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CAST/CNMR: highly accurate ^{13}C NMR chemical shift prediction system considering stereochemistry

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Abstract—Accurate, practical prediction of ^{13}C NMR chemical shifts has been achieved with a new system, CAST/CNMR, taking account of stereochemistry. The CAST/CNMR system has solved the critical problem of the accurate distinction of differences and similarities in stereochemical structures around a specific carbon, which has not yet been achieved by any other database-oriented system for prediction of ^{13}C NMR chemical shifts. CAST/CNMR uses a three-dimensional structural database together with a ^{13}C NMR spectral database. Absolute/relative configurational and conformational structural information are described by the CAST (CAnonical-representation of STereochemistry) coding method. This paper provides an overview of the CAST/CNMR system, and describes its application to two natural products as examples.

1. Introduction

Many computer systems for prediction of NMR chemical shifts and for structural elucidation have been developed and widely used.[1–19] The systems help in making spectral assignments, and the predicted values are useful for verification of candidate structures. The combination of NMR chemical shift prediction systems with structure-elucidation systems is becoming a powerful approach for automatic structural determination and identification. However, no currently available database-oriented NMR chemical shift prediction system is practically useful in analyses of stereochemistry or in structural determination of stereoisomers; indeed, few of them consider stereochemistry. Some NMR chemical shift prediction systems using neural networks with consideration of stereochemistry have been reported,[13,18] but they have not yet achieved sufficient accuracy practically. Another approach for the calculation of NMR chemical shift by quantum chemical calculations has been developed, in combination with conformational search based on molecular mechanical and dynamical aspects.[11,19] However, the calculations are complex and time-consuming, especially for large-molecular systems.

In general, different chemical shifts are observed for nuclei having different stereochemical environments with the same planar structure. A successful study of stereochemical assignments based on correlation rules between synthetic stereoisomers and ^{13}C NMR chemical shifts was reported.[20] It is clear that a practical NMR chemical shift prediction system requires a consideration of stereochemistry, especially for treating structures containing complicated stereochemistry, such as natural products and intermediates of chemical synthesis. Indeed, we believe that it is impossible to predict accurate NMR chemical shifts without a precise consideration of stereochemical environments.

We developed a stereochemical coding method, CAST (CAnonical-representation of STereochemistry)[21,22] and utilized it to solve the problem of stereochemical treatment by computer. The CAST method employs canonical codes based on the dihedral angles. A three-dimensional structural database from which appropriate partial and whole chemical structures containing desired stereochemistry can be selected, was first achieved by application of the extended CAST method.[23]

The CAST coding method has been successfully applied to ^{13}C NMR chemical shift prediction system, called CAST/CNMR. The CAST/CNMR system uses the three-dimensional structural database together with a NMR chemical shift database. CAST/CNMR predicts chemical shifts according to the concept that precise search for the same partial structure having the same stereochemical environment will lead to efficient selection of chemically and magnetically equivalent carbon atoms from a database. Here, we describe the concepts and execution of the CAST/CNMR system. Its

Keywords: arisugacin F; 20-hydroxyecdysone; ^{13}C NMR assignments; natural products; database.

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examples, applications of CAST/CNMR to a terpenoid and a steroid are also described.

2. Results and discussion

2.1. CAST/CNMR system

A computer system for prediction of ^{13}C NMR chemical shifts have been developed and named CAST/CNMR. The key characteristics of the CAST/CNMR system are effective utilization of a spectral-structural database including stereochemical information to achieve highly accurate prediction of NMR chemical shift values for molecules exhibiting stereochemical complexity. In the CAST/CNMR system, chemical shift values are predicted by using databases, in which structural data are linked with the observed ^{13}C NMR chemical shift values. Stereochemical information in the database is described by means of extended CAST coding method.[23]

Its prediction procedure is shown in Figure 1, in which the chemical shift of C5 of arisugacin F (**1**) is predicted as an example. From the input query structural information, planar, conformational, and configurational CAST notations are constructed automatically.[21–23] The specified types of structural information are used for comparison with the database. CAST/CNMR searches the database and find molecules that have the same partial structures around carbon atoms as those of the query structure.The procedure

