ISOEFF98. A program for studies of isotope effects using Hessian modifications

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A new program for calculations of isotope effects has been developed. It requires only force constants for substrate and transition state as the external data. All other calculational steps are integrated into the program. ISOEFF98 has features of Hessian modification and scale factor optimization. The first of these allows studies of isotope effect changes upon weakening or strengthening of internal coordinates. The second feature allows fitting of the calculated isotope effect to the experimental value by scaling of molecular frequencies.

1. Introduction

In the 50 years history of isotope effects studies the BEBOVIB program [16] played important role in providing quantification of intuitive estimations. It requires geometries and force fields for the reactants and transition state as the input and yields predicted value for the isotope effect in question. The requirement of having the force field as input parameters places these calculations among molecular mechanics methods. A lot of flexibility is given to the user, allowing exotic structures to be used in modeling in order to achieve the agreement between experimental and calculated values. In hands of a skillful chemist, however, these calculations proved to be very useful and surprisingly precise [17]. The major strength of the BEBOVIB method lies in the studies of trends and laid background for our understanding of relations between force constants, isotope effects, and transition state structures. This was possible because the most fruitful calculations did not aim at the reproduction of experimentally observed values but rather were used to systematic studies of how isotope effects change upon changes in stretching or bending force constants of bonds directly involved in the reaction, or those being remote to the reaction center.

In recent years the advent of quantum-chemistry packages and fast computers allows calculations of isotopic properties of reactants and transition states, such as

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vibrational frequencies, which in turn yield isotope effects. These calculations suffer, however, from the lack of error evaluations. In other words, a quantum-chemical result yields only one "exact" value of an isotope effect which is correct provided the geometries and resulting frequencies obtained at the particular theory level are exactly correct. While geometries of stable structures can be quite reasonably modeled nowadays by sufficiently high ab initio or DFT methods, frequencies are usually overestimated in these calculations [5,15]. Furthermore, structures of transition states cannot be verified due to the lack of experimental techniques. Calculated isotope effects depend on the theoretical model and basis set used. Variations have been shown to be quite considerable and except for extremally high end calculations [11], possible for systems containing only a few atoms, not systematically improving with the level of theoretical scrutiny [3,7,12].

In order to fill the gap between the BEBOVIB-type of modeling of isotope effects and quantum-chemical calculations of "exact" values we have upgraged our program Isoeff[1] in a way which enables the user to modify selected force constants, obtained from the quantum calculations, and see how these modifications affect the value of isotope effect. The functionality of this new utility can thus be described as "quantum-BEBOVIB".

Previously our program was a mere multi-format reader which allowed for automatization of calculations. The modifications necessary to achieve Hessian manipulations required the whole program to be completely rewritten. We have named this new release ISOEFF98 to stress significant difference from previous versions. In this communication we present the main feature of this program on the example of isotope effects which were extensively studied in our group and which were not successfully modeled thus far.

2. Theoretical part

The concept of chemical bond is central for chemistry and very important in understanding how structural factors determine reaction mechanisms. Thus it is important to learn the extent to which weakening or strengthening of bonds, angles, and torsions affects isotope effects.

The minimal information required for the theoretical calculations of isotope effects consists of isotopic frequencies for the reactant and either for the transition state (kinetic isotope effects) or for the product (equilibrium isotope effects). Under the assumption of conventional transition state theory with Teller–Redlich rule applied [13] kinetic isotope effect can be calculated from frequencies of normal modes of vibra-

