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SEMIEMPIRICAL SCF-MO CALCULATIONS OF KINETIC ISOTOPE EFFECTS

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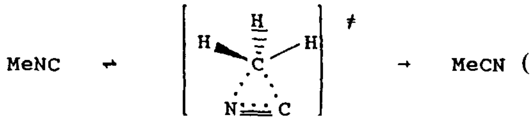
Carbon and deuterium kinetic isotope effects (KIEs) on the isomerization of methyl isocyanide were calculated by using the geometries and force fields obtained with MNDO, AM1 and PM3 Hamiltonians. These theoretical KIE values were compared with the corresponding experimental values. None of the hamiltonians used proved to be superior to any of the others. The best agreement for the carbon isotope effect was obtained by using the PM3 method; however, the deuterium isotope effect obtained by this method gave the poorest fit to the experimental data. The opposite is true when the MNDO Hamiltonian was used.

INTRODUCTION

Semiempirical self-consistent field molecular orbital (SCF-MO) calculations are found to be a useful and efficient tool in a wide range of chemical problems. Recently, new hamiltonians have been developed; viz. the PM3, AM1. The advantages and fields of application of these are, however, still debatable.[1]

We feel that determining isotope effects by using SCF-MO is a very good test of the usefulness of the new semiempirical methods. Theoretical isotope effects are calculated by a comparison of the properties of isotopic molecules (masses, moments of inertia and frequencies of normal vibrations). Thus even crude calculations should yield reasonable values of isotope effects because both isotopomers have the same geometry and force field. Moreover, in order to calculate a kinetic isotope effect, a transition state force field is also required. Past studies of kinetic isotope effects have often suffered from an arbitrary choice of this force field. Semiempirical methods, therefore, can yield an unbiased force field within a reasonable computing time period. Thus, performing semiempirical calculations employing different hamiltonians on model reactions should benefit both the development of semiempirical methods and the calculations of isotope effects.

In this paper we present studies of MNDO, AM1 and PM3 calculations of the kinetic isotope effects on the isomerization of methyl isocyanide (equation 1).



(1)

This reaction was studied earlier using the EHT and MINDO/2 methods.[2,3] Moreover, carbon[4] and deuterium[5] kinetic isotope effects on this reaction were also measured.

PROCEDURE

Version 5.0 of the MOPAC program[6] running on an IBM 9370-90 computer was used. The Broyden–Fletcher–Goldfarb–Shanno method (with PRECISE option) was used in the geometry optimization. The results of the calculations for reactant and product did not depend upon the use of symmetry functions. A combination of PATH, DRC and SIGMA options was used for the location of the transition state on the potential surface. No symmetry functions were used in the calculations of the transition state. The ANALYT option was used in force field calculations and the same force field was used to calculate frequencies of normal vibrations of all isotopomers of each structure.

Kinetic isotope effects were calculated from the primary equation.[7] The reactant and the transition state species have the same molecular mass and hence there is no mass contribution to the isotope effect. Because only fully deuterated molecules were considered in the theoretical calculations carbon or hydrogen isotopic substitution did not result in symmetry changes. This then allowed us to neglect any summetry numbers. The primary equation for kinetic isotope effects is therefore

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reduced to:

$$k_L/k_H = \left[\frac{(A_L^{\neq} B_L^{\neq} C_L^{\neq})(A_H B_H C_H)}{(A_H^{\neq} B_H^{\neq} C_H^{\neq})(A_L B_L C_L)}\right]^{1/2} \times \prod_{i}^{3n^{\neq}-7} \frac{\sinh u_{iH}^{\neq}/2}{\sinh u_{iL}^{\neq}/2} \prod_{i}^{3n-6} \frac{\sinh u_{iL}/2}{\sinh u_{iH}/2} \qquad (2)$$

where k_L/k_H is the isotope effect, A, B and C are the principal moments of inertia, n is the number of atoms in a molecule, $u_i = h\nu_i/kT$, h and k are Planck and Boltzman constants, respectively, T is absolute temperature, and ν_i are the frequencies of normal vibrations. Indexes L and H correspond to light and heavy species, and $\neq$ indicates properties of the transition state. The expression in the square bracket constitutes the rotational contribution to the isotope effect. The remaining products represent vibrational contributions to the isotope effect.

RESULTS

Kinetic isotope effects on reaction (1) were calculated by using MNDO, AM1 and PM3 Hamiltonians and the results are summarized in Table 1 along with the experimentally measured values. Only a mean value of the ^{13}C kinetic isotope effects for both carbon atoms of methyl isocyanide was measured because of the experimental methodology used.

The data presented in Table 1 reveal that no one particular hamiltonian tested gave an acceptable value of both deuterium and carbon kinetic isotope effects at the same time. For example, the PM3 Hamiltonian gave the best fit of the carbon isotope effect to the experimental value but gave the poorest estimation of the deuterium isotope effect. The opposite is true for the MNDO calculations. The AM1 method yielded intermediate results for both carbon and hydrogen kinetic isotope effects.