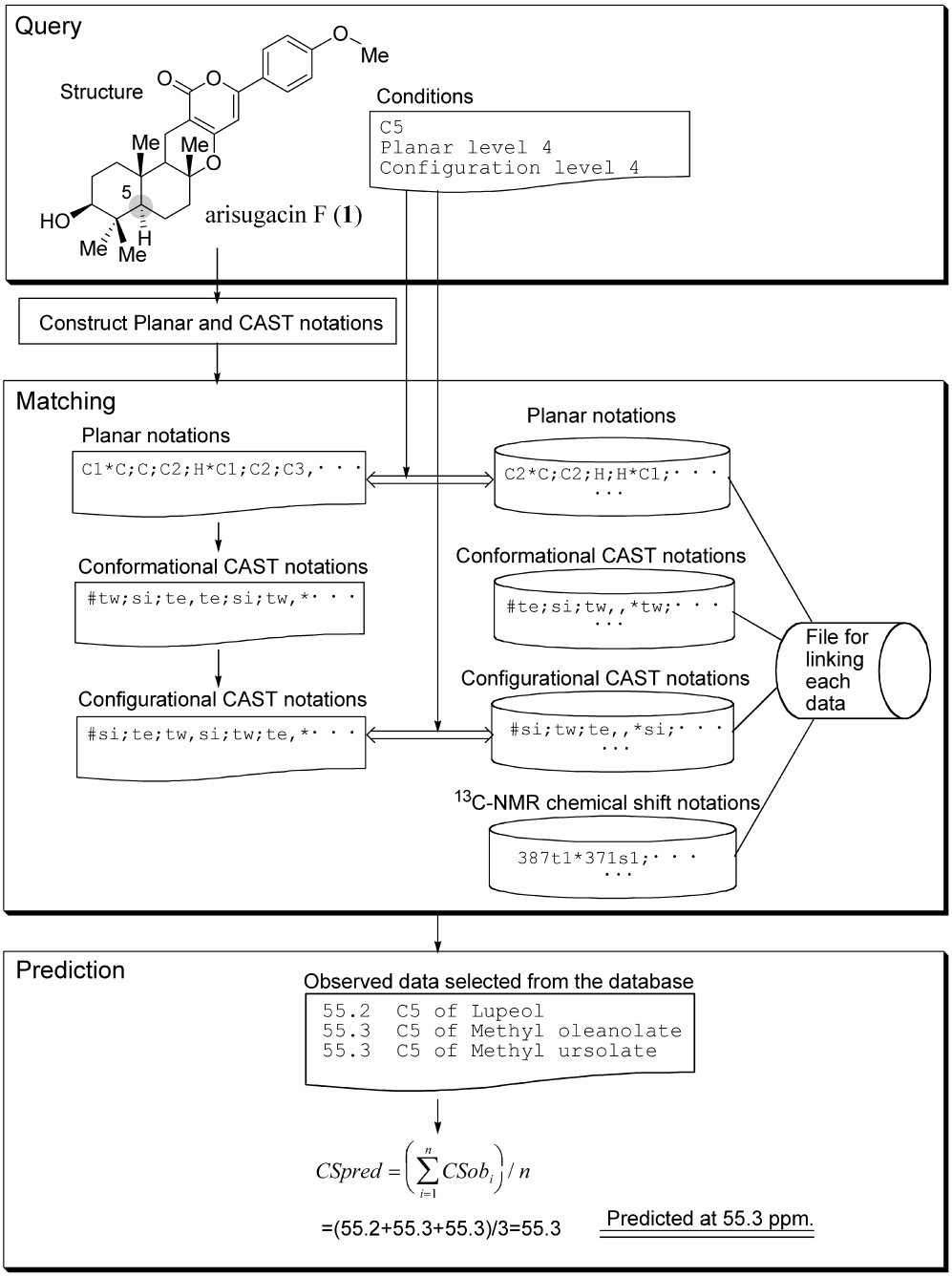

Figure 1. Prediction procedures of CAST/CNMR.