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[1] All Isoeff programs are available free of charge upon request from Prof. Paneth (`paneth@ck-sg.p.lodz.pl`) or can be downloaded from `http:\\ck-sg.p.lodz.pl\isoeff.html`

tions [10]:

$$\frac{k_{\text{L}}}{k_{\text{H}}} = \frac{\nu_{\text{L}}^{\neq}}{\nu_{\text{H}}^{\neq}} \prod_{i}^{3n^{\text{R}}-6} \frac{u_{i\text{H}}^{\text{R}} \cdot \sinh(u_{i\text{L}}^{\text{R}}/2)}{u_{i\text{L}}^{\text{R}} \cdot \sinh(u_{i\text{H}}^{\text{R}}/2)} \prod_{i}^{3n^{\neq}-7} \frac{u_{i\text{L}}^{\neq} \cdot \sinh(u_{i\text{H}}^{\neq}/2)}{u_{i\text{H}}^{\neq} \cdot \sinh(u_{i\text{L}}^{\neq}/2)}, \tag{1}$$

where ν isotopic frequencies for reactants, R, and transition states, $\neq$; $u = h\nu/(kT)$; and L and H denote the light and heavy isotopes, respectively; $\nu^{\neq}$ are imaginary frequencies of crossing the barrier; T is temperature; h and k are Planck's and Boltzmann's constants, respectively. A similar expression holds for equilibrium isotope effects.

The most popular method of describing of molecular vibrations is within the harmonic force field approximation. In this scheme the potential energy surface of nuclear motion (in vicinity of a stationary point) is assumed to be adequately described by the quadratic Taylor series expansion. Diagonalization of the mass-weighted matrix of Cartesian second derivatives of the energy leads to the determination of harmonic frequencies and normal coordinates [8].

Because the information about molecular structure and frequencies is plunged into force constants it is sufficient in the first approximation to manipulate the diagonal elements of force constants matrix artificially increasing or decreasing some of them. This controlled manipulation changes molecular frequencies and the resulting isotope effect and sets qualitative relation between these quantities.

In order to be able to perform such a modification of diagonal elements Hessian needs to be convert from Cartesian coordinates to internal ones. The Hessian in Cartesian coordinates cannot be the subject of modifications because the strength of one normal coordinate changes the strength of a number of other internal coordinates over which it is delocalized. Of course, change of strength of some internal parameters affects not only its diagonal elements but also appropriate off-diagonal matrix elements since these reflect mutual interactions of internal coordinates. Their changes can be, however, neglected in the first approximation.

The general scheme of mapping between Cartesian and internal coordinates [1] which has been used in ISOEFF98 is the same as implemented in GAMESS [14]. In the following discussion we use bold font to denote matrices and italic font to denote vectors. Right superscripts $^{\text{T}}$ and $^{-1}$ indicate transposition and inversion of matrices, respectively. The relation between Cartesian and internal coordinates is established by the matrix $\mathbf{B}$ that transforms the Cartesian coordinates X into the internal coordinates R:

$$R = \mathbf{B}X. \tag{2}$$

If $\mathbf{f}$ is Cartesian force constant matrix defined as $f_{ij} = \partial^2 E/(\partial x_i \partial x_j)$ and $\mathbf{F}$ is internal-coordinate force constants matrix defined as $F_{ij} = \partial^2 E/(\partial r_i \partial r_j)$ then $\mathbf{F}$ is related to $\mathbf{f}$ through the following transformations:

$$\mathbf{F} = \left(\mathbf{B}^{-1}\right)^{\text{T}} \mathbf{f} \mathbf{B}^{-1} \quad \text{and} \quad \mathbf{f} = \mathbf{B}^{\text{T}} \mathbf{F} \mathbf{B}. \tag{3}$$

Note that the transformation forward and then back from Cartesian coordinates to internal ones will restore original force constants matrix.

Harmonic frequencies Λ and normal-coordinate displacements $\mathbf{L}$ are determined via diagonalization of $\mathbf{f}'$, the mass-weighted Cartesian force constants matrix:

$$\mathbf{L}\Lambda = \mathbf{f}'\mathbf{L}, \quad \mathbf{f}' = \left(\mathbf{M}^{-1/2}\right)^{\mathrm{T}}\mathbf{f}\mathbf{M}^{-1/2}, \tag{4}$$

where $(M^{-1/2})_{ij} = \delta_{ij}m_i^{-1/2}$ is the diagonal matrix of reciprocal square roots of the atomic masses m_i.

