MM2 Force Field Parameters for Oximes

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The MM2 force field method has been extended to include oximes. Necessary parameters have been developed by using formaldoxime, (*E*)- and (*Z*)-acetaldoxime, and acetone oxime. The "methylene tilt" of formaldoxime has been successfully reproduced and calculated rotational barriers, moments of inertia, and dipole moments are in good agreement with the available experimental data.

Introduction

Aldoximes and ketoximes, common carbonyl derivatives, have long been the objects of experimental[1a,b] and theoretical[1c–j] studies. Recent work utilizing various oximes as pesticides,[2] therapeutics,[3] and metal extractants[4] as well as ongoing theoretical examination of the phenomenon of isomerization between the *E* and *Z* isomeric forms[1g,h] attests to continued interest; however, the link between structural data and readily calculated accurate models, which might aid in further exploration, has not yet been forged. Indeed, the most recent work[1j] using a consistent force field potential energy function to calculate physical parameters produced results that did not agree well with experimental data (or, where that was unavailable, with ab initio results).[1d,e,h] Published semiempirical calculations for oximes using CNDO/2,[1d,f] INDO,[1c] and MINDO/3[1g] have also met with mixed success.

We have now extended the MM2 force field method to include oximes by using structural data and ab initio calculations to define the parameters for formaldoxime (**1**), (*E*)- and (*Z*)-acetaldoxime (**2a,b**), and acetoxime (**3**).

General Procedure and Oxime Parameters

The most recent revised version of MM2[5] was utilized. Calculations were performed at Temple University on the CDC Cyber 750 computer. As is standard in parameterization of MM2,[6] calculations were restricted to molecules in the gas phase and intermolecular interactions were ignored. In general, microwave and gas-phase IR data were used for parameterization and comparison of calculated values. Where no experimental data was available, ab initio results were used for comparison.

In the MM2 force field, the total steric energy of a molecule can be described as the summation of the stretching, bending, torsional, dipole, and van der Waals energies as shown in eq 1. Each term requires an optimized set of parameters, as shown in eq 2–7.

Table I. Stretching and Dipole Moment Parameters for Aliphatic Oximes 1, 2a,b, and 3

bond	K_s	r_0[a]	moment[b]
C=N	9.53[c]	1.2716	1.17
N—O	4.18[c]	1.4014	0.11
$2e^-$—O	4.60[d]	0.6000	−0.90
H—O	4.60[d]	0.9570	1.12
$2e^-$—N	6.10[d]	0.6000	−1.00
C_{sp^3}—C_{ox}	4.40[e]	1.4990	0.55
H—C_{ox}	4.60[f]	1.0836	0.00

[a] The values for r_0 were taken, initially, from microwave[10,11,17] data or (for the $2e^-$ data) by analogy with MM2 programmed parameters and then adjusted until final bond lengths matched microwave data for the compounds. [b] The bond moments were assigned initially by analogy with similar bond types parameterized in MM2 and were adjusted to fit so as to reproduce the experimental dipole moments. [c] Average value of IR force constants for **1**, **2a,b**, and **3**.[18–21] [d] By analogy with internal MM2 parameters for hydroxyl or unshared pairs on oxygen or nitrogen. [e] Average value for **1** and **3**.[21] [f] Average value for **1** and **2a,b**.[18–20]

Table II. Bending Parameters for Aliphatic Oximes 1, 2a,b, and 3

angle	K_b	σ_0[a]	angle	K_b	σ_0[a]
H-C-N	0.319[b]	116.1	C_{sp^3}-C-N	0.520[d]	116.8
	0.307[c]	117.0	O-N-$2e^-$	0.400[e]	125.0
N-O-H	0.582[f]	103.687	$2e^-$-O-N	0.400[e]	109.00
C-N-O	0.941[f]	106.123	C-N-$2e^-$	0.500[e]	122.80
$2e^-$-O-H	0.240[e]	101.01	$2e^-$-O-$2e^-$	0.240[e]	131.00
H-C_{ox}-H	0.290[c]	125.30	C_{sp^3}-C_{ox}-C_{sp^3}	0.350[d]	119.20
C_{sp^3}-C_{ox}-H	0.360[g]	117.90	H-C_{sp^3}-C	0.360[e]	110.00