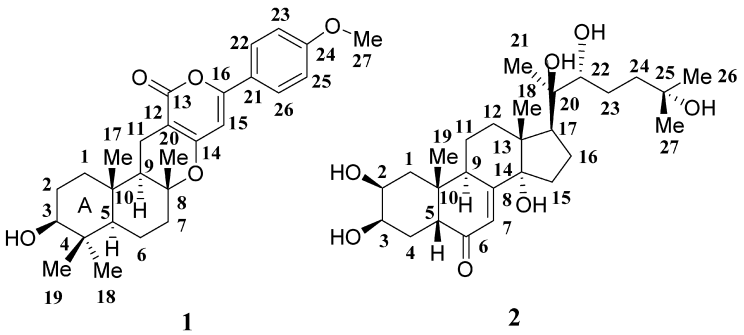

Figure 2. Structures of arisugacin F (**1**) and 20-hydroxyecdysone (**2**) and the numbering of each carbon atom.

of ^{13}C NMR chemical shift prediction in CAST/CNMR is simple. The average of the ^{13}C NMR chemical shift values of the hit molecules is given as the predicted value according to the following equation:

$$CS_{pred} = \left(\sum_{i=1}^{n} CS_{obi}\right)/n$$

where CS_{pred} is a predicted chemical shift value, CS_{ob} is an observed chemical shift value selected from the database results in the matching, and n is the number of hit carbon atoms.

2.2. Applications to natural products

Two natural products, arisugacin F (**1**)[24] and 20-hydroxyecdysone (**2**),[25] were chosen as examples for demonstration of the system. The application to **1** demonstrates that not only analogs but also structures having various skeletons can be useful in prediction of chemical shifts. The second application to **2** shows importance and necessity of stereochemical information and how the stereochemical information was effectively taken into account for highly accurate prediction. Structures of **1** and **2** and the numbering of each carbon atom are shown in Figure 2. The execution of CAST/CNMR shown here took account of both planar and relative configuration, and used observed data of structures that have the same partial structure within three bonds from a carbon atom as that of the query structure to be predicted.

Table 1. Predicted results for arisugacin F (**1**), the observed data, and differences between them

No. of carbon atom	Predicted ^{13}C chemical shift values (ppm)	Observed ^{13}C chemical shift values[24] (ppm)	Δ (predicted−observed values)
1	38.6	37.5	1.1
2	27.3	27.1	0.2
3	78.6	78.5	0.1
4	38.8	38.8	0
5	55.3	55.0	0.3
6	19.4	19.4	0
7	40.1	40.4	−0.3
8	80.6	80.5	0.1
9	51.3	51.6	−0.3
10	37.7	36.9	0.8
11	17.3	17.2	0.1
12	99.2	98.4	0.8
13	164.4	164.7	−0.3
14	163.3	163.5	−0.2
15	97.5	96.7	0.8
16	158.4	158.3	0.1
17	16.1	15.1	1.0
18	27.7	28.1	−0.4
19	15.3	15.5	−0.2
20	20.7	20.7	0
21	124.1	124.0	0.1
22	127.0	127.0	0
23	114.2	114.2	0
24	160.1	161.5	−1.4
25	114.2	114.2	0
26	127.0	127.0	0
27	55.3	55.4	−0.1

2.2.1. Prediction for arisugacin F. Predicted ^{13}C NMR chemical shift values of arisugacin F (**1**)[24] obtained with CAST/CNMR, the observed data, and differences between the predicted and the observed values are listed in Table 1. Figure 3 presents a graphical description, in which ordinate and abscissa show the numbering of atoms and the differences between observed and predicted values, respectively. Absolute values of the differences are within 1.5 ppm for 100% of the carbon atoms (all 27 carbon atoms), within 1.0 ppm for 93% of the carbon atoms (25 atoms), and within

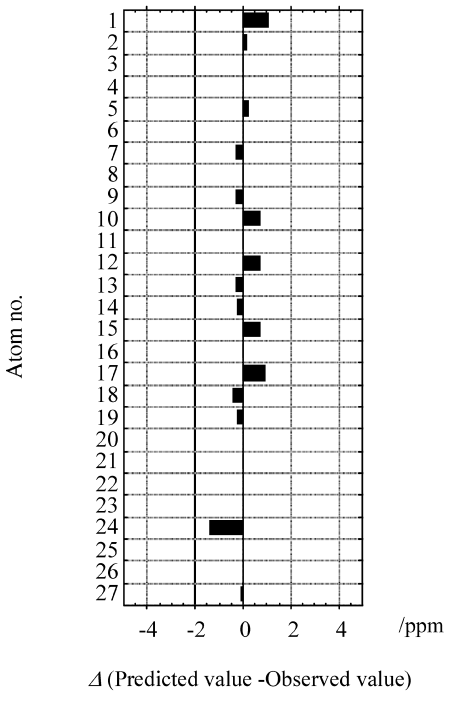

Figure 3. Deviations between predicted ^{13}C NMR chemical shift values from CAST/CNMR and the observed values of arisugacin F (**1**).

