

Computer-Assisted Organic Synthesis of Volatile Heterocyclic Compounds in Food Flavors

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The ability to predict the course of various organic reactions has long been the goal of research in the area of computer-assisted organic synthesis (CAOS), and a number of reviews devoted to CAOS are available. However, in the field of heterocyclic food flavors and aromas, CAOS represents a new approach. This is the first attempt to summarize the efforts in this particular area, with several practical examples of formation of heterocyclic food flavors as studied by CAOS.

Vast accomplishments in food technology have been made in the past three decades, which, in turn, have stimulated research in various areas of food science including flavor chemistry. Because many heterocyclic compounds play a prominent role among flavors and fragrances, current interest in the chemistry of heterocyclic flavors and aromas is highly topical, timely, and not at all surprising.

Different types of reactions leading to heterocyclic food flavors have been well documented in the literature (Maillard, 1912; Rohan, 1963, 1964; Shigematsu et al., 1972; Drawert, 1975; Shibamoto and Russell, 1976; Vernin and Párkányi, 1982; Vernin et al., 1982; Waller and Feather, 1983), with the Maillard reaction receiving considerable attention in recent years. Model systems have been used to study some of these reactions and to predict the formation and occurrence of heterocyclic compounds in food flavors. Another possibility, i.e., the computer-assisted synthesis (computer simulation) of reactions leading to the formation of food flavors, has been explored as well. This is a relatively new field and, to our knowledge, no review covering this particular topic is available.

The goal of this paper is to review the advances in computer-assisted synthesis of heterocyclic food flavors and to provide several examples of successful applications of this approach.

As an introduction to the general area of food flavors, several randomly chosen references are mentioned here as examples: Bullard, 1978; Charalambous and Inglett, 1978; Teranishi, 1978; Ohloff and Flament, 1979; Maarse and Belz, 1981; Morton and MacLeod, 1982; Vernin, 1982a; Nykänen and Suomalainen, 1983; Waller and Feather, 1983; Adda 1985.

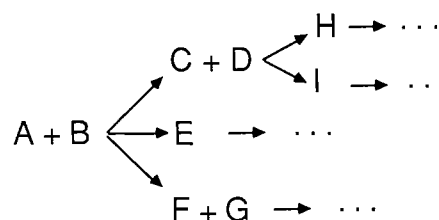
COMPUTER-ASSISTED ORGANIC SYNTHESIS (CAOS)

After several early suggestions in the literature that computers could be used in organic synthesis (Vleduts, 1963; Sarett, 1964), Corey and Wipke (1969) published their pioneering paper which, from the practical point of view, represents a milestone in the area of computer-assisted organic synthesis (also called computer-aided organic synthesis (CAOS)). Research in this area has continued at a steadily increasing pace, and at present, numerous

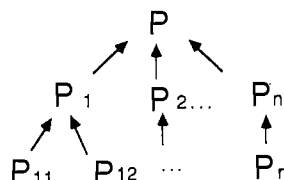
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Scheme I. Two Possible Approaches in CAOS

Synthetic approach (based on the starting materials)



Retrosynthetic approach (with the product as the starting point)



groups in various countries working on CAOS and quite a few general reviews on the topic have become available. Selected examples of these reviews include but are not limited to the following ones: Bersohn and Esack, 1976; Gund, 1977; Wipke and Howe, 1977; Gund et al., 1979; Carlson et al., 1983; Haggin, 1983; Long et al., 1983. An up-to-date review on the subject has been written by Barone and Chanon (1986a).

The latter review discusses the various research groups in different countries that are involved in CAOS and lists the names, origin, and year of the 48 computer programs available for this purpose, from Corey and Wipke's original OCSS program (1969) to Barone and Chanon's new TAMREAC program (1985). Although there are many countries with interest in CAOS, most of the recent advances have been made in the following countries: Belgium, Canada, Czechoslovakia, Federal Republic of Germany, Finland, France, German Democratic Republic, Great Britain, Italy, Japan, The Netherlands, People's Republic of China, Sweden, United States, USSR, and Yugoslavia. The available computer programs use languages ranging from Basic to Fortran. Barone and Chanon's paper (1986a) also gives a very complete, up-to-date bibliography on the use of CAOS, which will not be repeated here.

Several important aspects of CAOS must be considered before a successful use of this approach can be made (Barone and Chanon, 1986a). They are the representation of molecules and the representation of different types of

reactions and their storage for computer use. Furthermore, it is important to realize that there are two possible approaches in CAOS: a synthetic approach and a retrosynthetic approach (Scheme I). The first approach tries to answer what products are obtained after mixing a certain combination of reactants. On the other hand, in the retrosynthetic approach, the desired answer provides information about the possible precursors of a particular product or products. It is obvious that a good program has to perform in both fashions.

Representation of a molecule means a transformation of a structural formula of a compound into a form suitable for computer processing (Dyson, 1949; Lynch et al., 1971; Lynch, 1974; Wipke et al., 1974; Ash and Hyde, 1975; Rush, 1976; Smith and Becker, 1976; O'Korn, 1977; Read, 1983; Vollmer, 1983). The choice of a representation system is determined by the nature of operations to be carried out, the hardware and software available for this purpose, and the desired balance between manual and machine processes. There are two main groups of representation modes. One is based on extensions of the classical nomenclature (Dyson, 1949; Smith and Becker, 1976). The second is based on a graph-theoretical approach (Gutman and Trinajstić, 1973; Balaban, 1976; Graovac et al., 1977; Trinajstić, 1977; Herndon and Párkányi, 1978, 1982; Herndon, 1983; Herndon and Leonard, 1983; Trinajstić et al., 1983). Several algorithms have been published that allow automatic conversion of one representation into another (Granito, 1973; Zamora and Dayton, 1976; O'Korn, 1977).

A detailed description of the numerous possibilities of representation of organic molecules has been published (Barone and Chanon, 1986a). In this paper, various representations of reactions and their storage are discussed. Basically, there are two classical approaches an organic chemist can use: the overall transformation approach and the mechanistic approach. On the other hand, the approaches of Hendrickson and Ugi represent a theoretical, most sophisticated treatment of this problem. According to Hendrickson, a reaction can be defined by the net structural change from substrate to products as measured in changes in σ and f (where σ represents the C-C bonds and f the functionality) at a given carbon atom (Hendrickson, 1971, 1978; Hendrickson et al., 1981). The three variables used for this purpose are the number of C-C bonds linked to a carbon atom (σ), the number of hydrogen atoms bonded to the same carbon (h), and its oxidation state X ($X = f - h$).

