

## Citation Classics

Sweeley C C, Bentley R, Makita M & Wells W W. Gas-liquid chromatography of trimethylsilyl derivatives of sugars and related substances. *Journal of the American Chemical Society* **85**:2497-507, 1963.

**The paper describes the separation and estimation of carbohydrates and related polyhydroxy compounds by gas-liquid chromatography of trimethylsilyl (TMS) derivatives. [The SC<sup>®</sup> indicates that this paper was cited 1258 times in the period 1961-1975.]**

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"This paper on the gas-liquid chromatography of carbohydrates came about because the right people were in the right place at the right time. It involved a collaboration among three friends holding faculty appointments in two different departments at the University of Pittsburgh and a Postdoctoral Fellow from Japan who was working with one of us. The starting point was the development by Makita and Wells of a simple, rapid, and quantitative method for the preparation of trimethylsilyl derivatives of bile acids which were subsequently used in gas chromatography.<sup>1</sup> The method used pyridine as a solvent and derivatization with hexamethyl-disilazane in the presence of trimethylchlorosilane. The possibility of using this method for polyhydroxy compounds was later discussed by Wells and Sweeley (who often drove to work together from the suburbs) and then with Bentley (who had a stock of carbohydrates). Preliminary experiments quickly confirmed the utility of the technique for carbohydrates and the next few months involved much harder but exciting developmental work. Most of the work reported in the paper was accomplished between October, 1962 and March of 1963.

"The trimethylsilyl group was becoming recognized as a valuable protecting agent for hydroxyl groups but the key observation was the development of the rapid preparative method by Makita and Wells. Prior to our work on carbohydrates, several investigators had prepared trimethylsilyl derivatives of carbohydrates and had subjected them to gas chromatography. However, the preparation methods were cumbersome and gave rise to mixtures and, furthermore, the column packings used were very inefficient. Our achievement was to put together a simple and reliable method for derivatization along with up-to-date gas chromatographic procedures and to apply them to a large number of compounds.

"The standard mixture that we developed for trimethylsilylation has been widely used and, indeed, is marketed under a variety of trademarks. It never occurred to any of us that so simple a mixture could have commercial possibilities. Furthermore, each of the three senior authors developed various other areas independently, following this work, and published a number of papers dealing with applications of the basic method. The problem of ordering the authors for publication was solved by a rotation process on the various papers in which we all collaborated and we have always regarded the three Pittsburgh authors as coequals in the achievement.<sup>2,3</sup> Although only Bentley remains at the University of Pittsburgh, Sweeley and Wells having moved to Michigan State University and Makita back to Japan (Faculty of Pharmaceutical Sciences, Okayama University), we all have remained the best of friends.

"It is perhaps noteworthy that we never had any direct grant support from any source for this research. In retrospect, it is remarkable that such a highly cited paper should not ever have received direct grant support from any federal agency."

1. Makita M & Wells W W. The quantitative analysis of fecal bile acids by gas-liquid chromatography. *Analytical Biochemistry* **5**:523-30, 1963.
2. Bentley R, Sweeley C C, Makita M & Wells W W. Gas chromatography of sugars and other polyhydroxy compounds. *Biochemical and Biophysical Research Communications* **11**:14-8, 1963.
3. Wells W W, Sweeley C C & Bentley R. Gas chromatography of carbohydrates, in *Biomedical applications of gas chromatography* (Szymanski H A, ed.) New York: Plenum Press, 1964, pp. 169-223.