Calculated frequencies of normal vibrations of the reactant are summarized in Table 2. The isotopic fre-

Table 1. Calculated kinetic isotope effects[a]

Method	$^{13}C_{Me}$	$^{13}C_{CN}$	Mean ^{13}C	D_3
AM1	1·0184	1·0331	1·026 (1·023)[b]	0·99
MNDO	1·0007	1·0092	1·005 (1·004)	1·04(1·03)
PM3	1·0224	1·0242	1·023 (1·022)	1·00
Experimental			1·019 ± 0·001[c]	1·053 ± 0·006[c]

[a] Values of isotope effects at 226 °C for carbon and at 230·4 °C for deuterium. Individual values calculated for carbon isotope effects are given in the first two columns. The third column is a mean of these values. The calculated isotope effects for the perdeuterated molecule are given in the fourth column.

[b] Values in parentheses were obtained from frequencies scaled down by 10%.

[c] Standard deviations estimated from the reported results.

Table 2. Frequencies (cm^{-1}) of normal vibrations of MeNC[a].

			PM3					
	MNDO	AM1	nat.	$^{13}C_{CN}$	$^{13}C_{Me}$	D_3	^{15}N	Observed
1	296*	343*	284*	280	283	269	278	263
2	1181	1130*	979*	979	973	758	978	945
3	1185*	1228	1021	1011	1007	841	1017	1011
4	1416*	1360*	1342	1340	1324	999	1341	1429
5	1509	1454	1358*	1358	1355	1183	1358	1467
6	2335	2418	2284	2245	2283	2238	2243	2166
7	3238*	3002*	3060*	3060	3048	2272	3060	2966
8	3308	3095	3124	3124	3121	2288	3124	3014

[a] Marked values are doubly degenerate.

Table 3. Calculated properties of the transition state

	Method				
Quantity	AM1	MNDO	PM3	MINDO/2[3]	EHT[2]
μ	3·049	2·615	2·863	2·70	
d_{C1H}(Å)	1·119	1·109	1·094	1·108	
d_{CC}	1·700	1·701	1·777	1·658	2·21
d_{C1N}	1·226	1·224	1·217	1·256	1·2[a]
d_{C2N}	1·803	1·797	1·831	1·492	2·23
∠CNC	65·0	65·4	67·9	~60	
∠CCH	99/128	99/130	99/125		90[a]
δ(H)[b]	+0·139	+0·048	+0·077	+0·0153	+0·058
$\delta(C_1)$	−0·082	−0·034	−0·075	−0·0542	+0·090
$\delta(C_2)$	−0·152	+0·120	+0·050	+0·1572	+0·418
δ(N)	−0·183	−0·232	−0·204	−0·1213	−0·683
$E^{\neq}$(kcal mol^{-1})[c]	83·0	68·2	58·0	34·3	

[a] CN bond length and planar structure of CH_3 moiety were assumed.

[b] Mean values are given for all three hydrogen atoms.

[c] The experimental activation energy is 38.4 kcal mol^{-1}.

quencies obtained by using the PM3 Hamiltonian are also listed. The best fit with the experimental values is obtained by using the PM3 Hamiltonian, as can be judged by taking the average mean square deviations.

In Table 3 we have compared our calculated transition state properties with those obtained in earlier studies by using MINDO/2 and EHT Hamiltonians.

Other properties of the reacting molecules that can be compared with the experimentally determined values are the dipole moments and the activation energy. We have obtained values for the dipole moment of 2·83, 2·17 and 3·69 for the reactant by using the AM1, MNDO and PM3 methods, respectively. The experimental value is 3·85. The corresponding values for the product are 2·89, 2·63 and 3·21. Again the PM3 calculations prove to be the closest to the experimental value of 3·92. Moreover, the best estimation of the activation energy (Table 3) is obtained by using the PM3 method, although agreement with experiment is poorer than the result obtained using MINDO/2.

DISCUSSION

Within the semiclassical treatment kinetic isotope effects are calculated on the basis of molecular masses, symmetry numbers, moments of inertia and frequencies of normal vibrations. These properties are determined for the isotopic species of the reactants and the transition states of a given reaction. The first two properties are easily determined. The last two properties represent the major portion of a theoretical calculation of kinetic isotope effects. Because isotopic substitution causes negligible change in most of the molecular properties, even crude estimates of geometry and force field usually lead to acceptable results of vibrational (isotopic frequencies) and rotational (moments of inertia) contributions to isotope effects.

Unfortunately, only a few experimental force fields for stable and relatively small molecules can be found in the literature, and no force fields are available for transition states. Thus, the major problem in theoretical calculations of isotope effects is represented in the inconsistency between force field models of the reactant and transition state species.