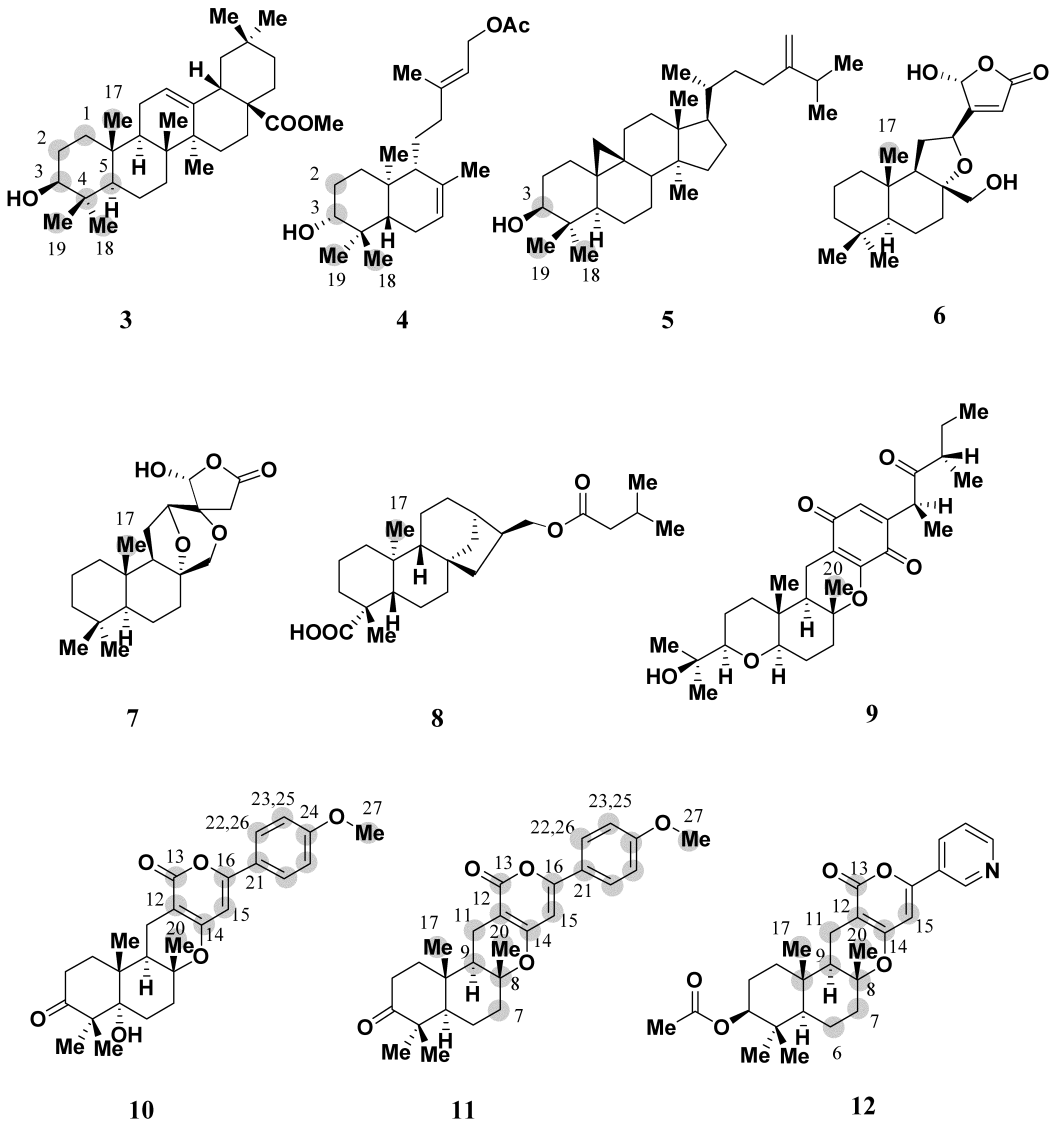

Figure 4. Structures selected in the prediction for arisugacin F (**1**). Carbon atoms for which observed data were selected in the prediction are denoted by gray circles and the number of the corresponding atom of arisugacin F (**1**) is shown.