Ugi and co-workers used a mathematical approach to reactions in which all chemical reactions correspond to interconversions of isomeric ensembles of molecules within a family of isomeric ensembles of molecules (Ugi and Gillespie, 1971; Ugi et al., 1972; Ugi, 1974; Brandt et al., 1977a; Brandt et al., 1977b; Gasteiger and Jochum, 1978).

As mentioned above, both retrosynthetic and synthetic approaches are of primary importance to an organic chemist.

There are still quite a few unresolved and difficult questions in CAOS. One of them is that of strategy and tactics by the computer, e.g., the ability of a computer to select only the feasible answers from a possibly astronomical number of answers. Nevertheless, at least some progress in this area has been made (Barone and Chanon, 1986b).

CAOS OF HETEROCYCLIC FOOD FLAVORS—PROGRAMS AND EXAMPLES

Maltol-Ammonia Reaction. The formation of heterocyclic food flavors by the Maillard reaction has been

discussed in detail elsewhere (Vernin and Metzger, 1981; Vernin and Párkányi, 1982; Waller and Feather, 1983). When one considers the large number of compounds present in food products which, of course, can also react with one another, the number of compounds that can be formed in the Maillard reaction is very high. In order to understand the origin of various food flavors, many authors studied model reactions or they tried to simulate them with a computer program. In the latter case, the computer replaces a reaction vessel and makes possible theoretical prediction of all the reaction products that can be formed in a particular reaction. The use of a computer facilitates the task of an analytical chemist by predicting the possible structures. Another advantage of this approach is its predictive ability, which makes it possible to predict new flavoring substances.

In the subsequent text we provide a brief description of the SOS program used in our laboratory for work on heterocyclic flavoring substances. Then, the applicability of the program will be shown on the example of a model reaction between maltol and ammonia (Barone and Chanon, 1986b).

The SOS program was used in a new version of an Apple II+ computer (two disk drives, 64 kbytes, Basic). The development of a more sophisticated version is now under way.

Description of the Program. The program can function in two different ways: (a) retrosynthetic (how is the reaction product formed) and (b) synthetic (what products can be formed from starting materials). In the example discussed here, the program has been used in the retrosynthetic fashion.

The program contains the following features: (1) description of the molecules, with a connectivity table; (2) description of the reactions by (a) the perception of the reaction course, (b) determination of the target (construction of the reaction product or products) [The reactions are coded on the basis of their mechanism. Thus, for example, in a nucleophilic substitution, the reaction course will be defined by the starting materials, $R-L + Nu-H$, and the reaction products will be $R-Nu + L-H$. In the program, the most important reaction mechanisms have been encoded (e.g., nucleophilic elimination, nucleophilic addition, oxidation and reduction reactions, etc.)], and (3) flow sheet (diagram) of the program (see Scheme II).

Model Reaction. Maltol and ammonia are important products of the Maillard reaction. The reaction between maltol [2-methyl-3-hydroxy-4*H*-pyranone] and ammonia has been experimentally studied by Shibamoto et al. (1981). The identified reaction products are shown in Figure 1.

Three different types of reactions are possible (Scheme III). The first group is the dimerization reactions of maltol, summarized in Figure 2. The second group of reactions is characterized by the ring opening of maltol followed by recyclization as shown in Figure 3. Finally, fragmentation reactions can take place as well. The fragments whose formation was predicted by computer are shown in Figure 4.

The products identified by Shibamoto et al. (1981) include those resulting from the cleavage of the maltol molecule and the subsequent interactions between the fragments. On the basis of the knowledge of the products shown in Figure 1 it is possible to deduce the structures of the fragmentation products. They are summarized in Figure 5.

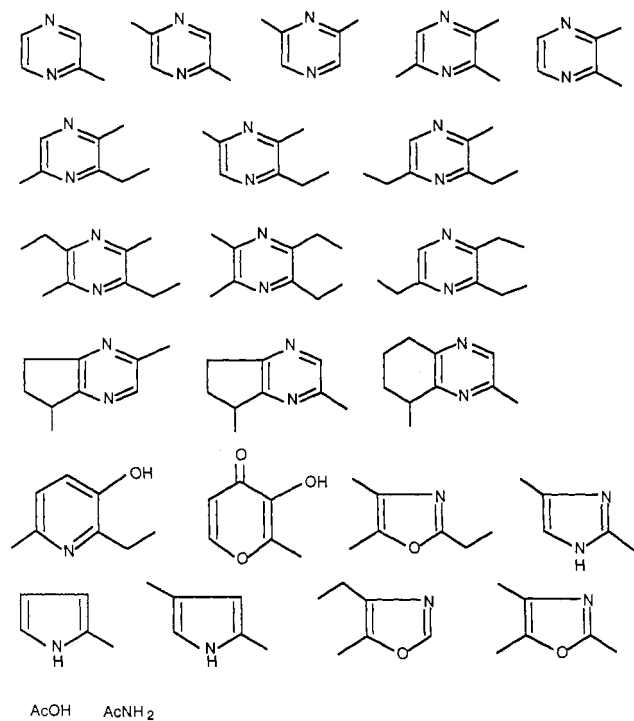


Figure 1. Products experimentally identified by Shibamoto et al. (1981) in the reaction of maltol with ammonia.

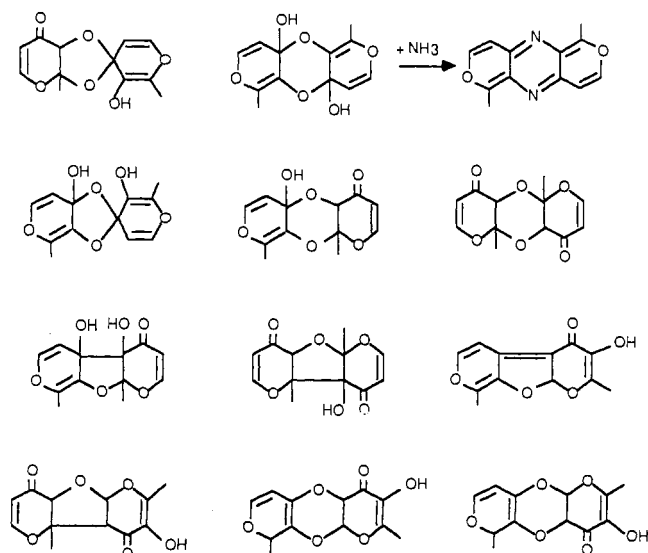


Figure 2. Products theoretically predicted by the computer for the dimerization of maltol.