SCF-MO calculations can produce unbiased force fields and geometries for both reactant and transition state species. *Ab initio* calculation of these is the best approach but for practical reasons it can only be applied to small systems.[8] Semiempirical methods, on the other hand, should prove useful in calculations of kinetic isotope effects for larger systems of interest to organic chemists.

It is disappointing that neither of the semiempirical procedures reproduces both hydrogen and heavy atom kinetic isotope effects at the same time. Our results suggest that the PM3 method should be used for heavy atom isotope effects whereas the MNDO method should only be used to calculate hydrogen isotope effects.

Because the PM3 Hamiltonian gives the best force field, we have calculated isotope effects by combining vibrational factors from these calculations with a rotational factor obtained by using the other two methods. This approach, however, gave poor fits with the experimental values and in fact gave inverse deuterium isotope effects. Systematic studies of these 'mixed' calculations revealed that the best results were obtained when the vibrational factor was taken from MNDO calculations. When the rotational factor from the PM3 method was used, a mean carbon isotope effect of 1·016 and a deuterium isotope effect of 1·06 were obtained (cf. experimental values of 1·019 and 1·07, respectively). The analogous results obtained by using the rotational factor calculated by the AM1 method are 1·020 and 1·05, respectively. These results are surprising because the force field calculated by using the MNDO method gave the poorest fit with the experimental frequencies. It is apparent, therefore, that more studies of other systems are required to judge whether this agreement of 'mixed' calculations with experimental results originates in a better theoretical model or is purely coincidental.

We have also performed calculations in which different methods were used for the calculations of properties of the reactant and the transition state. Because the PM3 method was developed to improve calculations for hypervalent molecules we felt that reasonable results should be obtained if this method was applied to the transition state calculations while MNDO was used for the reactant. The resulting mean carbon kinetic isotope effect was 1·012. The deuterium kinetic isotope effect obtained from these calculations was 1·50. This last result is a good example of the risk associated with using different force field models for the ground and transition states.

Obtaining the geometry of the transition state is always a primary goal in studies of reaction mechanisms. In studies of the reaction pathway for isomerization (1) using the EHT method,[2] an ionic transition state structure with a planar methyl moiety was postulated. Later, these findings were criticized on the basis of MINDO/2 calculations[3] that suggested formation of an intermediate rather than a π-complex transition state. We have studied the reaction coordinate using the PATH, DRC and SIGMA keywords. No stationary points along the reaction coordinate were detected. The transition state nature of the geometry obtained was confirmed by the presence of one imaginary frequency. All of the methods employed yielded similar structures of the transition state (Table 3). The most striking feature of these structures is the lack of equivalency of hydrogen atoms. While two of hydrogen atoms approach planarity ($\angle$CCH = 99° compared to about 109° in both reactant and product) the third hydrogen atom bends in the opposite direction (∠CCH = 128°). This atom occupies a position over the nitrogen atom (∠NCCH dihedral equals to zero).

CONCLUSIONS

While none of the three semiempirical SCF-MO methods proved to be superior for theoretical calculations of kinetic isotope effects, acceptable results were obtained by using the PM3 method for the carbon isotope effect and the MNDO method for the deuterium isotope effect. The discrepancy between theoretical and experimental results can originate either from the inaccuracy of the semiempirical treatment, or from the inadequacy of semiclassical calculations of isotope effects using equation (2). It is not possible, at the present time, to decide which is the primary factor, since no high quality *ab initio* calculations have been performed for the reaction under consideration. However, of the two factors, variational and tunnelling, which are neglected in equation (2), the first affects isotope effects only at low temperature[8] and the second has very little influence on carbon isotope effects. It is thus possible that the inaccurate approximations within the semiempirical framework are responsible for the observed discrepancies. Evidently, more model studies are necessary to test the usefulness of the various hamiltonians for theoretical estimations of isotope effects.

REFERENCES

1. J. J. P. Stewart, *J. Comput. Chem.* **11**, 543 (1990).
2. G. W. van Dine and R. Hoffmann, *J. Am. Chem. Soc.* **90**, 3227 (1968).
3. M. J. S. Dewar and M. C. Kohn, *J. Am. Chem. Soc.* **94**, 2704 (1972).
4. J. F. Wettaw and L. B. Sims, *J. Phys. Chem.* **72**, 3440 (1968).
5. F. W. Schneider and B. S. Rabinovitch, *J. Am. Chem. Soc.* **85**, 2365 (1963).
6. J. J. P. Steward, *QCPE* No. 581 (1989).
7. L. Melander, *Isotope Effects on Reaction Rates.* Ronald Press Co., New York (1960).
8. D. Lu, D. Maurice and D. G. Truhlar, *J. Am. Chem. Soc.*, **112**, 6206 (1990), and references therein.