[a] σ_0 values were chosen on the basis of internal MM2 parameters for similar atom types or, if available, from microwave spectroscopic data. Parameters were adjusted to insure that the final calculated angle matched the values from microwave spectroscopy where that information was available. [b] Average value for **2a,b**.[18,19] [c] Average value for **1**.[20,21] [d] Average value for **3**.[21] [e] By analogy with MM2 internal parameters for similar atom types. [f] Average value for **1**, **2a,b**, and **3**.[18–21] [g] Average value for **2a,b**, and **3**.[18,19,21]

$$E_{\text{total}} = E_{\text{stretch}} + E_{\text{bend}} + E_{\text{str-bnd}} + E_{\text{vdw}} + E_{\text{torsn}} + E_{\text{dipole}} \quad (1)$$

Stretching Parameters. The parameters K_s, the stretching force constant (mdyn/Å), and r_0, the equilibrium bond length (Å), were developed to fit eq 2 to give E_{stretch} in kcal/mol.

$$E_{\text{stretch}} = 71.94K_s(r - r_0)^2[1 - 2.00(r - r_0)] \quad (2)$$

This expression is part of the MM2 standard force field.[7] The force constants shown in Table I were generally either

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Table III. Torsional Parameters for Aliphatic Oximes 1, 2a,b, and 3

dihedral angle	υ_1	υ_2	υ_3	dihedral angle	υ_1	υ_2	υ_3
H–O–N–C[a]	2.00	4.45	−2.00	2e$^-$–O–N–C[b]	0.00	0.00	0.00
H–C–N–O[c,d]	1.20	17.00	0.00	H–C–N–2e$^-$ [b]	0.00	10.0	0.00
2e$^-$–O–N–2e$^-$ [b]	0.00	0.00	0.00	H–O–N–2e$^-$ [b]	0.00	0.00	0.00
N–C–C_{sp^3}–H[e]	0.00	0.00	−0.14	O–N–C–C_{sp^3}[c,d]	0.00	17.00	0.00
C_{sp^3}–C–N–2e$^-$ [b]	0.00	10.00	0.00	H–C_{sp^3}–C_{ox}–H[e,f]	0.00	0.00	0.52
C_{sp^3}–C_{ox}–C_{sp^3}–H[f]	0.00	0.00	0.54				

[a] The values have been adjusted to fit the calculated rotational barrier.[14] [b] We have assumed that unshared pairs make negligible contribution to the torsional energy. [c] The values were adjusted to fit the barrier as determined by ab initio calculations.[9] [d] For double bonds, υ_2 corresponds (approximately) to the rotational barrier divided by 2. Contributions from υ_1 are used to adjust the final steric energy for **2a,b** to give a $\Delta G°$ comparable to experiment. [e] The values were adjusted to fit the rotational barrier as determined by microwave spectroscopy.[10] [f] By analogy with internal MM2 parameters.

average values for the corresponding IR force constants for **1**, **2a,b**, and **3** or were determined by analogy with programmed parameters for hydroxyl groups and oxygen or nitrogen unshared electron pairs. The values for the equilibrium bond length, r_0, were initially taken from microwave data as trial values and adjusted until calculated final bond lengths fit experimental data.

Bending and Stretch-Bend Parameters. The parameters, K_b, the bending force constant (mdyn/Å rad^2), and σ_0 (degrees), the equilibrium bond angle, were developed to fit the standard MM2 eq 3, where E_{bend} is in kcal/mol.

$$E_{bend} = (2.194 \times 10^{-2})K_b(\sigma - \sigma_0)^2[1 + (7.00 \times 10^{-8})(\sigma - \sigma_0)^4] \quad (3)$$

As indicated earlier, force constants were based on average IR values or developed by analogy with MM2 standard parameters (Table II). The values for equilibrium angles were obtained similarly.

When an sp^2-type atom is the central atom of an angle, additional force constants are required for the out-of-plane bending components. Hence, the oxime carbon and nitrogen were assigned K_b values of 0.050 in accord with internal MM2 parameters.