In the first approximation diagonal elements of force constant matrix in internal coordinates can be attributed to the hardness or softness of the appropriate internal coordinate (skipping off-diagonal elements). Thus manually increasing or decreasing of the value of chosen diagonal element will artificially modify the strength of the appropriate internal coordinate. Back transformation of the force constants matrix from the internal to the Cartesian coordinates followed by frequency calculations leads to the modified value of the isotope effect, which reflects the change of the internal parameter (chemical bond, angle or torsion).

Because force constants in Cartesian coordinates depend on the orientation of a molecule in space and some semiempirical methods lead to non-invariant force constants it is important to verify validity of transformation of force constants into internal coordinates. To achieve this goal we have included in ISOEFF98 the vibrational density analysis [1]. Expression that relates molecular normal-coordinate frequencies and force constants in internal coordinates can be written as

$$\Lambda = \mathbf{L}^{\mathrm{T}}\mathbf{f}'\mathbf{L} = \mathbf{I}^{\mathrm{T}}\mathbf{f}\mathbf{I} = \mathbf{I}^{\mathrm{T}}\left(\mathbf{B}^{\mathrm{T}}\mathbf{F}\mathbf{B}\right)\mathbf{I} = \mathbf{D}^{\mathrm{T}}\mathbf{F}\mathbf{D}, \tag{5}$$

where $\mathbf{I} = \mathbf{M}^{-1/2}\mathbf{L}$ and $\mathbf{D} = \mathbf{B}\mathbf{I}$. From this equation the vibrational density matrix is defined as

$$P_{mn}^i = D_{mi}F_{mn}D_{ni}/\lambda_i. \tag{6}$$

P_{mn}^i is analogous to the overlap population matrix encountered in ab initio SCF energy calculations. The diagonal elements P_{mm}^i represent the contribution of the internal coordinate r_m to the normal-coordinate force constant k_i. Thus $\sum_m \sum_n P_{mn}^i = 1$. This expression allows verification of the validity of the transformation of force constants from Cartesian coordinates to internal ones.

Force constants matrix obtained from most quantum-chemical packages, such as GAMESS, GAUSSIAN [6], MOPAC [19], is usually in the Cartesian coordinates and it depends only on the level of theory used. It is required that the force constants matrix be rotationally invariant. All ab initio packages produce valid invariant Hessians both non-empirical and semiempirical. MOPAC93 and most of other semiempirical programs do not produce invariant Hessians and because of this deficiency cannot be used with Hessian modification routines of ISOEFF98.

3. Brief description of the program

The program flow diagram is given in figure 1. The program reads force constants and Z-matrix from quantum-chemical output, calculates **B** and $\mathbf{B}^{-1}$ matrices,

Read force constants and molecular geometry
from GAMESS, GAUSSIAN or MOPAC output

Get Z-matrix from input file and store it in archive

Read Z-matrix from global group of control file and store it in archive

Start new job and read job definitions

Read Z-matrix for given job from job group of control file

Does Z-matrix exist in job group or archive?

No   Yes

Calculate isotope effect for   Calculate B and B^{-1} matrixes
given temperature

Perform scale factor optimization   Calculate Hessian in internal coordinates

Is there new value of temperature?   Check validity of the Hessian in internal
                                      coordinates by vibrational density analysis

Yes   No   Calculate isotope effect for
                                      given temperature

                                      Perform scale factor optimization

                                      Modify the Hessian and
                                      calculate modified isotope effect

                                      Is there new value of temperature?

