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Flow Ozonolysis Using a Semipermeable Teflon AF-2400 Membrane To Effect Gas−Liquid Contact

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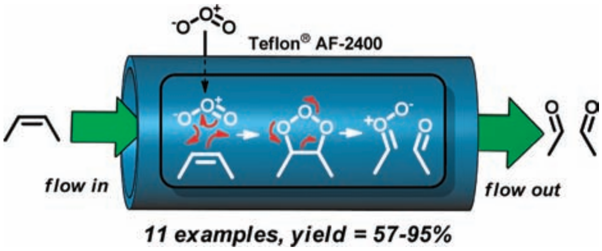
ABSTRACT



A flow-through chemistry apparatus has been developed which allows gases and liquids to contact via a semipermeable Teflon AF-2400 membrane. In this preliminary investigation, the concept was proven by application to the ozonolysis of a series of alkenes.

Flow chemistry and related continuous processing techniques have emerged over recent years as enabling tools which can offer advantages over the corresponding batch methods.[1] For instance, repetitive and labor intensive purification operations can often be eliminated from the synthesis scheme when solid-supported reagents and scavengers are incorporated into a flow chemistry sequence.[2] Additionally, as only relatively small volumes of reactive material are being processed at any one time, flow techniques can enhance the overall safety profile of the process. This is particularly true for reactions which involve hazardous or explosive intermediates or for reactions which require high temperatures and pressures.[3] The ozonolysis of alkenes represents a good example of such a reaction as the potentially dangerous nature of the intermediate ozonides (and peroxy compounds derived from them) is well documented.[4] As ozonolysis is also an extremely useful synthetic transformation[5] and is considered to be more environmentally acceptable than alternative processes using metal species such as the toxic and volatile osmium tetraoxide,[6] its development into a flow procedure is highly desirable and is consequently an active area

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(1) (a) Baxendale, I. R.; Ley, S. V. *Ernst Schering Found. Symp. Proc.* **2006**, 151–85. (b) Baxendale, I. R.; Hayward, J. J.; Lanners, S.; Ley, S. V.; Smith, C. D. In *Microreactors in Organic Synthesis and Catalysis*; Wirth, T., Ed.; Wiley: New York, 2008. (c) Ahmed-Omer, B.; Brandt, J. C.; Wirth, T. *Org. Biomol. Chem.* **2007**, *5*, 733–740. (d) Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. *Chem. Rev.* **2007**, *107*, 2300–2318. (e) Anderson, N. G. *Org. Process Res. Dev.* **2001**, *5*, 613–621. (f) Kirschning, A.; Solodenko, W.; Mennecke, K. *Chem.*−*Eur. J.* **2006**, *12*, 5972–5990. (g) Seeberger, P. H. *Nat. Chem.* **2009**, *1*, 258–260.

(2) (a) Palmieri, A.; Ley, S. V.; Polyzos, A.; Ladlow, M.; Baxendale, I. R. *Beilstein J. Org. Chem.* **2009**, 5, No. 23. (b) Ley, S. V.; Massi, A.; Rodriguez, F.; Horwell, D. C.; Lewthwaite, R. A.; Pritchard, M. C.; Reid, A. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1053–1055. (c) Smith, C. D.; Baxendale, I. R.; Tranmer, G. K.; Baumann, M.; Smith, S. C.; Lewthwaite, R. A.; Ley, S. V. *Org. Biomol. Chem.* **2007**, *5*, 1562–1568. (d) Siu, J.; Baxendale, I. R.; Lewthwaite, R. A.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 3140–3160. (e) Benito-López, F.; Egberink, R. J. M.; Reinhoudt, D. N.; Verboom, W. *Tetrahedron* **2008**, *64*, 10023–10040. (f) Baumann, M.; Baxendale, I. R.; Martin, L. J.; Ley, S. V. *Tetrahedron* **2009**, *65*, 6611–6625.

(3) (a) Saaby, S.; Knudsen, K. R.; Ladlow, M.; Ley, S. V. *Chem. Commun.* **2005**, 2909–2911. (b) Carter, C. F.; Baxendale, I. R.; O'Brien, M.; Pavey, J. B. J.; Ley, S. V. *Org. Biomol. Chem.* **2009**, *7*, 4594–4597. (c) Baxendale, I. R.; Ley, S. V.; Mansfield, A. C.; Smith, C. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 4017–4021. (d) Brandt, J. C.; Wirth, T. *Beilstein J. Org. Chem.* **2009**, 5, No. 30.