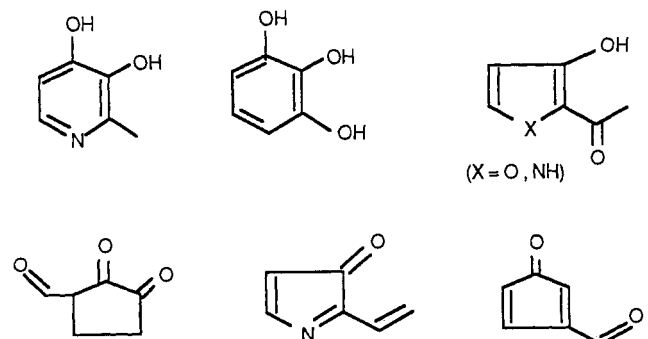
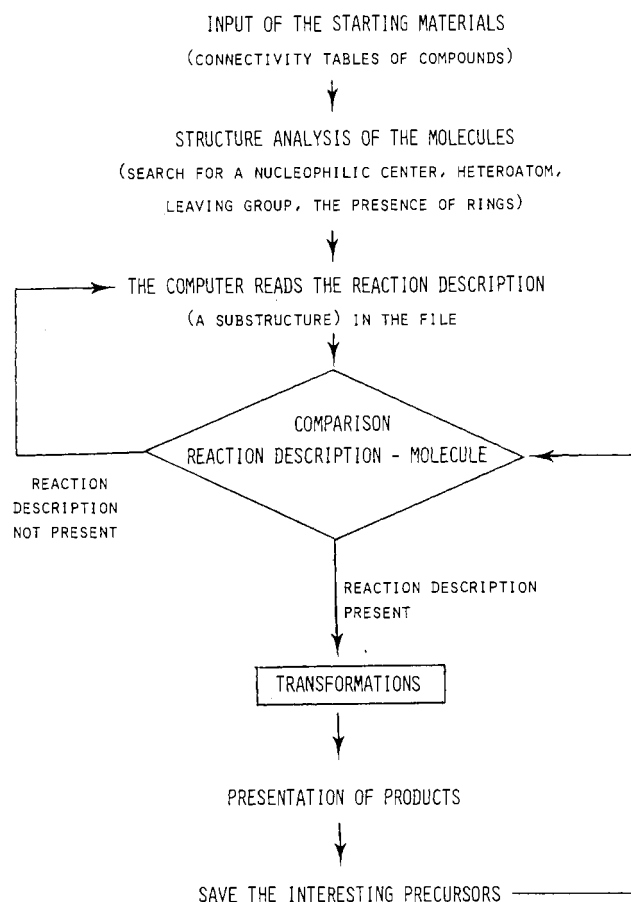


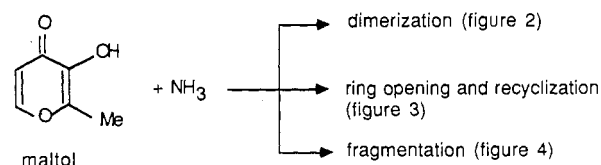
Figure 3. Products theoretically resulting from the ring opening of maltol.

The second stage of the study involves prediction of the products that could be formed from different fragments. To make the prediction, the fragments in Figure 5 that

Scheme II. Flow Diagram of the CAOS Program



Scheme III. Different Types of Reactions Arising from the Condensation of Maltol with Ammonia



correspond to the actually identified products and are very close to those predicted by the computer were used.

The number and structural types of compounds that have been predicted by CAOS are very large, and it does not seem practical to list them. The basic heterocyclic structures whose formation has been predicted are shown in Figure 6 (1-16). Among these heterocycles several structural types represent well-known flavoring substances: 4,5-dihydro-3(2*H*)-furanones (1, X = O), furans (4 and 5, X = O), oxazoles (10, X = O), pyridines (11), and especially pyrazines (15).

As a more detailed example, we list the various pyrazines, 1,4-dioxines, imidazoles, and oxazoles predicted by our program. The pyrazines and 1,4-dioxines are listed in Table I, which also indicates the products actually identified by Shibamoto et al. (1981). The imidazoles and oxazoles are listed in Tables II and III. In Table III, the experimentally identified products are again indicated.

The pyrazines and 1,4-dioxines listed in Table I can be formed as in Scheme IV.

Similarly, the imidazoles and oxazoles (Tables II and III) can be obtained as in Scheme V.

An analogous explanation can be provided for many other structural types that can be formed. These have been predicted by the computer in numbers comparable to those given in the tables.

Aldehydes:

HCHO, MeCHO, Et CHO,

Acids:

HCOOH, MeCOOH, Et COOH

Ketones:

MeCO Me, MeCO Et

Unsaturated carbonyl compounds:

 $\text{CH}_2=\text{C}=\text{O}$, $\text{CH}_2=\text{CHCO}$ Et, $\text{MeCH}=\text{C}=\text{O}$, $\text{MeCOCH}=\text{CH}$ Me α,β -Dicarbonyl compounds:

CHOCHO, MeCOCOMe, MeCOCOEt

 α -Hydroxylated carbonyl compounds:MeCOCH₂OH

Miscellaneous:

CHOCH₂CHO, HCOCH₂COOH, $\text{CH}_2=\text{CHCOCH}_2\text{OH}$,MeCOCHOHCH₂OH, MeCOCH₂CHO, MeCHOHCOCH₂OH,HCOCH₂COCH₂OH, MeCOCHOHCOMe, MeCOCHOHCOCH₂CHO

Figure 4. Fragmentation products obtained from maltol. The formation of these products can be explained as due to retroaldolization and retro-Diels-Alder reactions of maltol and its partially reduced derivatives.