                                      No   Yes

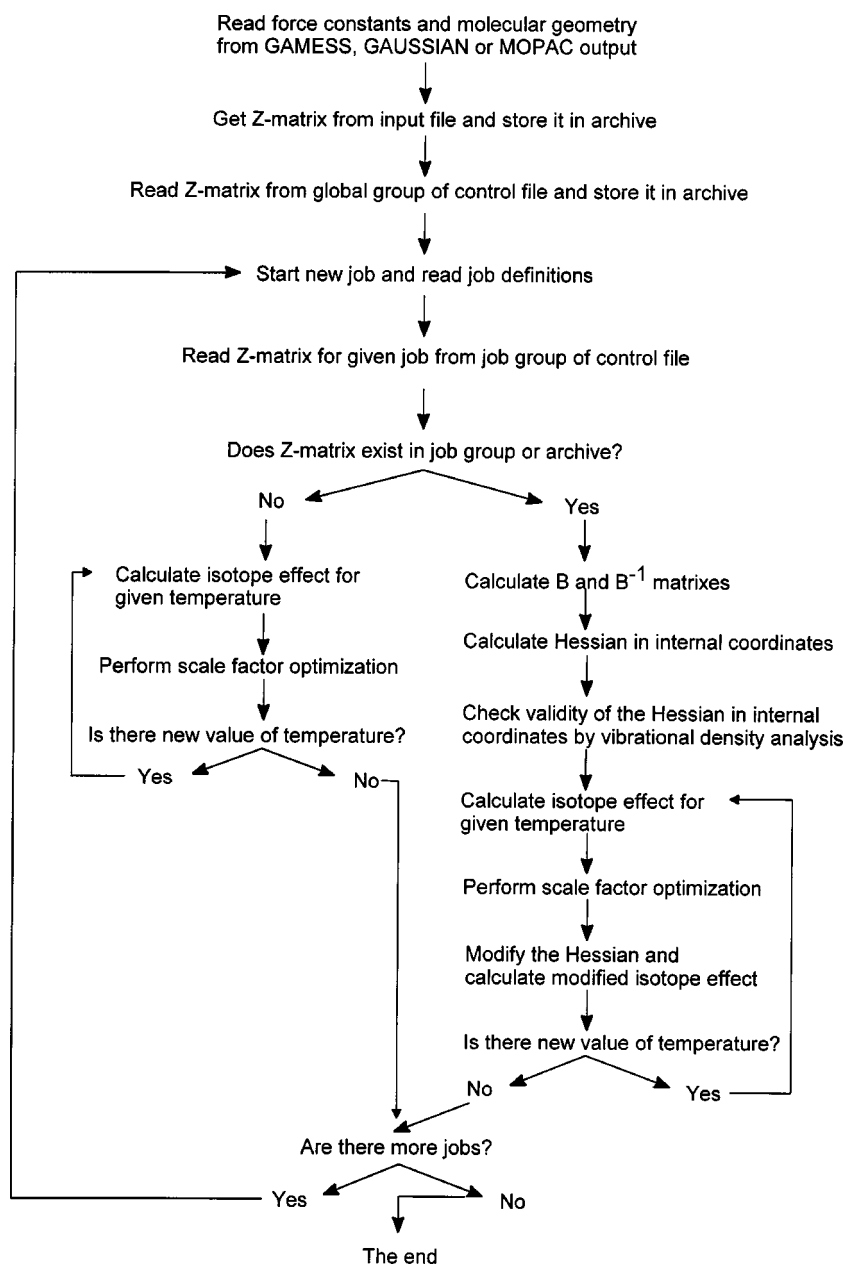Are there more jobs?

Yes   No

The end

Figure 1. Algorithm of ISOEFF98 calculations.

converts the Hessian into internal coordinate basis, performs the Hessian modification, transforms back force constants to Cartesian coordinates, performs isotope substitution, and finally calculates frequencies from mass-weighted force constants and the isotope effect for given temperature. If invoked it performs also scale factor optimization. In the absence of Z-matrix, $\mathbf{B}$ and $\mathbf{B}^{-1}$ matrixes calculations and the Hessian modification steps can be omitted.

Within ISOEFF98 isotope effects can be calculated from ab initio and semi-empirical packages. Most of semiempirical packages, however, list only abbreviated Hessians which are not sufficient for restoring original Hessian in the form suitable for frequency calculations. If the source code is available, uncommenting appropriate lines (e.g., line 42 and 43 in the freqcy.f file of MOPAC93 rev. 2) allows results from these programs to be used (for isotope effects calculations but not modifications, as described above).