A stretch-bend potential function (eq 4) is also included so that bonds tend to stretch when the angle is compressed and to shrink when the angle is widened.

$$E_{str\text{-}bnd} = 2.51124K_{sb}(\sigma - \sigma_0)[r(1) - r_0(1) + r(2) - r_0(2)] \quad (4)$$

Here, K_{sb} is the stretch-bend constant (mdyn/rad), and the angle in question has the equilibrium value σ_0 (degrees) between nuclei separated from the pivotal atom by equilibrium bond lengths $r_0(1)$ and $r_0(2)$. The value 2.51124 is an energy conversion factor (mdyn/rad to kcal/mol). The internal MM2 values for K_{sb} required no modification.

van der Waals Parameters. Nonbonded interaction energies (excluding 1,3 interactions) are calculated with the modified Buckingham equation as shown in eq 5,

$$E_{vdw} = K_{vdw}[(2.90 \times 10^5)e^{-12.50/p} - 2.25p^6] \quad (5)$$

where $p = r^*/r$, and r^* is the sum of van der Waals radii of two atoms, (1) and (2), while r is the distance between the two atoms. When one of the atoms (1) and (2) is hydrogen or deuterium, the distance is reduced by 0.915. Here, the constant, K_{vdw}, is defined as $[\epsilon(1)\epsilon(2)]^{1/2}$, where $\epsilon(1)$ and $\epsilon(2)$ are the van der Waals constants (a measure of hardness) for the atoms (1) and (2), respectively, and whose values are in kcal/mol. The values of ϵ and r utilized in the calculations reported here were standard MM2 parameters except for those of the carbon, nitrogen, and oxygen of the oxime itself (i.e., C=N—O) which were, however, developed by analogy to similar atom types in MM2. They are C_{ox} ($\epsilon = 0.044$, $r = 1.9400$); N_{ox} ($\epsilon = 0.055$, $r = 1.8200$); O_{ox} ($\epsilon = 0.050$, $r = 1.7400$).

Torsional Parameters. The parameters provided in Table III were adjusted to fit the standard MM2 eq 6.

$$E_{torsion} = (\upsilon_1/2)(1 + \cos\omega) + (\upsilon_2/2)(1 - \cos 2\omega) + (\upsilon_3/2)(1 + \cos 3\omega) \quad (6)$$

Here, ω is the dihedral angle (degrees) and υ_1, υ_2, and υ_3 are one-, two-, and threefold torsional constants (kcal/mol). In general it was assumed that unshared pairs make a negligible contribution to the torsional energy. Further, as shown in Table III, a υ_1 contribution was used to adjust for the energy difference favoring (*E*)-acetaldoxime (**2a**) over the *Z* isomer (**2b**) (estimated at 0.29–0.61 kcal/mol)[11,8] and a υ_2 contribution, adjusted to mimic a rotational barrier for the C=N bond, was made (the values were derived from ab initio calculations).[9] In this one case, since the pure rotational barrier was calculated to be unusually high (ca. 100 kcal/mol), the inversion barrier (37.5 kcal/mol) was selected for parameterization. To keep the magnitude of υ_2 small, it was necessary to include parameters for unshared pairs. Contributions to υ_1, υ_2, and υ_3 for rotation around the N–O bond are included because of the bond's asymmetry and values were chosen to reproduce the N–O rotational barrier as determined for the differences between the s-cis and s-trans N–OH conformations by the ab initio work. Finally, microwave data[10] was used to adjust the methyl group rotational barrier.

Dipole Interaction Energy and Dipole Moment. Bond moments for polar bonds are required to obtain dipole moments and dipole interaction energies. The bond moments are found by choosing some trial value which is then refined to reproduce experimental dipole moments. The dipole interaction energy is calculated by using eq 7,

$$E_{dipole} = k\mu_A\mu_B(\cos\chi - 3\cos\alpha_A\cos\alpha_B)/R^3D \quad (7)$$

where R is the length of the line between the midpoints of the two bonds (Å), μ_A and μ_B are their respective bond moments (debye), χ is the angle between the bond vectors, α_A and α_B are the angles between the bond axes and the line along which R is measured, and D is the effective dielectric constant[6] (here taken as 1.5); the energy in kcal/mol can be obtained by use of the conversion factor k (erg/molecule to kcal/mol) whose value is taken as 14.39418.