0.5 ppm for 78% of the carbon atoms (21 atoms). The results show the high accuracy of CAST/CNMR-predicted chemical shift values.

In the prediction for arisugacin F (**1**), both congeners of arisugacin F (**1**) and compounds with quite different types of carbon skeleton incorporating similar partial structures were selected. Figure 4 shows some of these compounds having similar partial structures **3**–**9**,[26–31] and analogs with similar skeletons **10**–**12**,[24,32] in which selected carbon atoms are denoted by gray circles labeled with the carbon number of **1** for which they are predictive. Observed data of some structures **3**–**12** are listed in Table 2. In the left column, numbering of each of the matched atoms of **1** is listed. The second to sixth columns show data for compounds incorporating similar partial structures (**3**, **4**, **5**, **6**, and **9**), and the seventh to ninth columns show data for analogs (**10**–**12**). In the last column, the number of selected data is listed. Structures having various skeletons were mainly used in prediction for ring A (atoms 1–5, 10, and 17–19) of arisugacin F (**1**), because ring A is a common partial structure of terpenoids. On the other hand, analogs were mainly used in prediction for the other parts of **1**, because it has characteristic structural features, especially the highly substituted α-pyrone moiety. The results demonstrate that CAST/CNMR can clearly distinguish differences and similarities in partial structures and use them to give highly accurate predictions.

2.2.2. Prediction for 20-hydroxyecdysone. The second example is 20-hydroxyecdysone (**2**).[25] The predicted ^{13}C NMR chemical shift values, the observed data, and differences between the predicted and the observed data are listed in Table 3. Figure 5 presents a graphical description, in which the ordinate and abscissa show the numbering of atoms and the values of the differences, respectively. They show that absolute values of the differences between the predicted and observed data are within 1.0 ppm for 100% of the carbon atoms (all 27 carbon atoms) and within 0.5 ppm for 85% of the carbon atoms (23 atoms). Thus, CAST/CNMR gave highly accurate predicted values for **2**.

Table 2. Some of the observed data selected for the prediction

No. of the matched atom of **1**	Data selected for prediction (ppm)								Total number of selected data
	3	**4**	**5**	**6**	**9**	**10**	**11**	**12**	
1	38.5								3
2	27.2	27.3							4
3	79.0	79.0	78.9						10
4	38.8								3
5	55.3								3
10								37.7	2
17	15.3			15.5			14.7	15.1	21
18	28.1	27.8	25.5						10
19	15.6	14.9	14.0						10
6								19.2	4
7							39.8	40.2	3
8							80.2	80.8	3
9							51.0	51.4	3
11							17.3	17.3	3
12						98.4	98.2	100.2	5
13						164.6	164.5	163.9	5
14						163.5	163.5	162.8	5
15						96.7	96.6	99.3	7
16						158.4	158.5		5
20					20.8	20.4	20.5	20.7	6
21						124.0	124.0		5
22, 26						127.0	127.0		5
23, 15						114.2	114.2		5
24						161.5	161.5		21
27						55.4	55.4		22

When stereochemical information was not considered in the prediction for **2**, accurate predicted values were not obtained, because observed data from compounds having inappropriate relative configurational stereochemistry were also selected for the prediction. For example, the distribution of data used in prediction for C11 of **2** is shown in Figure 6. Figure 6(a) shows the observed ^{13}C NMR chemical shift value of C11, which is 21.3 ppm. Figure 6(b) and (c) shows the predicted value and data selected for the prediction by considering only planar structural information, and by considering also relative configurational stereochemistry, respectively, where predicted and selected observed data are denoted by long red and short pinkish lines, respectively. As shown in Figure 6(b), when only

Table 3. Predicted results for 20-hydroxyecdysone (**2**), the observed data, and differences between them