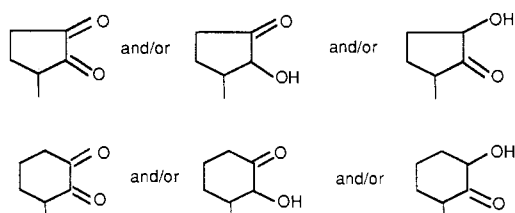
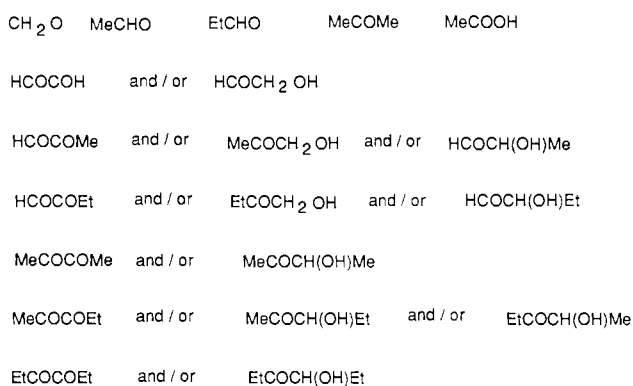
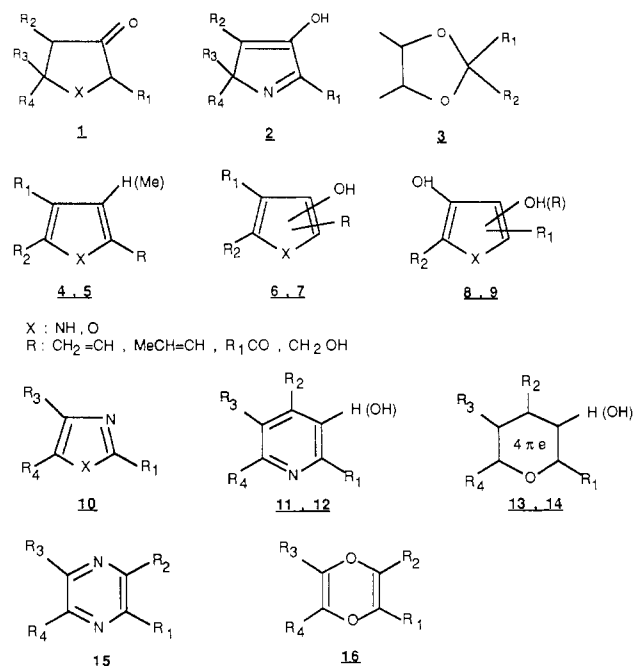


Figure 5. Fragments deduced on the basis of structures identified by Shibamoto et al. (1981).

In this particular approach, the computer does not evaluate the actual probability of the various reactions, which means that some of the predicted structures are unlikely to form. However, the computer correctly identifies several large groups of heterocyclic compounds commonly present in food flavors, such as the pyrazines and oxazoles.

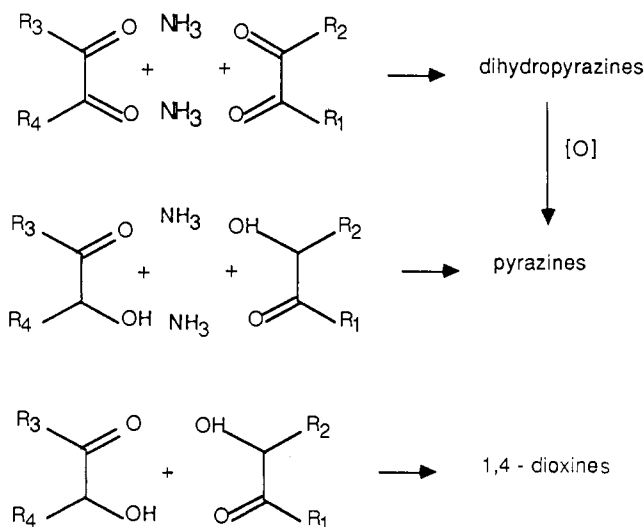
In the case of the reaction studied, a comparison of the predicted structures with the experimental data shows that the CAOS approach in the area of chemistry of heterocyclic food flavors is of interest, especially in view of the relatively small number of actually identified compounds when one compares them with the number of predicted structures.



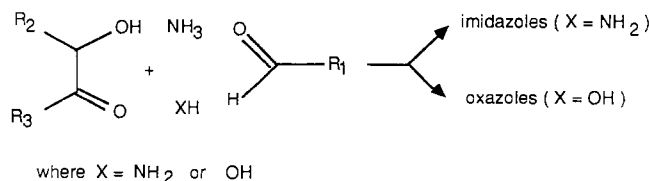
In 1 through 16, $\text{R}_1, \text{R}_2 = \text{H, Me, Et, MeCHCH}_2\text{CH}_2$ and $\text{MeCH}(\text{CH}_2)_2\text{CH}_2$
Analogous R_3 and R_4

Figure 6. Computer-predicted heterocycles resulting from the reaction of maltol with ammonia.

Scheme IV. Formation of Pyrazines and 1,4-Dioxines



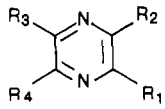
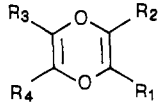
Scheme V. Formation of Imidazoles and Oxazoles



The pyrazines can serve as a typical and significant example: while 51 structures have been predicted, only 14 of them have been experimentally identified so far.

Because mass spectrometry coupled with gas chromatography serves as one of the best tools for identification of heterocyclic food flavors, it is clear that identification of additional compounds will be greatly facilitated by the availability of a bank of mass spectral data (Petitjean et al., 1981a, 1983). Such banks appear to be absolutely

Table I. Computer-Predicted Pyrazines and 1,4-Dioxines^a

R ₁	R ₂	R ₃	R ₄	
H	H	H	H	
H	H	H	Me	×
H	H	H	Et	
H	H	Me	Me	×
H	Me	H	Me	×
H	Me	Me	H	×
H	Et	H	Me	
H	H	Me	Et	
H	Me	Et	H	
H	H	Et	Et	
H	Et	H	Et	
H	Et	Et	H	
H	H	CH ₂ CH ₂ CH(Me)		
H	H	CH ₂ CH ₂ CH ₂ CH(Me)		
H	Me	Me	Me	×
H	Me	Me	Et	×
H	Me	Et	Me	×
H	Me	Et	Et	
H	Me	CH ₂ CH ₂ CH(Me)		×
H	Me	CH(Me)CH ₂ CH ₂		×
H	Me	CH ₂ CH ₂ CH ₂ CH(Me)		
H	Me	CH(Me)CH ₂ CH ₂ CH ₂		×
H	Et	Me	Me	
H	Et	Me	Et	
H	Et	Et	Me	×
H	Et	Et	Et	×
H	Et	CH ₂ CH ₂ CH(Me)		
H	Et	CH(Me)CH ₂ CH ₂		
H	Et	CH ₂ CH ₂ CH ₂ CH(Me)		
H	Et	CH(Me)CH ₂ CH ₂ CH ₂		
Me	Me	Me	Me	
Me	Me	Me	Et	
Me	Me	Et	Et	×
Me	Et	Me	Et	×
Me	Et	Et	Me	
Me	Et	Et	Et	
Me	Me	CH ₂ CH ₂ CH(Me)		
Me	Me	CH ₂ CH ₂ CH ₂ CH(Me)		
Me	Et	CH ₂ CH ₂ CH(Me)		
Me	Et	CH(Me)CH ₂ CH ₂		
Et	Et	Et	Et	
Et	Et	CH ₂ CH ₂ CH(Me)		
Et	Et	CH ₂ CH ₂ CH ₂ CH(Me)		
CH ₂ CH ₂	CH(Me)	CH ₂ CH ₂ CH ₂		
CH ₂ CH ₂	CH(Me)	CH(Me)CH ₂ CH ₂		
CH ₂ CH ₂	CH(Me)	CH ₂ CH ₂ CH ₂ CH(Me)		
CH ₂ CH ₂	CH(Me)	CH(Me)CH ₂ CH ₂ CH ₂		
CH ₂ CH ₂ CH ₂	CH(Me)	CH ₂ CH ₂ CH ₂ CH(Me)		
CH ₂ CH ₂ CH ₂	CH(Me)	CH(Me)CH ₂ CH ₂ CH ₂		