In order to perform Hessian modifications two outputs from quantum-chemical packages containing Hessians for the reactants and transition state, respectively are necessary. At present output files from GAUSSIAN and GAMESS are acceptable. Internal coordinates can be used as they were defined in the output files of the program used for Hessian calculations or they can be defined within the data file using $ZMAT groups ($ZMATSS and $ZMATTS for reactants and transition state, respectively) and IZMAT arrays. The selection of independent internal coordinates is not trivial and can significantly affect results of isotope effects calculations, as is exemplified below. The Hessian modifications are controlled by two logical variables (SSMDFY and TSMDFY) defining wheather Hessian of reactants or transition state should be modified, and two arrays (SSMVAL and TSMVAL) indicating the percentage of the change which should be applied to a force constant corresponding to particular internal coordinate. Thus, for example, TSMDFY = .T. and TSMVAL(9) = −0.2 requests 20% decrease of the force constant corresponding to the nineth internal coordinate of the transition state.

4.   Examples

As the model reaction the decarboxylation of 3-carboxyisoxazoles has been used (see figure 2). This reaction has been chosen as the model for two reasons. First, kinetic isotope effects for this reaction have been extensively studied both experimentally and theoretically [2,3,9,20]. Second, theoretical predictions of isotope effects failed to reproduce reasonably the experimentally observed values of all theoretical levels studied; from semiempirical AM1 [4] and PM3 [18] to B3LYP and MP2 6-31++G** levels.

For simplicity the results of semiempirical calculations for the isoxazole derivative will be used (A = B = H). This model was used in MP2 calculations (F. Jensen and P. Czyryca, unpublished) while all experimental data were obtained for 5-nitro- and unsubstituted benzisoxazole derivatives. Calculations of isotope effects using AM1 Hamiltonian yielded 1.0579 for the carbon kinetic isotope effect and 1.0208 for the ni-
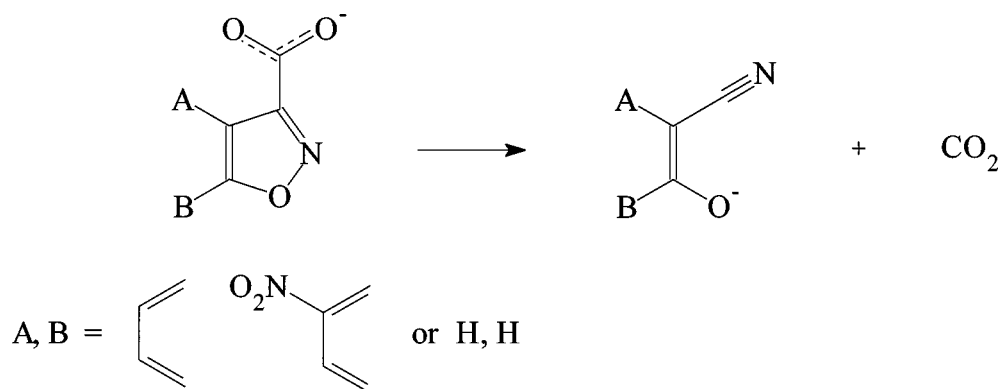
Figure 2. Model reaction – decarboxylation of 3-carboxyisoxazoles.
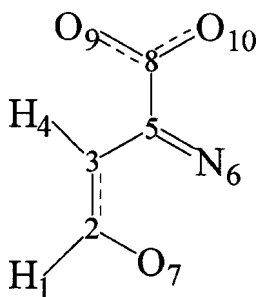

Figure 3. Atom numbering in the AM1 transition state model.

trogen kinetic isotope effect. In order to reproduce experimentally observed values of carbon and nitrogen kinetic isotope effects (1.045 and 1.032, respectively) from AM1 calculations it is necessary to modify at least force constants of C=N and C5–C8 (for atom numbering see figure 3) stretching vibrations by 30% and −40%, respectively. From the chemical point of view this means that the AM1 Hamiltonian underestimates the C–N bond tightening and C–C bond loosening in the transition state predicting it to be too "early".