No. of carbon atom	Predicted chemical shift values (ppm)	Observed chemical shift values[25] (ppm)	Δ (predicted−observed values)
1	37.9	38.1	−0.2
2	68.4	68.3	0.1
3	68.3	68.2	0.1
4	32.6	32.5	0.1
5	51.2	51.5	−0.3
6	204.1	203.6	0.5
7	122.4	121.8	0.6
8	166.1	166.1	0.0
9	34.4	34.7	−0.3
10	38.7	38.8	−0.1
11	21.1	21.3	−0.2
12	32.0	32.3	−0.3
13	48.1	48.3	−0.2
14	84.0	84.4	−0.4
15	31.8	31.9	−0.1
16	21.4	21.6	−0.2
17	49.9	50.3	−0.4
18	17.9	18.0	−0.1
19	23.7	24.6	−0.9
20	76.8	77.1	−0.3
21	21.1	21.8	−0.7
22	77.4	77.7	−0.3
23	27.3	27.6	−0.3
24	42.6	42.6	0.0
25	69.6	69.9	−0.3
26	29.8	30.1[a]	−0.3
27	29.8	30.2[a]	−0.4

[a] Exchangeable.

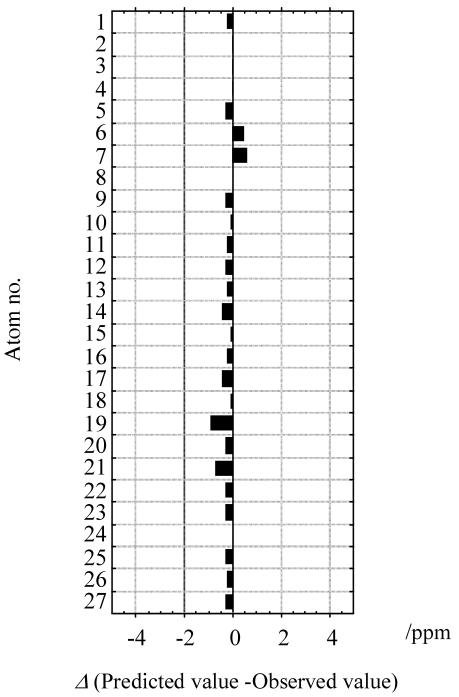

Figure 5. Deviations between predicted ^{13}C NMR chemical shift values from CAST/CNMR and the observed values of 20-hydroxyecdysone (**2**).

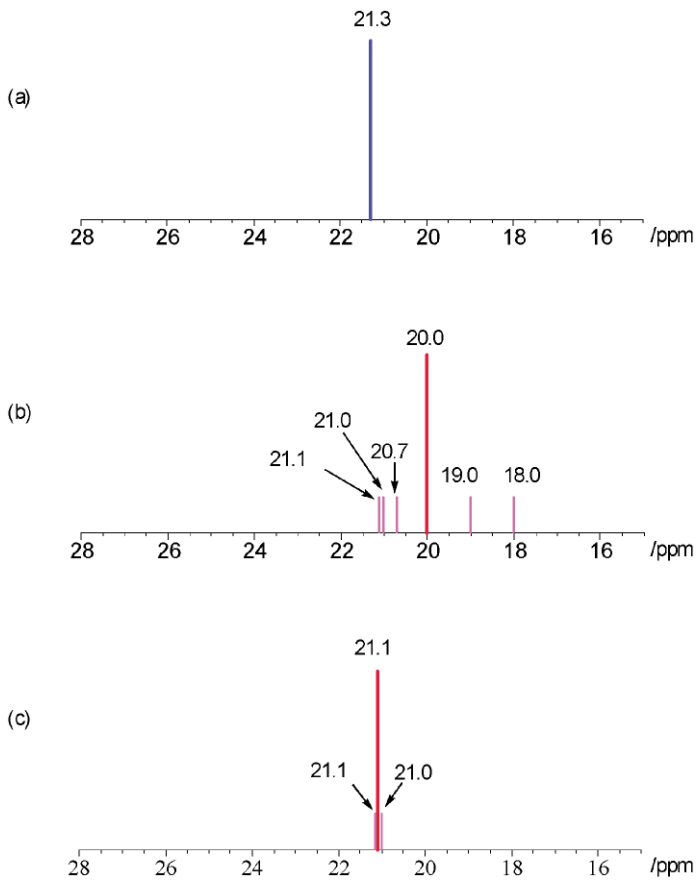

Figure 6. Effects of including stereochemical information on the distribution of observed data selected in the prediction of ^{13}C NMR chemical shift value for C11 of 20-hydroxyecdysone (**2**). (a) Observed ^{13}C NMR chemical shift value for C11 of **2**. (b) Predicted ^{13}C NMR chemical shift value and the observed data selected in the prediction by considering only planar structural information. A long red line denotes the predicted value, and short pinkish lines denote the observed ones. (c) Predicted ^{13}C NMR chemical shift value and the observed data used in the prediction by considering both planar structural and relative configurational stereochemical information. The meaning of the lines is the same as in (b).