^a An × indicates a pyrazine experimentally identified by Shibamoto et al. (1981).

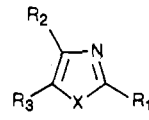
essential for this purpose, and a number of them are now available.

A number of computerized techniques used for interpretation of mass spectral data have been described in the literature (Heller, 1974; Jurs, 1974; Smith et al., 1974; Chapman, 1978; Vernin et al., 1986). They can be divided into three basic types: (1) pattern recognition; (2) artificial intelligence; (3) comparative methods involving library search. The third approach seems to have been used most extensively.

The number of matches between predicted structures and those experimentally identified will undoubtedly show a substantial increase in the near future.

Other Examples. In addition to the reaction of maltol with ammonia, several other reactions in the area of heterocyclic food flavors have been studied by the CAOS and two examples will be presented here.

Table II. Computer-Predicted Imidazoles and Oxazoles^a

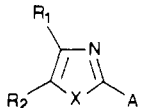


X = NH, O

R ₁	R ₂	R ₃	
H	H	H	
H	H	Me	
H	Me	H	
Me	H	H	
H	H	Et	
H	Et	H	
Et	H	H	
Me	H	Me	
Me	Me	H	×
H	Me	Me	
H	Et	Me	×
H	Me	Et	
H	Et	Et	
Me	H	Et	
Me	Et	H	
Me	Me	Me	×
Me	Me	Et	
Me	Et	Et	
H	CH ₂ CH ₂ CH(Me)		
H	CH(Me)CH ₂ CH ₂		
H	CH ₂ CH ₂ CH ₂ CH(Me)		
H	CH(Me)CH ₂ CH ₂ CH ₂		
Me	CH ₂ CH ₂ CH(Me)		
Me	CH(Me)CH ₂ CH ₂		
Me	CH ₂ CH ₂ CH ₂ CH(Me)		
Me	CH(Me)CH ₂ CH ₂ CH ₂		
Et	H	Me	
Et	Me	H	
Et	H	Et	
Et	Et	H	
Et	Me	Me	×
Et	Me	Et	
Et	Et	Me	
Et	Et	Et	
Et	CH ₂ CH ₂ CH(Me)		
Et	CH(Me)CH ₂ CH ₂		
Et	CH ₂ CH ₂ CH ₂ CH(Me)		
Et	CH(Me)CH ₂ CH ₂ CH ₂		
CH ₂ OH	H	H	
CHO	H	H	
CH ₂ OH	H	Me	
CHO	H	Me	
CH ₂ OH	Me	H	
CHO	Me	H	
CH ₂ OH	Me	Me	
CHO	Me	Me	
CH ₂ OH	H	Et	
CHO	H	Et	
CH ₂ OH	Et	H	
CHO	Et	H	
CH ₂ OH	Me	Et	
CHO	Me	Et	
CH ₂ OH	Et	Me	
CHO	Et	Me	
CH ₂ OH	Et	Et	
CHO	Et	Et	
CH ₂ OH	CH ₂ CH ₂ CH(Me)		
CHO	CH ₂ CH ₂ CH(Me)		
CH ₂ OH	CH(Me)CH ₂ CH ₂		
CHO	CH(Me)CH ₂ CH ₂		
CH ₂ OH	CH ₂ CH ₂ CH ₂ CH(Me)		
CHO	CH ₂ CH ₂ CH ₂ CH(Me)		
CH ₂ OH	CH(Me)CH ₂ CH ₂ CH ₂		
CHO	CH(Me)CH ₂ CH ₂ CH ₂		

^a An × indicates an oxazole experimentally identified by Shibamoto et al. (1981).

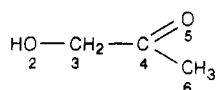
Oxygen Heterocycles by the Maillard Reaction. As a continuation of the initial efforts (Barone, 1976; Barone and Chanon, 1978), one of the first groups of reactions was

Table III. Additional Computer-Predicted Imidazoles and Oxazoles


X = NH, O; A = COMe, COEt, CH=CH₂, CH=CHMe

R ₁	R ₂
H	H
H	Me
Me	H
H	Et
Et	H
Me	Me
Me	Et
Et	Me
Et	Et
CH ₂ CH ₂ CH(Me)	
CH(Me)CH ₂ CH ₂	
CH ₂ CH ₂ CH ₂ CH(Me)	
CH(Me)CH ₂ CH ₂ CH ₂	

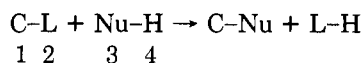
the Maillard reaction leading to the formation of various oxygen heterocycles, with D-glucose, 4-hydroxy-3(2*H*)-furanone, hydroxyacetone, maltol, and isomaltol (Barone et al., 1980; Barone and Chanon, 1982). The starting molecules were represented by a connectivity table:



no.	atom	bonded atoms	mult of bonds
1	H		
2	O	1 3	1 1
3	C	2 1 1 4	1 1 1 1
4	C	3 5 6	1 2 1
5	O	4	2
6	C	4 1 1 1	1 1 1 1

The hydrogen atoms were assigned number 1. The table shows the types of atoms, the bonds existing between atoms, and their multiplicity. From this table, one can also obtain information about the functions, rings, the nucleophilic center, the leaving group, etc. All this information is coded and can be used in the program.

