

New Perspectives in Computer-Assisted Formal Synthesis Design—Treatment of Delocalized Electrons[†]

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The Dugundji–Ugi theory of the be- (bond and electron) and r- (reaction) matrices provides no straightforward method for the representation and manipulation of molecular structures containing delocalized electrons. This article introduces a modification of the model that overcomes this restriction. It permits the treatment of molecules with multicenter bonds, π electron systems, and even of electron donor–acceptor complexes by formal computer programs.

1. INTRODUCTION

This article presents a concept for the representation of molecules containing delocalized electrons. It is an extension of the theory of the be- (bond and electron) and r- (reaction) matrices¹ that brings compounds with multicenter bonds, π electron systems, or π complexes of unsaturated organic molecules within the reach of *formal* synthesis design. There is no intention to simulate the quantum mechanics of reality.

About 25 years ago the theory of the be- and r-matrices was developed by Dugundji and Ugi. It is the algebraic model of the constitutional chemistry of a fixed collection of n atoms. Any ensemble of molecules (EM) can be described by an $n \times n$ symmetric be-matrix. The integer entries reflect a specific distribution of the valence electrons of the n atoms as covalent bonds and free electrons. A be-matrix is the direct representation of a molecular graph which may contain multiple edges (double or triple bonds) or loops (free electrons). The “electron pushing” patterns corresponding to chemical reactions are represented by r-matrices. The additive transformation of a be-matrix B by an r-matrix R yields the be-matrix E of the resulting product EM according to the fundamental equation $B + R = E$.

On this mathematical basis computer programs have been developed that deal with the constitutional aspect of organic chemistry in a formal manner. The most prominent examples are IGOR^{2–4} and RAIN.^{5,6} Such programs generate chemical reactions by producing sets of matrix transformations. Obviously, it is necessary to limit the combinatorial abundance of possible solutions. For this purpose several formal parameters were introduced⁷ that can be adjusted by the user in compliance with his special demands.

This formal mathematical concept allows to generate reactions that are not confined to known chemistry. Programs like IGOR and RAIN can stimulate the discovery of new types of reactions.⁸

However, the theory of the be- and r-matrices was designed for the formal description and computer-assisted manipulation of organic compounds that can be represented by a standard molecular graph. These only contain localized single, double, or triple bonds. So far, no uniform framework for the treatment of delocalized electrons has existed,

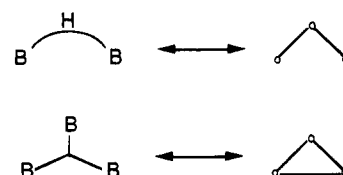


Figure 1. Open and closed 3c2e bonds and their corresponding graphs.

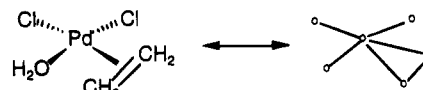


Figure 2. Ethene–Pd complex and its assigned graph.

although some aspects like resonance structures or possible structures of certain boranes have been investigated with RAIN.^{9,10}

2. THE REPRESENTATION OF MOLECULES WITH DELOCALIZED ELECTRONS—sXBE-MATRICES

2.1. The Molecular Graph. Graph theory or the topologies associated with molecular graphs are powerful tools for the description of structures and bonding patterns.¹¹ In the case of compounds containing delocalized electrons it is sometimes difficult to assign a unique graph. Therefore the pairwise relations between the atoms must be formally defined. These are then called “formal bonds” and give the edges of the molecular graph.

For instance, to open and closed 3c2e boron hydrogen bonds^{12,13} the graphs shown in Figure 1 can be assigned. They bear the closest resemblance to the conventional structural formulas.

In the case of π electron systems the σ bonds can be treated as localized. This σ skeleton defines the molecular graph.

π Complexes of metal ions and unsaturated ligands are formally associated with graphs containing edges that join the central ion to each atom of the ligand according to the hapticity. Figure 2 illustrates this procedure.

The edges of such molecular graphs are then labeled according to the bond type they represent. The following types have been defined:

“single”, “double”, and “triple” are used for covalent bonds of order 1, 2, or 3.

[†] Dedicated to Joshua Lederberg.