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of research.[7] Typically, gas–liquid contact in flow chemistry devices involves the mechanical mixing of two phases.[8] We envisaged that a more efficient, controllable, and reliable phase contact might be realized using a semipermeable membrane which can have extremely high effective surface areas and selectively allow gases (but not liquids) to cross from one side to the other. One commercially available material whose permeability to a range of gases (including ozone) has been demonstrated is Teflon AF-2400,[9] an amorphous copolymer of tetrafluoroethylene and a perfluorodimethyldioxolane (shown in Figure 1).

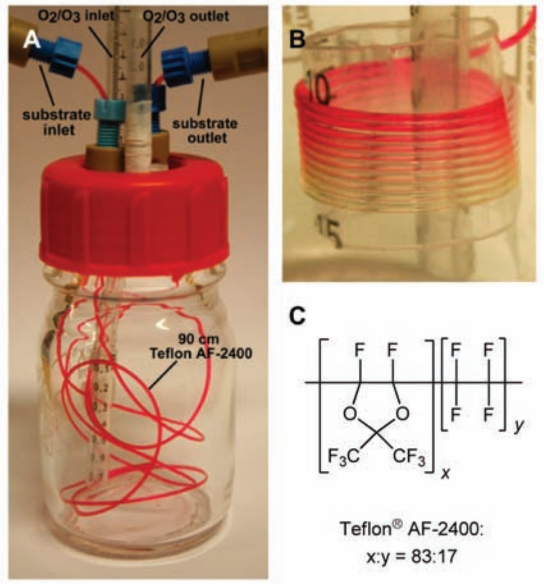

Figure 1. (A) Flow ozonolysis apparatus (tubing filled with dye). (B) Bleaching of Sudan red 7B in flow, tubing coiled for clarity. (C) Molecular formula of Teflon AF-2400.

The presence of the perfluorodioxolane units prevents the polymer from achieving the semicrystalline microstructure typical of other perfluorinated polymers such as poly(tetrafluoroethylene) (PTFE). Instead, a highly microporous, amorphous structure is obtained which has a low dielectric constant,[10] low refractive index,[11] and high gas permeability.[12] In addition, Teflon AF-2400 retains much of the high chemical resistance of PTFE making it an attractive material for use in chemical synthesis environments (poly(dimethylsiloxane)/silicone/PDMS is also permeable to ozone[13] but suffers from significant swelling in a range of common organic solvents).[14] As this material is commercially available in the form of narrow-bore, thin-walled tubing (providing a high surface-to-volume ratio), a practical, simple, proof-of-concept apparatus consisting of a length of membrane tubing that passes through a chamber which is supplied with a flow of ozone from an ozone generator (Peak Scientific OZ06) was constructed (Figure 1). For the purposes of this preliminary investigation Teflon AF-2400 (0.6 mm i.d., 0.8 mm o.d.) was used, although it is possible to fabricate this material into tubing and membranes with narrower walls and higher surface-to-volume ratio.[15] In order to ascertain whether the supplied ozone was permeating this tubing, a short length (3 cm) was filled with solutions (1 mM) in various solvents of either Sudan-red 7B or oil-red O (dyes which are known to be bleached by ozone)[16] and capped at the ends. While an external oxygen atmosphere had no observable effect on any dye solution, both dyes were bleached when the sealed tubing was exposed to ozone at atmospheric pressure, Sudan-red 7B being bleached at a faster rate than oil-red O. The relative rates of bleaching of Sudan-red 7B in various solvents are shown in Table 1.

Table 1. Relative Rates of Bleaching of 1 mM Sudan-red 7B

entry	solvent	time[a] (min)
1	MeOH	1.15
2	MeCN	1.20
3	DCM	2.30
4	$CHCl_3$	2.30
5	EtOAc	2.34
6	EtOH	>8

[a] Time required for complete discoloration.