The reactions were coded on the basis of their reaction mechanisms. For example, a nucleophilic substitution was coded as follows:



Here, L is a leaving group and Nu is the nucleophilic center in the nucleophile. The program recognizes the reaction type, breaks bonds 1-2 and 3-4, and forms new bonds 1-3 and 2-4. The results obtained in the study describe the various mechanistic stages of the reactions, the possibilities of equilibrium processes, dehydration reactions, the different possibilities of the heterocyclic ring closure, etc. The program has correctly predicted a number of structures close to those described in the literature as actually found [e.g., Fagerson (1969) and Feather and Harris (1973)] and, in addition, also a number of structures unidentified so far. However, the program does not offer any discrimination of structures likely to be formed and those unlikely.

Reaction of Furfural with Ammonia and Hydrogen Sulfide. Another reaction studied was that of furfural with ammonia and hydrogen sulfide (Barone et al., 1981; Petitjean et al., 1981b; Barone and Chanon, 1982). This is an interesting reaction because it takes place in almost all processed foods. Thermal degradation of sugars pro-

duces furfural, hydrogen sulfide is formed from cystine, cysteine, and thiamine, and ammonia is one of the products of pyrolysis of α -amino acids. Thus, the reactions stored in the computer program in this case included nucleophilic additions and substitutions, eliminations, oxidations, and some cycloadditions.

Shibamoto (1977) investigated this reaction experimentally, and all the compounds identified in his study were also correctly identified by the computer, in addition to the various products identified in the Maillard reaction. The structures included furans, pyrroles, thiophenes, oxazoles, thiazoles, imidazoles, pyrans, pyridines, pyrazines, etc.

The reaction was reinvestigated by Vernin (1982b) who identified additional structures with the pyridine ring not reported by Shibamoto (1977). All in all, the computer predicted more than 1000 structures, only a small fraction of which have been actually found in food products so far.

CONCLUSION

This paper represents a summary of several applications of CAOS in the field of heterocyclic food flavors and shows what help experimental chemists can expect from it. Although the success of CAOS is not negligible and, as a matter of fact, is quite remarkable, there is still a long way to go and there are many obstacles to overcome.

One problem lies in CAOS itself. As has been mentioned in the text, so far the CAOS programs used in the area of heterocyclic food flavors cannot predict the probability with which a particular possible product will be formed; i.e., they do not distinguish between likely and unlikely products. In this respect, a knowledgeable organic chemist is still superior—he or she can predict, with a fair degree of accuracy, the likely products to be formed from given starting materials. An improvement in this direction is certainly needed in CAOS of heterocyclic flavors.

It should be pointed out here, however, that such efforts have already been successful in other areas of CAOS. Thus, e.g., Djerassi's REACT program has been designed to carry out representations of chemical reactions in the synthetic direction (Buchanan and Smith, 1977; Varkony et al., 1978a,b). A given compound is subjected to a repetitive application of a set of reactions with a twofold purpose: to simulate the biosynthesis of natural products and to suggest solutions in structure elucidation problems.

The CAMEO program developed by Jorgensen (1983) mimics the mechanistic reasoning of organic chemists and predicts the products of organic reactions on the basis of starting materials and reaction conditions. It is able to handle a number of different types of processes, such as (1) base-catalyzed and nucleophilic reactions (Salatin and Jorgensen, 1980); (2) electrophilic reactions (with carbocations as the reactive species) (Roos-Kozel, 1981; Schmidt Burnier and Jorgensen, 1983); (3) the chemistry of ylides and the organometallic chemistry of lithium, magnesium, and lithium cuprates (Salatin et al., 1981); (4) thermal polycyclic reactions, cycloadditions, electrocyclic reactions, and sigmatropic rearrangements (Schmidt Burnier and Jorgensen, 1983, 1984); and (5) reactions of unsaturated electrophiles including electrophilic aromatic substitution (Peishoff and Jorgensen, 1985). It has been adapted to organosilicon chemistry as well (Peishoff and Jorgensen, 1983). The program can identify rings, functional groups (more than a 100), aromaticity, stereochemistry, and potential nucleophilic and electrophilic sites. It can estimate pK_a values and check for unstable functional groups, tautomers, and highly strained rings (Ross-Kozel and Jorgensen, 1981). The program reflects the fact that hundreds of reactions involve different combinations of

only a few identical mechanistic steps. It means that it is preferable to thoroughly understand the behavior of this limited number of fundamental steps and the competition among them, rather than to create tables for huge numbers of specific reactions.

The second problem is related to the difficulties connected with the identification of the various flavors in food products, which is not an easy task. In everyday chemistry on which most of the currently known reactivity rules are based, products formed in amounts smaller than 1% are often neglected or not detected at all. The field of flavor chemistry is quite special in this respect—even trace amounts of a heterocyclic compound can represent the basis of a food flavor. Thus, an improvement of the identification methods is needed. As pointed out above, a combination of gas chromatography and mass spectrometry is one of the most successful approaches available today. A correct identification is normally arrived at through use of a bank of mass spectral data. Thus, the second most important task awaiting the flavor chemist is to generate satisfactory data banks and computer programs that will match the spectrum of the unknown substance with a reference spectrum in the bank of mass spectral data and identify the compound. Efforts in this area are under way.

One of the most promising novel identification approaches is FT infrared spectroscopy coupled with gas chromatography (Griffiths et al., 1983).

To summarize, there is no question that CAOS will play an important role in the chemistry of heterocyclic food flavors in the years to come.