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Table 1. Bond Types

bond type	implicit electrons
"single"	$\mathcal{G}(\text{single}) = 1$
"double"	$\mathcal{G}(\text{double}) = 2$
"triple"	$\mathcal{G}(\text{triple}) = 3$
"edsys"	$\mathcal{G}(\text{edsys}) = 0$
"pisys"	$\mathcal{G}(\text{pisys}) = 1$
"coord"	$\mathcal{G}(\text{coord}) = 0$

"edsys" (electron deficient system) is used for the conceptual skeleton (i.e., the formal bonds) of a multicenter bond system.

"pisys" is used for the σ bonds of a conjugated π system.

"coord" is used to indicate interactions between metal atoms and the atoms of an unsaturated organic ligand.

2.2. The Electron Balance. The main progress of the transition from atom connectivity matrices ACM¹⁴ to be-matrices lies in the double bookkeeping capability of the latter: be-matrices account not only for covalent bonds but also for free valence electrons of the individual atoms. Therefore be-matrices were the first adequate device to represent chemical reactions, since the latter involve redistributions of bonds and free electrons.

Naturally, any extension of this model capable of dealing with delocalized electrons must retain this bookkeeping property for all valence electrons: localized bonds, free electrons; and delocalized electrons.

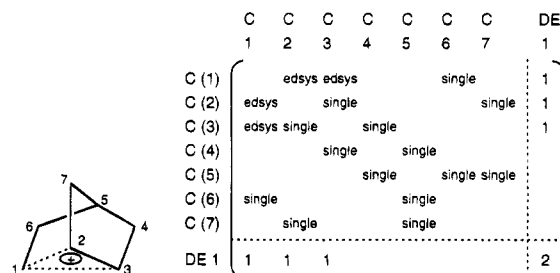
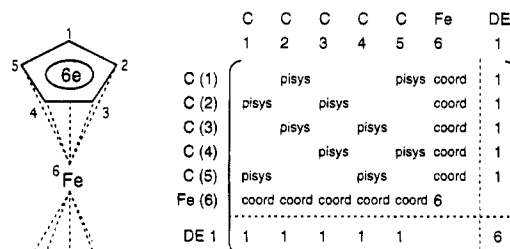
For each of the above defined types of bonds a specific "electron content" is defined (Table 1). The bond types "single", "double", and "triple" represent one, two, or three electrons per atom. The type "edsys" assigned to the formal bonds of a multicenter bond system has an implicit electron content of "0". In this case all electrons of the multicenter bond are listed separately (as shown below). "Pisys" accounts for the σ bonds of π electron systems. This implies one electron per atom. Again, the delocalized π electrons are treated separately. Since the bond type "coord" is just an indicator for electron donor-acceptor interactions, no electrons are attributed to it.

2.3. Delocalized Electrons. The formal bonds between pairs of atoms represent the electrons apportioned to common single, double, or triple bonds or the σ bonds of π electron systems. The remaining delocalized electrons are explicitly assigned to the so-called "DE-systems":

Definition. A set of neighboring atoms over which electrons are delocalized is called "DE-system"; the atoms are connected by formal bonds of type "edsys" or "pisys".

2.4. sXBE-Matrices. Be-matrices can easily be modified according to the considerations outlined above (2.1–2.3). The resulting sXBE-matrices (symbolic eXtended Bond- and Electron-matrices) are able to represent molecules with delocalized electrons in a form that makes them accessible by formal computer programs.

An sXBE-matrix consists of two parts: a "BE" part describing the formal bonds and a "DE" part for the delocalized electrons. An off-diagonal entry sxb_{ij} of the BE part characterizes the type of the bond between the atoms A_i and A_j (single, double, triple, edsys, pisys, coord). A diagonal entry sxb_{ii} is equal to the number of free electrons at A_i , i.e., $\mathcal{G}(sxb_{ii}) = sxb_{ii}$. The DE extension of this matrix (one extra row and column per DE-system) contains the information of how many electrons are delocalized among which atoms. An entry $sxb_{i,n+k} = sxb_{n+k,i}$ ($1 \leq i \leq n$; $1 \leq$

**Figure 3.** Nonclassical norbornyl cation and its sXBE-matrix.**Figure 4.** Part of the ferrocene system (only one ligand) and its sXBE-matrix.