The rate of bleaching did not differ after repetition of the test using the same piece of tubing (10 times). All subsequent

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(4) (a) McCreary, M. D.; Lewis, D. W.; Wernick, D. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 1038–1054. (b) Rigaudy, J.; Cuong, N. K.; Albouy, J.-P.; Chétrit, A. *Tetrahedron Lett.* **1976**, *17*, 1089–1092. (c) Pryde, E.; Moore, D.; Cowan, J. *J. Am. Oil Chem. Soc.* **1968**, *45*, 888–894. (d) Murray, R. W.; Hagen, R. *J. Org. Chem.* **1971**, *36*, 1098–1102. (e) Greenwood, F. L.; Durham, L. J. *J. Org. Chem.* **1969**, *34*, 3363–3366. (f) Greenwood, F. L. *J. Org. Chem.* **1965**, *30*, 3108–3111. (g) Wojciechowski, B. J.; Chiang, C. Y.; Kuczkowski, R. L. *J. Org. Chem.* **1990**, *55*, 1120–1122. (h) Thompson, Q. E. *J. Org. Chem.* **1962**, *27*, 4498–4502. (i) Noller, D.; Mazurowski, S.; Linden, G.; De Leeuw, F.; Mageli, O. *Ind. Eng. Chem.* **1964**, *56*, 18–27. (j) Bailey, P. S.; Bath, S. S.; Dobinson, F.; Garcia-Sharp, F. J.; Johnson, C. D. *J. Org. Chem.* **1964**, *29*, 697–702. (k) Kula, J. *Chem. Health Saf.* **1999**, *6*, 21–22.

(5) (a) Bailey, P. S. *Chem. Rev.* **1958**, *58*, 925–1010. (b) Bailey, P. S. *Ozonation in Organic Chemistry*; Academic Press: New York, 1982; Vol. II. (c) Bailey, P. S. *Ozonation in Organic Chemistry*; Academic Press: New York, 1978; Vol. I. (d) Van Ornum, S. G.; Champeau, R. M.; Pariza, R. *Chem. Rev.* **2006**, *106*, 2990–3001.

(6) Hammond, C. R. In *CRC Handbook of Chemistry and Physics*, 90th ed.; Lide, D. R., Ed.; CRC Press: Boca Raton, FL; pp 4–25.

(7) (a) Hübner, S.; Bentrup, U.; Budde, U.; Lovis, K.; Dietrich, T.; Freitag, A.; Küpper, L.; Jähnisch, K. *Org. Process Res. Dev.* **2009**, *13*, 952–960. (b) www.thalesnano.com/products/o-cube, accessed March 2010.

(8) (a) Csajagi, C.; Borcsek, B.; Niesz, K.; Kovacs, I.; Szekelyhidi, Z.; Bajko, Z.; Urge, L.; Darvas, F. *Org. Lett.* **2008**, *10*, 1589–1592. (b) Jones, R. V.; Godorhazy, L.; Varga, N.; Szalay, D.; Urge, L.; Darvas, F. *J. Comb. Chem.* **2006**, *8*, 110–116. (c) Fukuyama, T.; Rahman, T.; Kamata, N.; Ryu, I. *Beilstein J. Org. Chem.* **2009**, 5, No. 34. (d) Rahman, M. T.; Fukuyama, T.; Kamata, N.; Sato, M.; Ryu, I. *Chem. Commun.* **2006**, 2236–2238. (e) Miller, P. W.; Jennings, L. E.; deMello, A. J.; Gee, A. D.; Long, N. J.; Vilar, R. *Adv. Synth. Catal.* **2009**, *351*, 3260–3268.

(9) (a) Resnick, P. R.; Buck, W. H. In *Fluoropolymers II*; HoughamG. G., Cassidy, P. E., Johns, K., Davidson, T., Eds.; Kluwer Academic: New York, 1999; pp 25–34. (b) Resnick, P. R. US Patent 3978030, 1976. (c) Nemser, S. M.; Roman, I. C. US Patent 5051114, 1991. (d) Polyakov, A.; Yampolskii, Y. *Desalination* **2006**, *200*, 20.

(10) (a) DuPont, Teflon AF-2400, product information: (b) Hammoud, A. N.; Baumann, E. D.; Overton, E.; Myers, I. T.; Suthar, J. L.; Khachen, W.; Laghari, J. R. *Technical Memorandum* **1992**, 105753, NASA.

(11) Yang, M. K.; French, R. H.; Tokarsky, E. W. *J. Micro-Nanolith. MEMS MOEMS* **2008**, 7, No. 033010.