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LITERATURE CITED

- Adda, J., Ed. *Progress in Flavour Research 1984*; Elsevier: Amsterdam, 1985.
- Ash, J. E.; Hyde, E. *Chemical Information Systems*; Ellis Horwood: Chichester, 1975; Chapter 11.
- Balaban, A. T., Ed. *Chemical Applications of Graph Theory*; Academic: New York, 1976.
- Barone, R. Doctoral Dissertation (Docteur ès Sciences), Marseille, 1976.
- Barone, R.; Chanon, M. *Nouv. J. Chim.* **1978**, *2*, 659.
- Barone, R.; Chanon, M. In *The Chemistry of Heterocyclic Flavours and Aroma Compounds*; Vernin, G., Ed.; Ellis Horwood: Chichester, 1982.
- Barone, R.; Chanon, M. Université d'Aix-Marseille III, Marseille, France, unpublished results, 1985.
- Barone, R.; Chanon, M. In *Computer Aids to Chemistry*; Vernin, G., Chanon, M., Eds.; Ellis Horwood: Chichester, 1986a; Chapter 1, pp 19-102.
- Barone, R.; Chanon, M. Université d'Aix-Marseille III, Marseille, France, unpublished results, 1986b.
- Barone, R.; Chanon, M.; Vernin, G.; Metzger, J. *Riv. Ital. EPPOS* **1980**, *62*(3), 136.
- Barone, R.; Chanon, M.; Vernin, G.; Petitjean, M.; Metzger, J. *Parfums, Cosmet., Aromes* **1981**, *38*, 71.
- Bersohn, M.; Esack, A. *Chem. Rev.* **1976**, *76*, 269.
- Brandt, J.; Friedrich, J.; Gasteiger, J.; Jochum, C.; Schubert, W.; Ugi, I. In *Computer Assisted Synthesis*; ACS Symposium Series 61; American Chemical Society: Washington, DC, 1977a; p 39.
- Brandt, J.; Friedrich, J.; Gasteiger, J.; Jochum, C.; Schubert, W.; Ugi, I. In *Computers in Chemical Education and Research*; Ludena, E. V., Sabelli, N. H., Wahl, A. C., Eds.; Plenum: New York, 1977b; p 401.
- Buchanan, B. G.; Smith, D. H. In *Computers in Chemical Education and Research*; Plenum: New York, 1977; p 401.
- Bullard, R. W., Ed.; *Flavor Chemistry of Animal Foods*; American Chemical Society: Washington, DC, 1978.
- Carlson, R.; Albano, C.; Hammarstöm, L. G.; Johansson, E.; Nilsson, A.; Carter, R. E. *J. Mol. Sci.* **1983**, *2*, 1.
- Chapman, J. R. In *Computers in Mass Spectrometry*; Academic: New York, 1978; p 149.
- Charalambous, G., Inglett, G. E., Eds. *Flavor of Foods and Beverages: Chemistry and Technology*; Academic: New York, 1978.
- Corey, E. J.; Wipke, W. T. *Science (Washington, D.C.)* **1969**, *166*, 178.
- Drawert, F. Proceedings of the International Symposium on Aroma Research, Wageningen, 1975; p 13.
- Dyson, G. M. *A New Notation and Enumeration System for Organic Compounds*, 2nd ed.; Longmans: London, 1949.
- Fagerson, J. S. *J. Agric. Food Chem.* **1969**, *17*, 747.
- Feather, M. S.; Harris, J. F. *Adv. Carbohydr. Chem. Biochem.* **1973**, *28*, 161.
- Gasteiger, J.; Jochum, C. *Top. Curr. Chem.* **1978**, *74*, 93.
- Granito, C. E. *J. Chem. Doc.* **1973**, *13*, 72.
- Graovac, A.; Gutman, I.; Trinajstić, N. *Lect. Notes Chem.* **1977**, *4*.
- Griffiths, P. R.; De Haseth, J. A.; Azarraga, L. V. *Anal. Chem.* **1983**, *55*, 1361.
- Gund, P. *Annu. Rep. Med. Chem.* **1977**, *12*, 288.
- Gund, P.; Grabowski, E. J. J.; Smith, G. M.; Andose, J. D.; Rhodes, J. B.; Wipke, W. T. *Computer Assisted Drug Design*; American Chemical Society: Washington, DC, 1979; p 527.
- Gutman, I.; Trinajstić, N. *Top. Curr. Chem.* **1973**, *42*, 49.
- Haggin, J. *Chem. Eng. News* **1983**, *61* (No. 9), 7.
- Heller, S. R. In *Computer Representation and Manipulation of Chemical Information*; Wipke, W. T., Heller, S. R., Feldman, R. J., Hyde, E., Eds.; Wiley: New York, 1974.
- Hendrickson, J. B. *J. Am. Chem. Soc.* **1971**, *93*, 6847.
- Hendrickson, J. B. *J. Chem. Educ.* **1978**, *55*, 216.
- Hendrickson, J. B.; Braun-Keller, E.; Toczko, G. A. *Tetrahedron* **1981**, *37* (Suppl. 1), 359.
- Herndon, W. C. *Stud. Phys. Theor. Chem.* **1983**, *28*, 231.
- Herndon, W. C.; Párkányi, C. *Tetrahedron* **1978**, *34*, 3419.
- Herndon, W. C.; Párkányi, C. *Tetrahedron* **1982**, *38*, 2551.
- Herndon, W. C.; Leonard, J. E. *Inorg. Chem.* **1983**, *22*, 554.
- Jorgensen, W. L. *Kagaku* **1983**, *38*, 483.
- Jurs, P. C. In *Computer Representation and Manipulation of Chemical Information*; Wipke, W. T., Heller, S. R., Feldman, R. J., Hyde, E., Eds.; Wiley: New York, 1974.
- Long, A. K.; Rubenstein, S. D.; Joncas, L. J. *Chem. Eng. News* **1983**, *61* (No. 9), 22.
- Lynch, M. F. *Computer-Based Information Services in Science and Technology*; P. Peregrinus: Herts, England, 1974.
- Lynch, M. F.; Harrison, J. M.; Town, W. G. *Computer Handling of Chemical Structure Information*; McDonald of London, American Elsevier of New York, 1971.
- Maarse, H.; Belz, R. *Isolation, Separation and Identification of Volatile Compounds in Aroma Research*; Akademie-Verlag: Berlin, 1981.
- Maillard, L. C. *R. Hebd. Seances Acad. Sci.* **1912**, *154*, 66.
- Morton, I. D.; MacLeod, A. J.; Eds. *Food Flavours. Part A. Introduction*; Elsevier: Amsterdam, 1982.
- Nykänen, L.; Suomalainen, H. *Aroma of Beer, Wine and Distilled Alcoholic Beverages*; D. Reidel: Dordrecht, 1983.
- Ohloff, G.; Flament, I. *Prog. Chem. Org. Nat. Prod.* **1979**, *36*, 231.
- O'Korn, L. J. In *Algorithms for Chemical Computations*; Christoffersen, R. E., Ed.; American Chemical Society: Washington, DC, 1977; p 122.
- Peishoff, C. E.; Jorgensen, W. L. *J. Org. Chem.* **1983**, *48*, 3923.
- Peishoff, C. E.; Jorgensen, W. L. *J. Org. Chem.* **1985**, *50*, 1056.
- Petitjean, M.; Vernin, G.; Metzger, J. *Ind. Aliment. Agric.* **1981a**, *9*, 741.
- Petitjean, M.; Vernin, G.; Metzger, J.; Barone, R.; Chanon, M. In *The Quality of Foods and Beverages, Chemistry and Technology*; Charalambous, G., Inglett, G., Eds.; Academic: New York, 1981b; Vol. 2, p 253.
- Petitjean, M.; Vernin, G.; Metzger, J. In *Instrumental Analysis of Foods. Recent Progress*; Charalambous, G., Inglett, G., Eds.;