$k \leq m$; n : number of atoms; m : number of DE-systems) is 1, if A_i participates in the k th DE-system, otherwise, it is 0. The diagonal DE entry $sxb_{n+k,n+k}$ is the total number of delocalized electrons of the k th DE-system.

An example is shown in Figure 3. For the sake of simplicity, the CH bonds and the corresponding entries have been omitted. This nonclassical carbocation contains one DE-system involving the atoms 1, 2, and 3 and the formal bonds 1–2 and 1–3 (edsys). The bond 2–3 is treated as a simple single bond.

The representation of organometallic compounds is illustrated by Figure 4. To keep it simple, only one of the two cyclopentadienyl ligands of ferrocene is considered in the sXBE-matrix. It has one "pisys" DE-system with six delocalized electrons. The coordination to the iron cation is not treated as DE-system. It is simply described as a set of five "coord" interactions between the central ion and the five atoms of the ligand.

The total number of valence electrons VE is equal to the sum of the electron contents of the BE part entries and the diagonal DE entries:

$$VE(EM) = \sum_{1 \leq i, j \leq n} \mathcal{G}(sxb_{ij}) + \sum_{1 \leq k \leq m} sxb_{n+k,n+k}$$

(n : total number of atoms; m : total number of DE-systems).

The formal electrical charge C of an atom A_i can be evaluated according to the following formula:

$$C(A_i) = Z(A_i) - \left(\sum_{1 \leq j \leq n} \mathcal{G}(sxb_{ij}) + \sum_{1 \leq k \leq m} sxb_{i,n+k} \right)$$

This is equivalent to the total number of valence electrons Z attributed to the chemical element A_i (if necessary, minus the number of implicit hydrogens) minus the electron contents (per atom) of its localized bonds, its free electrons, and minus 1 per DE-system involving A_i .

Each DE-system has a formal delocalized charge if the number of participating atoms is different from the number of delocalized electrons:

$$C(DE_k) = \left(\sum_{1 \leq i \leq n} sxb_{i,n+k} \right) - sxb_{n+k,n+k}$$

The pisys DE-system of the cyclopentadienyl ligand of Figure 4 has a formal delocalized charge of -1 (six electrons, five atoms).

3. THE REPRESENTATION OF CHEMICAL REACTIONS: SXR-MATRICES

The matrices representing chemical reactions have to be modified in analogy to the sXBE-matrices.

The off-diagonal entries of an sXR-matrix (symbolic eXtended Reaction-matrices) affecting localized bonding are functions that transform the types of the formal bonds in a well defined way and keep track of the electron balance. Some of these functions cause interconversions of the simple bond types like "single", "double", and "triple" by increasing or reducing the bond order. The other functions induce transformations between the bond types "edsys"/"pisys"/"coord" and the localized bond types. The complete matrix of all conceivable interconversions together with their influence on the electron balance $\Delta\mathcal{E}$ is shown in Table 2.

A diagonal entry $sxr_{i,i}$ ($1 \leq i \leq n$) indicates the change of the number of free electrons at the atom A_i ($\Delta\mathcal{E}(sxr_{i,i}) = sxr_{i,i}$).

sXR-matrices are augmented by rows and columns for those DE-systems that are involved in the reactions. The off-diagonal entries of this DE part can assume the values -1 (atom A_i loses its membership in the DE-system), $+1$ (atom A_i becomes member of the DE-system), or 0 (no change). The diagonal entry indicates the gain or loss of delocalized electrons in the DE-system. This DE part of the resulting sXR-matrix is then simply added to the DE part of the sXBE-matrix to reflect formations or break-ups of DE-systems in the course of a chemical reaction.

The main restriction on r-matrices is that the total number of valence electrons must remain constant. This is of course also valid for sXR-matrices:

$$\sum_{1 \leq i,j \leq n} \Delta\mathcal{E}(sxr_{i,j}) + \sum_{1 \leq k \leq m} sxr_{n+k,n+k} = 0$$

The representation of reactions may be illustrated by the sXBE- and sXR-matrices describing the asymmetrical cleavage of diborane (Figures 5 and 6). The function "p1" (plus 1) increases the bond order by one; in the example new bonds are formed between the boron atoms and the donor ligands.