The GAUSSIAN output reader strips redundant coordinates (if available) to $3n-6$ only unless the ASIS logical variable is set to TRUE in which case the user has to set up a list of appropriate coordinates manually. If only $3n-6$ coordinates have been archived the internal coordinate system can be changed by introducing one of the $ZMATXX (XX = SS for reactants or TS for transition state) group with the GAMESS type Z-matrix. This is helpful in studies of the influence of internal coordinates, which are not present in original set of GAUSSIAN coordinates on isotope effects. We will illustrate this with the following example in which the Gaussian Z-matrix for the transition state:

Table 1

Atoms		Coordinate						Coordinate	
No.	Type	i	j	k	l	m	n	(Bohr, rad)	(ang, deg)
1	stretch	2	1					2.0771868	1.0992000
2	stretch	3	2					2.6476951	1.4011000
3	bend	3	2	1				2.1556562	123.5100000
4	stretch	4	3					2.0444945	1.0819000
5	bend	4	3	2				2.2448425	128.6200000
6	torsion	4	3	2	1			.0005236	.0300000
7	stretch	5	3					2.7332997	1.4464000
8	bend	5	3	2				1.8837339	107.9300000
9	torsion	5	3	2	1			3.1410691	179.9700000
10	stretch	6	5					2.3854011	1.2623000
11	bend	6	5	3				2.1038199	120.5400000
12	torsion	6	5	3	2			.0005236	.0300000
13	stretch	7	2					2.4443606	1.2935000
14	bend	7	2	1				2.0949187	120.0300000
15	torsion	7	2	1	3			3.1410691	179.9700000
16	stretch	8	5					3.0704268	1.6248000
17	bend	8	5	3				2.0280726	116.2000000
18	torsion	8	5	3	2			3.1410691	179.9700000
19	stretch	9	8					2.3430713	1.2399000
20	bend	9	8	5				1.9823450	113.5800000
21	torsion	9	8	5	3			1.5697491	89.9400000
22	stretch	10	8					2.3430713	1.2399000
23	bend	10	8	5				1.9821704	113.5700000
24	torsion	10	8	5	3			−1.5758578	−90.2900000

```
H
C      1      r2
C      2      r3           1      a3
H      3      r4           2      a4      1      d4      0
C      3      r5           2      a5      1      d5      0
N      5      r6           3      a6      2      d6      0
O      2      r7           1      a7      3      d7      0
C      5      r8           3      a8      2      d8      0
O      8      r9           5      a9      3      d9      0
O      8      r10          5      a10     3      d10     0
```

has been changed in ISOEFF98 control file. In the original Z-matrix which includes 24 internal coordinates given in table 1, the position of the oxygen O_7 atom is defined by its distance from the C_2 atom (internal coordinate 13). For the purpose of this example we have changed internal coordinates so that the position of this oxygen is defined based on the N_6 nitrogen atom. This allowed introduction of bending (O_7–N_6–C_5) and torsional (O_7–N_6–C_5–C_3) coordinates of the ring (coordinates 14

Table 2

Atoms		Coordinate						Coordinate	
No.	Type	i	j	k	l	m	n	(Bohr, rad)	(ang, deg)
1	stretch	2	1					2.0771868	1.0992000
2	stretch	3	2					2.6476951	1.4011000
3	bend	3	2	1				2.1556562	123.5100000
4	stretch	4	3					2.0444945	1.0819000
5	bend	4	3	2				2.2448425	128.6200000
6	torsion	4	3	2	1			0.0005236	0.0300000
7	stretch	5	3					2.7332997	1.4464000
8	bend	5	3	2				1.8837339	107.9300000
9	torsion	5	3	2	1			3.1410691	179.9700000
10	stretch	6	5					2.3854011	1.2623000
11	bend	6	5	3				2.1038199	120.5400000
12	torsion	6	5	3	2			0.0005236	0.0300000
13	stretch	7	6					3.7163969	1.9666327
14	bend	7	6	5				1.6628028	95.2715814
15	torsion	7	6	5	3			−0.0005882	−0.0336989
16	stretch	8	5					3.0704268	1.6248000
17	bend	8	5	3				2.0280726	116.2000000
18	torsion	8	5	3	2			3.1410691	179.9700000
19	stretch	9	8					2.3430713	1.2399000
20	bend	9	8	5				1.9823450	113.5800000
21	torsion	9	8	5	3			1.5697491	89.9400000
22	stretch	10	8					2.3430713	1.2399000
23	bend	10	8	5				1.9821704	113.5700000
24	torsion	10	8	5	3			−1.5758578	−90.2900000

