl); 2.14–2.23 (m, 1H, cyclopropyl); 4.05–4.50 (m, 2H, $CH_2CF_2$) ppm. $^{19}$F NMR ($CD_3CN$, both isomers) $\delta$: −80.87 (t, $J$=9.5 Hz, 3F, $CF_3$); −119.3 (m, 2F); −121.7 (m, 4F); −122.6 (m, 2F); −122.7 (m, 2F); −125.9 [m, 2F $(CF_2)_6$] ppm. MS *m/z*: 499, 501 ($M^+$). Analysis: Calc. for $C_{12}F_{15}H_5ClNO$: C, 28.8; H, 1.0; F, 57.0; N, 2.80%. Found: C, 28.9; H, 0.94; F, 57.3; N, 2.66%.

### 3.9. Thermolysis of diazirine 8 with acrylonitrile

To a pentane solution of diazirine **8**, prepared from 3.0 mmol of isourea **6**, was added 5 ml of freshly distilled acrylonitrile. The pentane was removed under reduced pressure and the diazirine acrylonitrile solution stirred in the dark for 24 h at 25 °C. Work-up as for **12** afforded 250 mg (0.3 mmol, 10%) of 1,1-bis-(1*H*,1*H*-pentadecafluorooctoxy)-2-cyanocyclopropane (**13**), m.p. 42.5–43.5 °C. $^1$H NMR ($CDCl_3$) $\delta$: 1.72–1.77, 2.01–2.11 (m, 3H, cyclopropyl); 4.10–4.42 (m, 4H, 2×$CH_2CF_2$) ppm. The $^{19}$F NMR ($CD_3CN$) spectrum was very similar to that of **12**. Analysis: Calc. for $C_{20}F_{30}H_7NO_2$: C, 27.8; H, 0.81; F, 66.0; N, 1.62%. Found: C, 27.6; H, 0.73; F, 66.0; N, 1.97%.

## Acknowledgement

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