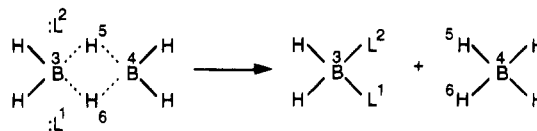


Figure 5. Asymmetrical cleavage of diborane.

$$\begin{array}{c} \begin{array}{cccccc} L & L & B & B & H & H & DE & DE \\ 1 & 2 & 3 & 4 & 5 & 6 & 1 & 2 \end{array} \\ \begin{array}{c} L(1) \\ L(2) \\ B(3) \\ B(4) \\ H(5) \\ H(6) \\ DE 1 \\ DE 2 \end{array} \left(\begin{array}{cccccc|cc} 2 & & & & & & & \\ & 2 & & & & & & \\ & & & & edsys & edsys & 1 & 1 \\ & & & & edsys & edsys & 1 & 1 \\ & & edsys & edsys & & & 1 & \\ & & edsys & edsys & & & & 1 \\ \hline & & & 1 & 1 & 1 & & 2 \\ & & & 1 & 1 & & 1 & 2 \end{array} \right) \oplus \end{array}$$

$$\begin{array}{c} \begin{array}{cccccc} L & L & B & B & H & H & DE & DE \\ 1 & 2 & 3 & 4 & 5 & 6 & 1 & 2 \end{array} \\ \begin{array}{c} L(1) \\ L(2) \\ B(3) \\ B(4) \\ H(5) \\ H(6) \\ DE 1 \\ DE 2 \end{array} \left(\begin{array}{cccccc|cc} -2 & & & & & & & \\ & -2 & p1 & & & & & \\ p1 & p1 & & & e_- & e_- & -1 & -1 \\ & & & & ep1 & ep1 & -1 & -1 \\ & & e_- & ep1 & & & -1 & \\ & & e_- & ep1 & & & & -1 \\ \hline & & & -1 & -1 & -1 & & -2 \\ & & & -1 & -1 & & -1 & -2 \end{array} \right) = \end{array}$$

$$\begin{array}{c} \begin{array}{cccccc} L & L & B & B & H & H \\ 1 & 2 & 3 & 4 & 5 & 6 \end{array} \\ \begin{array}{c} L(1) \\ L(2) \\ B(3) \\ B(4) \\ H(5) \\ H(6) \end{array} \left(\begin{array}{cccccc} & & & & & \\ & & single & & & \\ & single & & single & & \\ single & single & & & single & single \\ & & & & single & single \\ & & & & single & \end{array} \right) \end{array}$$

Figure 6. sXBE- and sXR-matrices (asymm cleavage diborane).

The function "ep1" (edsys plus 1) transforms an "edsys" bond into a single bond; "e₋" breaks an "edsys" bond.

3.1. Determination of the Chemical Distance. The chemical distance (CD) is a quantitative measure of the complexity of a reaction.¹⁵ In terms of the be- and r-model it is defined as the sum of the absolute values of all entries of an r-matrix, which is twice the number of electrons participating in the reaction. The CD of a reaction involving delocalized bonding may be defined analogously provided that only the net electronic changes in the surroundings of the participating atoms are counted; e.g., if at the start of a