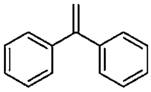
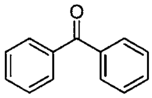
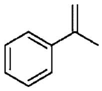
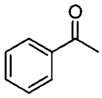
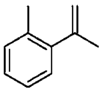
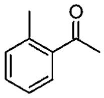
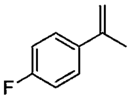
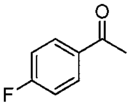
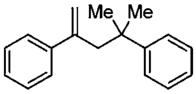
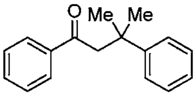
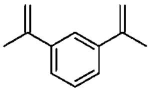
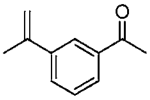
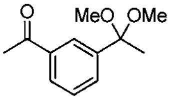
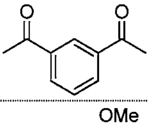
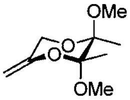
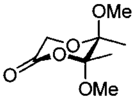
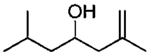
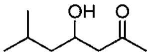
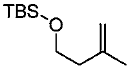
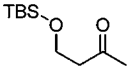
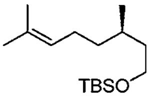
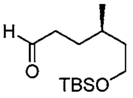
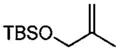
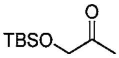
(12) Pinnau, I.; Toy, L. G. *J. Membr. Sci.* **1996**, *109*, 125–133.

(13) Shanbhag, P. V.; Sirkar, K. K. *J. Appl. Polym. Sci.* **1998**, *69*, 1263–1273.

(14) Lee, J. N.; Park, C.; Whitesides, G. M. *Anal. Chem.* **2003**, *75*, 6544–6554.

(15) Supplied by Biogeneral Inc., 9925 Mesa Rim Rd, San Diego, CA (www.biogeneral.com), accessed March 2010.

Table 2. Results for Flow Ozonolyses

entry	substrate	product		convn (%)[a]	yield (%)[b]
1			**1**	100	87
2			**2**	100	83
3			**3**	100	93
4			**4**	100	95
5			**5**	100	88
6			**6a**	100	2
			**6b**		5
			**6c**		75
7			**7**	100	73
8			**8**	100	90
9			**9**	100	93
10			**10**	100	57
11			**11**	100	76

[a] Conversion determined by TLC and NMR analysis of crude reaction products. [b] Isolated yield after column chromatography on silica gel.

investigations were carried out using methanol as the solvent. In a control experiment, no bleaching was observed when the tubing was replaced with standard PTFE tubing of corresponding dimensions. In a microscale experiment with Teflon AF-2400 tubing, using 1,1-diphenylethene as a substrate (0.1 M solution in methanol) followed by quenching the product with triphenylphosphine, it was found (according to TLC analysis) that 1 h of exposure to the supplied ozone was sufficient to effect complete conversion to benzophenone. Using a 90 cm length of the AF-2400 tubing connected to a syringe-pump (Infors AG, HT-Precidor) set up to deliver a 1 h residence time in the apparatus, the ozonolysis of a series of alkenes was then carried out in flow (Table 2). In order to facilitate rapid purification and simplify the analysis of products, the reaction streams were quenched by dropping into a flask containing a 4-fold excess of polymer-supported triphenylphosphine suspended in methanol. Initial purification was carried out simply by filtration and concentration under reduced pressure (*Caution! As ozonides and/or peroxides can be explosive and shock-sensitive, solvent was only removed when the solutions tested negative with peroxide test strips*). After NMR analysis the products were further purified by chromatography on silica gel. As can be seen, complete conversion of substrate was observed in all cases, and yields were generally good to excellent.

Shown in Figure 1B is the bleaching of a solution of Sudan red 7B in methanol in flow, with the same length of membrane tubing (90 cm) coiled for clarity. The gradual and steady disappearance of color over the length of the tubing can clearly be seen, indicating that the ozone is permeating in a fairly uniform manner.

In summary, we have constructed a simple and convenient flow chemistry device to bring about the ozonolysis of alkenes via gas-to-liquid transfer through semipermeable Teflon AF-2400 tubing. In future versions we plan to incorporate the quenching step in flow, by either mixing the ozonide stream with a stream of quench reagent or by passing the ozonide stream through a cartridge packed with solid-supported quench reagent. This will allow us to combine the ozonolysis with other chemical transformations as part of a multistep flow sequence. Additionally, splitting the stream of substrate into several flow tubes of greater length running parallel to each other will increase the throughput. Many extensions and modifications of the apparatus can be envisaged, including the manufacture of microfluidic devices and variable temperature and pressure control, as well as the incorporation of other reactive gases for chemical transformations (such as CO, H_2, ethylene, acetylene, NO, Cl_2, O_2 etc). Moreover, by exposure of the flow stream to different gases (or vacuum), it should be possible to inject or remove the gases in a controlled sequence, thereby allowing multistep gas−liquid flow sequences to be carried out. Work is underway to exploit these concepts.

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Supporting Information Available: Experimental details and NMR spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807–810.