For the oximes studied, the parameters not already defined in MM2 (Table I) were determined by analogy with similar bond types provided in MM2 and then they were adjusted so as to generate the experimentally determined dipole moment (Table IV).

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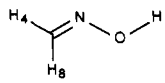
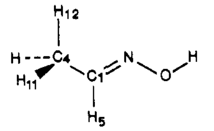
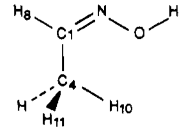
Table IV. Experimental and Calculated Structural Data for Oximes 1, 2a,b and 3



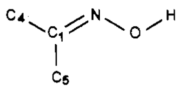
formaldoxime (**1**)



(*E*) acetaldoxime (**2a**)



(*Z*) acetaldoxime (**2b**)



acetoxime (**3**)

formaldoxime (**1**)			(*E*) acetaldoxime (**2a**)			(*Z*) acetaldoxime (**2b**)			acetoxime (**3**)		
bond	expt[a,b]	calcd[c]	bond	expt[b,d]	calcd[c]	bond	.expt[b,e]	calcd[c]	bond	expt[b,f]	calcd[c]
C-N	1.276	1.276	C-N	1.276	1.275	C-N	1.276	1.276	C-N	1.29	1.276
C-H_4	1.086	1.085	N-O	1.408	1.408	N-O	1.408	1.405	C_1-C_4	1.49	1.511
C-H_8	1.085	1.086	C_1-C_4	1.506	1.505	C_1-C_4	1.504	1.508	C_1-C_5	1.55	1.510
N-O	1.408	1.408	C_1-H_8	1.085	1.088	C_1-H_5	1.085	1.087	N-O	1.36	1.405
O-H	0.956	0.956	O-H	0.956	0.956	O-H	0.956	0.956	O-H		0.956
N-C-H_4	115.55	116.05	C_4-H_{10}	1.094	1.114	C_4-H_{10}	1.090	1.114	N-C_1-C_4	131	125.42
N-C-H_8	121.77	121.16	C_4-H_{11}	1.094	1.114	C_4-H_{11}		1.114	N-C_1-C_5	113	116.77
C-N-O	110.20	110.21	C_4-H_{12}	1.094	1.114	C_4-H_{12}		1.113	C_4-C_1-C_5	117	117.79
H_4-C-H_8	122.7[g]	122.79	N-C_1-C_4	119.34	119.25	N-C_1-C_4	126.4	126.60	C_1-N-O	111	112.10
N-O-H	102.68	102.68	N-C_1-H_8	121.77	121.87	N-C_1-H_5	115.6	115.61	N-O-H		102.38
dipole	0.44 D	0.44 D	C_4-C_1-H_8	118.89	118.89	C_4-C_1-H_5		117.79	dipole	0.82 D[h] 1.06 D[i]	1.06 D
I_x	7.4690[j]	7.4880	C-N-O	110.20	110.12	C-N-O	110.2	111.80	I_x		59.3768
I_y	42.6275[j]	42.4773	N-O-H	102.68	102.56	N-O-H	102.68	102.56	I_y		124.1869
I_z	50.1514	49.9652	C_1-C_4-H_{10}		112.07	C_1-C_4-H_{10}	112.0	109.32	I_z		176.9862
CN-OH barrier		8.43	C_1-C_4-H_{11}		109.84	C_1-C_4-H_{11}	109.4	109.32			
H-C=N-O barrier		37.7	C_1-C_4-H_{12}		109.84	C_1-C_4-H_{12}	118.0	115.08			
$\Delta G°$ (N-O rotation)		6.08	H_{10}-C_4-H_{11}	108.80	108.20	H_{10}-C_4-H_{12}	107.6	107.44			
			dipole	0.938 D	0.940 D	dipole	0.828 D	0.812 D			
			I_x		11.233	I_x		29.080			
			I_y		119.303	I_y		78.293			
			I_z		128.420	I_z		104.094			
			CN-OH barrier		8.06	CN-OH barrier		9.05			
			CH_3-C barrier	1.84	1.84	CH_3-C barrier	0.375	0.892			
			$\Delta G°(Z \rightarrow E)$[k]	0.31							