planar structural information was considered, selected observed data were widely distributed and the predicted value was 20.0 ppm, which differs from the observed value of C11 of **2** by −1.3 ppm. Five compounds **13**–**17**[33–35] having the same or different stereochemistry for C5 and C10 were selected in the prediction without stereochemical information, as shown in Figure. 7, in which the C11 carbon atoms are denoted by gray circles and the observed data are shown. When stereochemical information were taken into account, only observed data of **16**[35] and **17**[25] were selected and used; data of **13**,[33] **14**,[33] and **15**[34] were rejected, because they have inappropriate relative configurations. In the prediction considering stereochemistry, the distribution of observed data is very narrow, and the outcome was the highly accurate prediction of 21.1 ppm. The difference between the predicted and observed data is only 0.2 ppm. The results show that CAST/CNMR can select only appropriate data for prediction by considering stereochemistry, and the predicted values are highly accurate. In other words, the results confirmed that consideration of stereochemistry is essential for accurate prediction of ^{13}C NMR chemical shift values for practical use.

In general, execution under more restrictive conditions gives more accurate results. When the selected chemical shift data show a wide distribution, increasingly restrictive conditions should be applied until a narrow distribution is obtained. Actually, when only data from compounds having the same partial structures within four bonds from a carbon atom were taken into account in the execution of prediction for 20-hydroxyecdysone (**2**), still more accurate predicted values were obtained, and the absolute values of the differences were within 0.5 ppm for 100% of the carbon atoms.

The two compounds used as examples here have relatively rigid structural features, except for the side chain portion of 20-hydroxyecdysone. In both cases, conformational information was not used in the ^{13}C NMR chemical shift prediction, because the configurational information alone was sufficient for the prediction. We also applied the CAST/CNMR system to open-chain flexible compounds in a preliminary study, and good results were obtained for compounds possessing stereogenic centers at adjacent positions by using configurational information (data not shown). The CAST/CNMR system can use conformational information together with configurational information, and conformational information may be important for the prediction of molecules having two or more stable conformers. Practical application of CAST/CNMR to several natural products and synthetic compounds will be reported elsewhere.