Table 2. Transformations of Bond Types

start	result						
	no bond $\mathcal{E} = 0$	single $\mathcal{E} = 1$	double $\mathcal{E} = 2$	triple $\mathcal{E} = 3$	edsys $\mathcal{E} = 0$	pisys $\mathcal{E} = 1$	coord $\mathcal{E} = 0$
no bond $\mathcal{E} = 0$		p1 $\Delta\mathcal{E} = 1$	p2 $\Delta\mathcal{E} = 2$	p3 $\Delta\mathcal{E} = 3$	e $\Delta\mathcal{E} = 0$	p1pi $\Delta\mathcal{E} = 1$	c $\Delta\mathcal{E} = 0$
single $\mathcal{E} = 1$	m1 $\Delta\mathcal{E} = -1$		p1 $\Delta\mathcal{E} = 1$	p2 $\Delta\mathcal{E} = 2$	m1e $\Delta\mathcal{E} = -1$	pi $\Delta\mathcal{E} = 0$	m1c $\Delta\mathcal{E} = -1$
double $\mathcal{E} = 2$	m2 $\Delta\mathcal{E} = -2$	m1 $\Delta\mathcal{E} = -1$		p1 $\Delta\mathcal{E} = 1$	m2e $\Delta\mathcal{E} = -2$	m1pi $\Delta\mathcal{E} = -1$	m2c $\Delta\mathcal{E} = -2$
triple $\mathcal{E} = 3$	m3 $\Delta\mathcal{E} = -3$	m2 $\Delta\mathcal{E} = -2$	m1 $\Delta\mathcal{E} = -1$		m3e $\Delta\mathcal{E} = -3$	m2pi $\Delta\mathcal{E} = -2$	m3c $\Delta\mathcal{E} = -3$
edsys $\mathcal{E} = 0$	e ₋ $\Delta\mathcal{E} = 0$	ep1 $\Delta\mathcal{E} = 1$	ep2 $\Delta\mathcal{E} = 2$	ep3 $\Delta\mathcal{E} = 3$		ep1pi $\Delta\mathcal{E} = 1$	ec $\Delta\mathcal{E} = 0$
pisys $\mathcal{E} = 1$	pim1 $\Delta\mathcal{E} = -1$	pi $\Delta\mathcal{E} = 0$	pip1 $\Delta\mathcal{E} = 1$	pip2 $\Delta\mathcal{E} = 2$	pim1e $\Delta\mathcal{E} = -1$		pim1c $\Delta\mathcal{E} = -1$
coord $\mathcal{E} = 0$	c ₋ $\Delta\mathcal{E} = 0$	cp1 $\Delta\mathcal{E} = 1$	cp2 $\Delta\mathcal{E} = 2$	cp3 $\Delta\mathcal{E} = 3$	ce $\Delta\mathcal{E} = 0$	cp1pi $\Delta\mathcal{E} = 1$	

reaction an atom is part of a DE-system with two electrons spread over three atoms (this is counted as 2/3 electron per atom) and in the end there is one single bond instead (counted as one per atom), the net change for this atom is 1/3. If the absolute values of these net changes for each atom are summed up, a formal CD is obtained. This procedure recognizes the equivalency of delocalized electrons and those of localized bonds.

For purposes of computer-assisted formal synthesis design the CD of a reaction is one of the most important parameters for the selection and classification of chemically meaningful synthetic routes.¹⁶ In general, chemical reactions obey the principle of minimal structural change.¹⁷ The quantitative version of this statement is the "principle of minimum chemical distance" (PMCD).¹⁵ By limiting the allowed CDs of generated reactions to comparatively small values a lot of unreasonable suggestions can be suppressed automatically.

4. THE AUTOMATIC GENERATION OF REACTIONS

The prerequisite for computer programs dealing with the formal solution of chemical problems without reference to data bases of empirical chemical information is a simple mathematical model of chemistry. So far, the theory of the be- and r-matrices has served very successfully as such an algebraic basis. Now even much more complex molecules may be processed automatically by means of the sXBE- and sXR-model.

A computer program for the generation of chemical reactions is the engine of any formal synthesis design program. Two types of reaction generators are conceivable:¹⁸ the first produces all EMs into which given starting materials may be converted by redistributing the available valence electrons; the second type generates all possible pairs (B, E) for a given reaction mechanism R. The program developed on the basis of the sXBE- and sXR-matrices is of the first type. To avoid the output of too much chemically unreasonable solutions some basic properties of chemical elements and structures must be taken into consideration. These properties may be edited interactively by the user, so that they are in accordance with his special problems and interests. Formal programs do not use any further empirical chemical data or heuristic evaluations; therefore, they are able to suggest even unprecedented reactions.

For each chemical element specific electronic surroundings (i.e., distributions of certain bond types and lone electrons) are characteristic. These preferred states are listed in so called "valence schemes". Such valence schemes were first defined according to the needs of the be- and r-model.⁵ For use with sXBE- and sXR-matrices these valence schemes have been adapted to the new bond types, they contain the following information:

- atomic number
- number of free electrons vs_e
- localized formal electrical charge vs_{lc}
- formal bonds:
 - number of "single" bonds vs_s
 - number of "double" bonds vs_d
 - number of "triple" bonds vs_t
 - number of "edsys" bonds vs_{ed}
 - number of "pisis" bonds vs_{pi}
 - number of "coord" interactions vs_c