[a] Microwave data[11] unless otherwise noted. [b] Angles are given in degrees, bond lengths in Å, and energies in kcal/mol. [c] Calculations are for this work only. The supplementary material contains these values and a comparison of them to those obtained by other computational methods. [d] Microwave data[10,17] unless otherwise noted. [e] Microwave data[10,22] unless otherwise noted. [f] X-ray crystallographic data[13] unless otherwise noted. [g] By difference. [h] After ref 23. [i] After ref 24. [j] After ref 12. [k] The *E* isomer is favored.

Results and Discussion

The MM2 calculated geometries for formaldoxime (1), (*E*)- and (*Z*)-acetaldoximes (**2a,b**), and acetoxime (3) are shown in Table IV, along with reported values from microwave and X-ray spectroscopy. Comparison to ab initio, semiempirical, and other force field (CFF) calculations is provided in the supplementary material.

The oxime portion of all four oximes (1, **2a,b**, and 3) is found to be planar, in accord with experiment.

Additionally, the calculations reproduce experimental bond lengths and angles for formaldoxime (1) extremely well. In particular, the "methylene tilt" in which the N-C-H angle on the "same side" as the unshared pair on nitrogen is calculated to be 116.0° and the opposite N-C-H angle to be 121.1° (compared to the values of 115.6° and 121.8°, respectively, from microwave spectroscopy)[11] is found. The dipole moment (0.44 D)[11] is reproduced, and the calculated moments of inertia are very similar to experimentally determined values.[12]

Similarly, experimental geometries for (*E*)- and (*Z*)-acetaldoximes (**2a,b**) and acetoxime (3) are well reproduced by MM2. Values for acetoxime (3) are within experimental error for those found by X-ray spectroscopy.[13]

Although the barrier for isomerization between (*E*)- and (*Z*)-acetaldoximes (**2a,b**) has not been experimentally determined in the gas phase, calculations have been produced assuming either a rotation process[1h,9] (ca. 100 kcal/mol) or a process involving inversion through nitrogen[9] (ca. 37.5 kcal/mol) to account for the conversion of one isomer to the other. The MM2 calculated barrier for isomerization around the C=N bond in formaldoxime was found to be 37.7 kcal/mol using the dihedral driver.

The isomerization in solution between (*E*)- and (*Z*)-acetaldoxime (**2a,b**) to the equilibrium mixture leads to values of the standard free energy ($\Delta G°$) lying between 0.29 and 0.61 kcal/mol for the two isomers.[1i,8] Ab initio calculations support a value in this range.[1i] MM2 (assuming a gas-phase process) produces a value of 0.31 kcal/mol for $\Delta G°$ in which the *E* isomer **2a** is favored.

The barrier to rotation around the N-O bond in formaldoxime (1) has been determined by ab initio methods to be on the order of 8-12 kcal/mol with the s-trans orientation favored ($\Delta G° \simeq$ 6 kcal/mol).[14-16] MM2 gives a barrier of 8.43 kcal/mol and a $\Delta G°$ of 6.08 kcal/mol. For (*E*)-acetaldoxime (**2a**), the N-O rotational barrier is comparable: 8.06 kcal/mol with a $\Delta G°$ of 5.01 kcal/mol. For the *Z* isomer **2b**, the barrier increases (presumably due to steric hinderance from the methyl group). MM2 gives a value of 9.05 kcal/mol with the s-cis form at the top of the energy barrier.

The barriers for methyl rotation of (*E*)- and (*Z*)-acetaldoximes (**2a,b**) have been determined experimentally by microwave spectroscopy[10,17] and for the *E* isomer **2a** the

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experimental value is 1.835 kcal/mol while the value from MM2 is 1.841 kcal/mol. For the *Z* isomer **2b**, the experimental value is 0.375 kcal/mol and the value from MM2 is 0.892 kcal/mol, which, while somewhat high, does reflect the increased ease of rotation in the *Z* isomer **2b**.