and 15) (see table 2). It was achieved by introducing a group containing GAMESS type Z-matrix:

```
$ZMATTS IZMAT (1)=1,2,1, 1,3,2, 2,3,2,1, 1,4,3, 2,4,3,2,
3,4,3,2,1, 1,5,3, 2,5,3,2, 3,5,3,2,1, 1,6,5, 2,6,5,3,
3,6,5,3,2, 1,7,6, 2,7,6,5, 3,7,6,5,3, 1,8,5, 2,8,5,3,
3,8,5,3,2, 1,9,8, 2,9,8,5, 3,9,8,5,3, 1,10,8, 2,10,8,5,
3,10,8,5,3 $END
```

The above substitution allowed for detection of very strong influence of the O_7–N_6–C_5 bending mode on the nitrogen kinetic isotope effect revealing that even 10% increase of the force constant of this coordinate causes the decrease of the isotope effect from 1.0579 to 1.0334.

Similarly, figure 4 illustrates the dependence of the nitrogen isotope effect on the O_7–N_6–C_5–C_3 torsional force constant also introduced in the new Z-matrix. This analysis can be done using data for transition state only by comparing modified and unmodified force fields in the equilibrium isotope effect mode (EIE = .T. and KIE = .F. keywords).
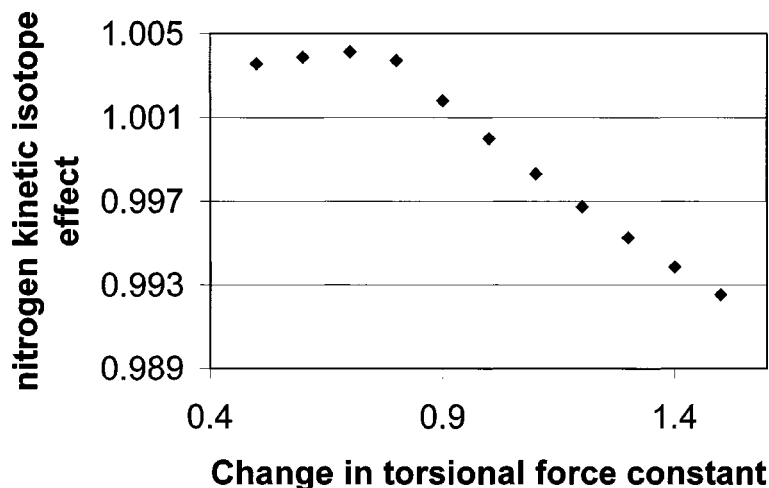
Figure 4. Dependence of nitrogen kinetic isotope effect on the force constant of the O_7–N_6–C_5–C_3 torsion.