Table 3. Valence Schemes of Boron

VS (B)	#	vs_e	vs_{lc}	vs_s	vs_d	vs_t	vs_{ed}	vs_{pi}	vs_c	example
	1	0	0	3	0	0	0	0	0	BF ₃
	2	0	+1	2	0	0	0	0	2	[Ph ₂ B(bipy)] ⁺
	3	0	-1	4	0	0	0	0	0	BH ₄ ⁻
	4	0	-1	2	1	0	0	0	0	
	5	0	-1	2	0	0	2	0	0	Diborane
	6	0	-1	2	0	0	3	0	0	
	7	0	-1	2	0	0	4	0	0	
	8	0	-1	3	0	0	2	0	0	
	9	0	-1	1	0	0	4	0	0	

Table 4. Edsys DE-Schemes

DS #	subgraph	e ⁻	examples
1		2	BHB 3c2e bond; nonclassical carbocations;
		3	transition state radicalic 1,2-shift;
		4	transition state S _N 2 reaction;
2		2	closed BBB 3c2e bond;

A list of conceivable valence schemes for the element boron can be found in Table 3. Most of the so called semitopological structures with multicenter bonds are contained here.

Additionally, it is necessary to specify the behavior of the elements in the course of chemical reactions. For that purpose "transition tables" were defined.⁵ They determine the allowed interconversions of the valence schemes of a given chemical element. This concept is now applied to the extended valence schemes.

In analogy to the above described valence schemes, so called "DE-schemes" were introduced to specify the permitted DE-systems. They contain the following information:

- type (edsys/pisis)
- subgraph defining the graph of a chemically reasonable DE-system
- possible numbers of delocalized electrons, usually in the range: number of atoms ± 2
- stability









Fortunately, only very few types of DE-systems are of importance in chemistry. For the type "edsys", the relevant DE-schemes are listed in Table 4.

"Pisis" DE-systems (Table 5) offer more structural possibilities. Of course, other DE-schemes proving important for the solution of a special problem may easily be defined by the user.

By carefully selecting appropriate valence schemes, transition tables, and DE-schemes the user can limit the combinatorial abundance of conceivable reactions very effectively.

In addition to the above described constraints another set of parameters is used to control the scope of the reaction generator. This includes the definition of the allowed interconversions of bond types (see Table 2), special rules about the use of the bond type "coord", e.g., when catalytic reaction sequences are to be investigated, and other charac-

Table 5. Pisys DE-Schemes

DS #	substructure	e ⁻	examples
1		2	allylic carbocation;
		3	allylic radical;
		4	allylic carbanion, -NO ₂ ;
2		4	σ complex S _E Ar;
		5	σ complex free-radical aromatic substitution;
		6	σ complex S _N Ar;
3		6	CO ₃ ⁻ , NO ₃ ⁻ ;
4		2	cyclopropenyl cation;
5		6	cyclopentadienyl anion, pyrrole, furan;
6		6	benzene, pyridine, pyrimidine;
7		6	tropylium cation;
8		6	benzylic cation;
		7	benzylic radical;
		8	benzylic anion;

teristic features of the permitted reactions (maximum CD, number of participating atoms, etc.).

The algorithm¹⁹ that generates all combinatorially conceivable successor/precursor molecules of a given reactant EM is quite similar to the procedure used in the program RAIN.²⁰ In the beginning all conceivable patterns of formal bonds are produced. This step is transition table guided, i.e., the changes of the formal bonds must be compatible with the allowed transformations of the valence schemes of both connected atoms. Then the remaining electrons are allotted to DE-systems and atoms. All structures that are not in accordance with the user-defined parameter set are discarded as early as possible in the generation process.

5. CONCLUSION

The present study describes a modification of the theory of the be- and r-matrices as the basis of computer programs that generate chemical reactions involving delocalized electrons. Compounds with multicenter bonds, π electron systems, or even metal π complexes of unsaturated organic molecules can be represented and manipulated in a formal way. A reaction generator capable of producing all conceivable successor EMs to a given reactant EM under user-defined constraints has already been implemented. Soon it will be integrated in a program similar to RAIN that searches

for possible reaction pathways connecting given starting materials and products provided that both sides are stoichiometrically complete. The new program will be especially designed for the investigation of reaction mechanisms or catalytic reaction sequences.

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