In the CAST/CNMR system, ^{13}C NMR chemical shifts are

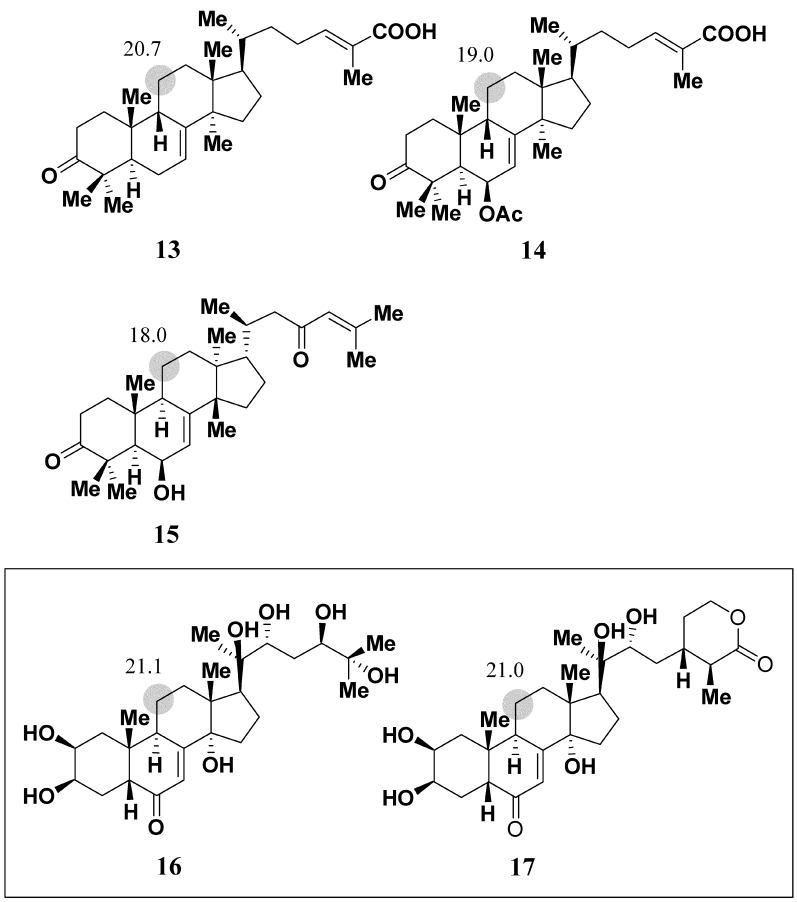

Figure 7. Structures selected in the prediction for C11 of 20-hydroxyecdysone (**2**). When stereochemical information was not considered, the five structures **13**–**17** were selected. They have the same or different relative configuration compared with **2**. When relative configurational information were considered, only **16** and **17** having the appropriate relative configuration were selected (enclosed by a rectangle).

the main target, but ^{1}H, ^{15}N, ^{19}F, ^{29}Si, and ^{31}P NMR chemical shifts can also be predicted. Since ^{1}H NMR signals are very sensitive to through-space interactions of functional groups such as aromatic rings and carbonyl groups, other methods will be required for accurate ^{1}H NMR chemical shift prediction.

The approach of CAST/CNMR is useful in organic chemistry, where NMR is generally used for characterization and analyses of chemical structures. In some cases of organic synthetic studies, NMR signals are not assigned because no 2D NMR data is measured. In the cases, CAST/CNMR can be used for confirmation of chemical structure with 1D NMR data and assignment of NMR signals partially or sometimes completely, even though there are no 2D NMR data. In other cases in structural characterization of natural products, both 1D and 2D NMR data is usually used. In the case, CAST/CNMR can be used for assignments of NMR signals, confirmation of candidate structures, and determination of stereochemical structures. Furthermore, it is also applicable to find NMR rules for stereochemical determinations.

3. Conclusion

A new system, CAST/CNMR, has been developed for highly accurate prediction of ^{13}C NMR chemical shift values by considering stereochemistry. Successful predictions for two natural products supported the validity of this approach. The CAST/CNMR is the first system that can be practically used in structural analysis and determination studies including stereochemistry.

As the number of reports of reliable assignments of ^{13}C NMR chemical shifts is rapidly increasing, the CAST/CNMR database will become applicable to a wider variety of compounds and will support increasingly accurate predictions of chemical shifts. In that sense, the new CAST/CNMR approach has great potential for stereochemical determination based on ^{13}C NMR chemical shift data and is expected to be a valuable tool in chemical structural analysis studies.

4. Experimental

4.1. Databases

In the database module of the CAST/CNMR system, planar (CANOST[36]), extended conformational and configurational CAST notations[21–23] are used for the description of structural data. Related data are linked with each other for flexible search. The structural data are also linked to the corresponding observed ^{13}C NMR chemical shift values. The ^{13}C NMR chemical shift data are described in CAST

notation style. The current database consists of 733 compounds, including natural terpenoids, steroids, polyketides, and polyethers, and synthetic intermediates used in total syntheses of some natural products.

4.2. Preparation of input data

Input query data is a MDL-molfile (MDL Information Systems, Inc) formatted file of a 3D-structure. In the current execution, we use CSC-ChemDraw and Chem3D (Cambridge Soft Corp.) programs for preparing the input molecular structural data.

4.3. Calculation in CAST/CNMR system

The structural search is performed by parallel comparison between the linear notations. Stereochemical and planar structural information are represented by CAST and CANOST coding methods, respectively. The construction and meaning of the linear notations have been described in previous papers.[21–23]

Query keys for the structural search are planar, configurational, and conformational environments with the minimum matching level. Matching level, i.e. partial structural size for search, can be specified arbitrary. Solvent and cyclic/acyclic features can also be specified. The user can specify the query key individually or in combinations. Typical partial structural size is three or four bonds from an atom to be predicted, and planar and configurational environments are usually used. Solvent and cyclic/acyclic features are sometimes used as optional query keys. Enantiomers can be considered in the search, namely, distinction of differences of absolute configuration and identification of the same relative configuration for an enantiomeric structure are available.

The average of the ^{13}C NMR chemical shift values of the hit molecules is given as the predicted value.

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