- Academic: New York, 1983; Vol. 1, p 97.
- Read, P. C. *J. Chem. Inf. Comput. Sci.* **1983**, *23*, 135.
- Rohan, T. A. *J. Sci. Food Agric.* **1963**, *14*, 799.
- Rohan, T. A. *J. Food Sci.* **1964**, *29*, 456.
- Ross-Kozel, B. L. Doctoral Dissertation (Ph.D.), Purdue University, 1981.
- Ross-Kozel, B. L.; Jorgensen, W. L. *J. Chem. Inf. Comput. Sci.* **1981**, *21*, 101.
- Rush, J. E. *J. Chem. Inf. Comput. Sci.* **1976**, *16*, 202.
- Salatin, T.; Jorgensen, W. L. *J. Org. Chem.* **1980**, *45*, 2043.
- Salatin, T.; McLaughlin, D.; Jorgensen, W. L. *J. Org. Chem.* **1981**, *46*, 5284.
- Sarett, L. H. *Synthetic Organic Chemistry. New Techniques and Targets*, presented before the Manufacturers Association, June 9, 1964.
- Schmidt Burnier, J.; Jorgensen, W. L. *J. Org. Chem.* **1983**, *48*, 3923.
- Schmidt Burnier, J.; Jorgensen, W. L. *J. Org. Chem.* **1984**, *49*, 3001.
- Shibamoto, T. *J. Agric. Food Chem.* **1977**, *25*, 206.
- Shibamoto, T.; Russell, G. F. *J. Agric. Food Chem.* **1976**, *24*, 843.
- Shibamoto, T.; Nishimura, O.; Mihara, S. *J. Agric. Food Chem.* **1981**, *29*, 643.
- Shigematsu, H.; Kurata, T.; Kato, H.; Fujimaki, M. *Agric. Biol. Chem.* **1972**, *36*, 1631.
- Smith, D. H.; Masinter, L. M.; Sridharan, N. S. In *Computer Representation and Manipulation of Chemical Information*; Wipke, W. T., Heller, S. R., Feldman, R. J., Hyde, E., Eds.; Wiley: New York, 1974.
- Smith, E. G.; Becker, P. A. *The Wisswesser Line Formula Chemical Notation*; Chemical Information Management: Cherry Hill, NJ, 1976.
- Teranishi, R., Ed. *Agricultural and Food Chemistry: Past, Present, Future*; Avi: Westport, CT, 1978.
- Trinajstić, N. *Mod. Theor. Chem.* **1977**, *7*, 1.
- Trinajstić, N.; Jericević, Z.; Knop, J. V.; Mueller, W. R.; Szymanski, K. *Pure Appl. Chem.* **1983**, *55*, 379.
- Ugi, I. *IBM-Nachr.* **1974**, *24*, 180.
- Ugi, I.; Gillespie, P. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 914, 915.
- Ugi, I.; Gillespie, P.; Gillespie, C. *Trans. N.Y. Acad. Sci.* **1972**, *34*, 416.
- Varkony, T. H.; Cahart, R. E.; Smith, D. H.; Djerassi, C. *J. Chem. Inf. Comput. Sci.* **1978a**, *18*, 168.
- Varkony, T. H.; Smith, D. H.; Djerassi, C. *Tetrahedron* **1978b**, *34*, 841.
- Vernin, G., Ed. *The Chemistry of Heterocyclic Flavouring and Aroma Compounds*; Ellis Horwood: Chichester, 1982a.
- Vernin, G. Université d'Aix-Marseille III, Marseille, France, unpublished results, 1982b.
- Vernin, G.; Metzger, J. *Bull. Soc. Chim. Belg.* **1981**, *90*, 553.
- Vernin, G.; Párkányi, C. In *The Chemistry of Heterocyclic Flavouring and Aroma Compounds*; Ellis Horwood: Chichester, 1982; p 151.
- Vernin, G.; Petitjean, M.; Metzger, J. In *Use of Enzymes in Food Technology*, Proceedings of an International Symposium, Versailles, May 5-7, 1982; Dupuy, P., Ed.; Technique et Documentation Lavoisier: Paris, 1982; p 25.
- Vernin, G.; Petitjean, M.; Metzger, J.; Fraisse, D.; Suon, K.-N.; Scharff, C. In *Capillary Chromatography in Essential Oil Analysis*; Bicchi, C., Sandra, P., Eds.; Hüthig Verlag: Heidelberg, 1986.
- Vleduts, G. E. *Inf. Storage Retr.* **1963**, *1*, 101.
- Vollmer, J. J. *J. Chem. Educ.* **1983**, *60*, 192.
- Waller, G. R.; Feather, M. S., Eds. *The Maillard Reaction in Foods and Nutrition*; American Chemical Society: Washington, DC, 1983.
- Wipke, W. T., Howe, W. J., Eds. *Computer-Assisted Organic Synthesis*; American Chemical Society: Washington, DC, 1977.
- Wipke, W. T.; Heller, S. R.; Feldman, R. J.; Hyde, E. *Computer Representation and Manipulation of Chemical Information*; Wiley: New York, 1974.
- Zamora, A.; Dayton, D. L. *J. Chem. Inf. Comput. Sci.* **1976**, *16*, 219.

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Volatile Flavor Components of *Annona atemoya* (Custard Apple)

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The volatiles of fresh custard apple (*Annona atemoya* cv. African Pride) were separated by simultaneous steam distillation-solvent extraction and analyzed by capillary gas chromatography and capillary gas chromatography-mass spectrometry. All of the compounds identified were mono- or sesquiterpenes with α - and β -pinene, germacrene D, and bicyclogermacrene constituting the major components. No marked change in the composition of the volatiles was observed during ripening.

The family Annonaceae contains a considerable number of fruits of economic significance (Idstein et al., 1984). Of these, *Annona atemoya* dominates the commercial market in Australia where it is known as custard apple. A tropical fruit originating in the lowland tropics or subtropics of South America, they have a light green bumpy skin and a flesh that is white, juicy, and aromatic.

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Despite the characteristic desirable flavor of this fruit, no detailed analysis of the volatiles responsible or of their changes during ripening have been reported. The fruit investigated in this study was one of the two varieties generally grown commercially in Australia, the hybrid *A. atemoya* cv. African Pride.

EXPERIMENTAL SECTION

Fruits. Fresh custard apple fruits (*A. atemoya* cv. African Pride) adjudged to be mature but green were purchased from commercial sources in Sydney, Australia. They were stored at room temperature (average 15-16 °C), and individual fruits were extracted at various intervals