As noted earlier, force constants in internal coordinates depend on the choice of the coordinates system. Different sets of internal coordinates will produce different force constants. Thus selection of internal coordinates is very important. Two types of "classic" Z-matrices (MOPAC and GAUSSIAN styles) are commonly used to simplify inputs of molecular coordinates for quantum-chemical packages. Their constructions starts with placing the first atom in the center of coordinates system. Second atom is placed on the X-axis. Third atom defines the XY planes. Following atoms are defined on the basis of distances and valence and torsional angles to previously introduced atoms. This kind of description of a molecule accomplishes two goals at the same time. First, it defines Cartesian coordinates of atoms of a molecule. This used to be a difficult task in years of nongraphic terminals when 3D visualization was not possible. Second, it defines internal coordinates, which can be useful in speeding up geometry optimization. Nowadays, 3D visualization packages produce Cartesian coordinates on the fly and the role of the classic Z-matrices has been significantly decreased. In ISOEFF98 we have adopted a very flexible way of description of internal coordinates as it is implemented in GAMESS. It is very easy to switch between different Z-matrices and see how this choice affects calculated isotope effect. We exemplify this on the reaction of ammonia inversion, which proceeds through a planar transition state (see figure 5). Classic kind of the Z-matrix requires in this case definition of one torsional angle, which does not reflect the C_{3v} symmetry of pyramidal ammonia. GAMMESS type of the Z-matrix allows to define additional valence angle instead. As can be see from the results listed in table 3 modifications of the strength of N–H bonds change the isotope effect in the same manner for both Z-matrixes. Modifications of isotope effect introduced by increasing or decreasing the strength of valence angles, however, depend on the Z-matrix definition. One expects the effect of such modifications to be additive. This is what
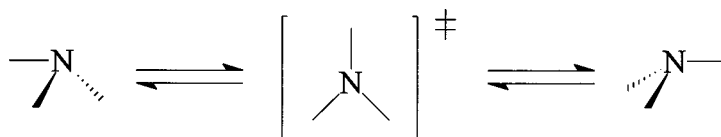
Figure 5. Inversion of ammonia.

Table 3
Influence of the internal coordinates systems used for the Hessian modification on the hydrogen kinetic isotope effect for the inversion of ammonia[a].

$N-H_1$	$N-H_2$	$N-H_3$	H_1-N-H_2	H_1-N-H_3	H_2-N-H_3	1st set of internals[b]		2nd set of internals[c]	
						increase[d]	decrease[e]	increase[d]	decrease[e]
–	–	–	–	–	–		1.0062		
10	–	–	–	–	–	1.0072	1.0051	1.0072	1.0051
10	10	–	–	–	–	1.0083	1.0040	1.0083	1.0040
10	10	10	–	–	–	1.0093	1.0029	1.0093	1.0029
–	–	–	10	–	–	1.0074	1.0049	1.0068	1.0056
–	–	–	10	10	–	1.0108	1.0001	1.0073	1.0050
–	–	–	10	10	10	–	–	1.0079	1.0044

[a] Hessian modification have been applied to initial state of ammonia (pyramidal geometry). First six rows identify internal coordinates which were subjected to 10% change.
[b] Classic *Z*-matrix: three N–H bonds, two H–N–H angles and one $H_1-N-H_2-H_3$ torsion angle.
[c] GAMESS type *Z*-matrix: three N–H bonds and three H–N–H angles.
[d] Increase of the force constant.
[e] Decrease of the force constant.

is observed only in the case of results obtained with the GAMESS type of the *Z*-matrix.

Apart from the Hessian modification routines ISOEFF98 contains another new feature, optimization of the scale factor. It was design in our attempt to find new ways of quantification of isotope effects by theoretical methods. Since frequencies calculated theoretically require scalling factor we have attempted to derive scalling factors by finding exact match of theoretical predictions to experimental values of isotope effects. Thus if the experimental value of the isotope effect is provided the program finds the scalling factor which causes the calculated value to match the experimental one. This functionality is invoked by the EXPIEF = x.x keyword, where x.x is the experimental value to be matched. The same scaling factor is used for all frequencies of both reactants and transition state. The initial results were, however, discouraging. The scaling factors for semiempirical results were unreasonably large or small (in terms of deviation from unity). For example, for the 3-carboxyisoxazole reaction the obtained scale factors were 1.231 (PM3) and 0.568 (AM1) for the carbon kinetic isotope effect, and 1.662 (PM3) and 1.895 (AM1) for the nitrogen kinetic isotope effect. The functionality is left in the code for future improvement and for testing with results obtained using higher theory levels.

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