Conclusion

The MM2 force field has been extended to include the oxime functional group and a set of parameters has been developed which reproduces, with reasonable accuracy, the experimentally available data. It is now possible to extend these parameters to more complicated systems and to attempt to predict their geometries. This work is underway.

Acknowledgment. Fruitful discussions with Professor N. L. Allinger and Dr. Y. H., Yuh are gratefully acknowledged.

Registry No. Formaldoxime, 75-17-2; (*E*)-acetaldoxime, 5780-37-0; (*Z*)-acetaldoxime, 5775-72-4; acetone oxime, 127-06-0.

Supplementary Material Available: Tables comparing the experimental data for **1**, **2a**,**b**, and **3** with other published computational [ab initio (STO-3G, 4-31G, SCF-DZ), semiempirical (CNDO/2, INDO), and force field (CFF)] results (10 pages). Ordering information is given on any current masthead page.

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Carbon-to-Nitrogen Rearrangement in *N*-(Arylsulfonoxy)amines as a Route to Azacyclic Compounds

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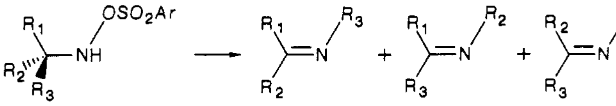
A series of cyclic amines **1**–**10** was converted to the *N*-((*p*-nitrophenyl)sulfonoxy)amine derivatives with (*p*-nitrophenyl)sulfonyl peroxide. These compounds rearranged to ring-expanded cyclic imines in fair to good yields. Conversion of the amine to its hydroxylamine analogue and treatment with *p*-nitrobenzenesulfonyl chloride/triethylamine also gave the ring-expanded cyclic imines; however, yields were superior due to the basicity of the reaction mixture.

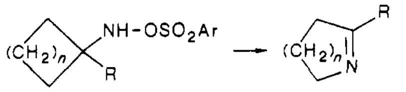
It was earlier demonstrated that, in the absence of base, *N*-(arylsulfonoxy)amines undergo facile carbon-to-nitrogen rearrangements to give imine products (eq 1).[1] A number



(1)

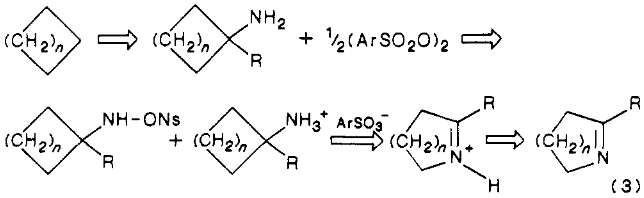
of studies suggest that concerted, cationic rearrangement of the migrating group accompanies ionization of the arylsulfonoxy group from nitrogen;[2] thus discrete cationic nitrenium ions are not involved in these rearrangements.[3]

When dissimilar migrating groups are attached to C-1 of the *N*-(arylsulfonoxy)amine precursor, a mixture of products can result. The relative proportions of products were found to depend on three factors: (a) the inherent migratory aptitudes of these groups, (b) electronic effects at the migration origin, and (c) stereoelectronic effects that require an antiperiplanar relationship between the departing arenesulfonate leaving group and the migrating group.[1] The interplay of these factors is not a priori predictable; however, it was observed that in cyclic amine substrates with tertiary carbon at the migration origin, only ring expansion was observed (eq 2).[1,3] It was concluded



(2)

that in such systems, stereoelectronic effects were the principal factor in determining the products of rearrangement.[1] The synthetic consequence of such behavior is that attachment of an amine functionality to a cyclic system, followed by conversion to the an *N*-arylsulfonoxy derivative and cationic rearrangement, could provide a convenient method for the insertion of nitrogen into rings to give ring-expanded iminium/imine products (eq 3).



(3)

Other reactions that accomplish this type of change (ring expansion and insertion of nitrogen) include the Beckman rearrangement[4] and the Schmidt reaction[5] of cyclic ke-

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