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Semiexperimental Equilibrium Structures for the Equatorial Conformers of *N*-Methylpiperidone and Tropinone by the Mixed Estimation Method

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S *Supporting Information*

ABSTRACT: *N*-Methylpiperidone (MPIP) and tropinone, which contain a structural motif found in numerous alkaloids, are too large to determine an accurate equilibrium structure either by ab initio methods or by experiment. However, the ground state rotational constants of the parent species and of all isotopologues with a substituted heavy atom (^{13}C, ^{15}N, ^{18}O) are known from microwave spectroscopy. These constants have been corrected for the rovibrational contribution calculated from an ab initio cubic force field. These semi-experimental equilibrium rotational constants have been supplemented by carefully chosen structural parameters from medium level ab initio calculations. The two sets of data have been used in a weighted least-squares fit to determine reliable equilibrium structures for both molecules. This work shows that it is possible to determine reliable equilibrium structures for large molecules (34 degrees of freedom in the case of tropinone) at a detailed level of accuracy, and the method could be applied without too much difficulty to still larger molecules.
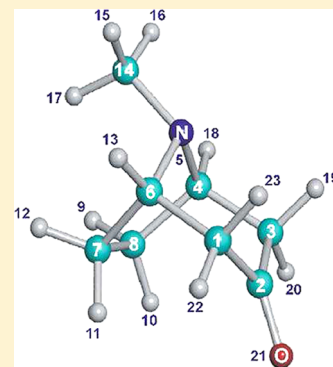
1. INTRODUCTION

The semiexperimental (SE) method is of growing importance for determining equilibrium rotational structures of molecules. A number of SE structures have been reported that were determined from semiexperimental equilibrium rotational constants for full sets of isotopologues.[1] Such SE structures have been obtained for polar molecules after correcting ground state (GS) rotational constants found from microwave spectroscopy, such as for *cis*-1,2-difluoroethylene[2] and 1,1-difluorocyclopropane.[3] SE structures have been obtained for nonpolar molecules starting with GS rotational constants found from high-resolution infrared spectroscopy, such as for ethylene and butadiene.[4] The resulting SE structures agree with high-level quantum chemical (QC) structures within 0.001 Å and 0.1°.[1−3,5] Many other examples of SE structures, which are in good agreement with high-level QC calculations, are cited in tables in this paper.

For larger molecules, obtaining GS rotational constants for a full set of isotopologues is not feasible with a reasonable expenditure of experimental effort. A solution is to join information from QC calculations with semiexperimental rotational constants to determine an SE structure. The rotational constants, which are often available for the substitution of the heavy atoms, carbon, oxygen, and nitrogen, from natural abundance measurements in the microwave region, determine the structure of the heavy atom backbone. QC calculations help determine the many CH bond lengths and bond angles. Important examples of this *mixed estimation* approach are SE structures for amino acids, including two conformers of glycine,[6] two conformers of alanine,[7] and proline.[8]

When all bond parameters cannot be determined from experiment, it has been common to fix some parameters or relationships among parameters (e.g., differences in bond lengths) at predicted values. However, this procedure is undesirable because the fixed parameters are assumed to be absolutely accurate, thereby introducing a non-negligible bias (systematic error) in the refined parameters. To avoid this
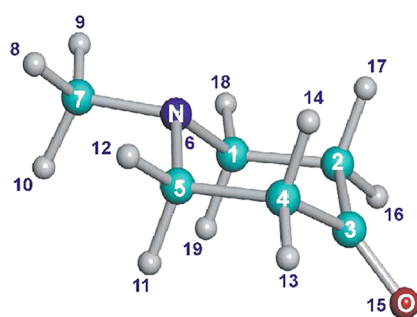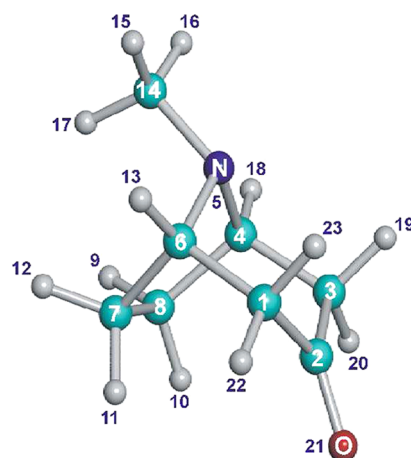
Equatorial 1-methyl-4-piperidone Equatorial tropinone

Figure 1. Structures of equatorial 1-methyl-4-piperidone and equatorial tropinone.

difficulty, it is advantageous to use the full mixed estimation technique where no parameter is constrained but auxiliary information is added directly to the data matrix during the least-squares fit.[9,10] This method was introduced in the field of electron diffraction as the "method of predicate observations" by Bartell et al.[11] and was used extensively under the name of SARACEN (Structure Analysis Restrained by Ab initio Calculations for ElectroN diffraction).[12] A similar method was applied in association with microwave spectroscopy to determine empirical structures of large molecules using the ground state rotational constants and ab initio structures.[13]

In the mixed estimation approach for SE structures of large molecules, GS rotational constants are converted to semi-experimental equilibrium rotational constants by means of the vibration−rotation constants (spectroscopic α's) obtained from QC calculations.[1] Estimates of bond lengths and bond angles are obtained from QC calculations at an accessible level of theory, improved by corrections based on comparisons between QC predictions at this level and known equilibrium structures for various types of bonds. Then, mixed estimate fits of bond parameters are made to the equilibrium rotational constants with appropriate uncertainties and concurrently to the predicate bond parameters found from QC calculations with appropriate uncertainties. In the most general form of the mixed estimation method, no specific constraints are introduced, in contrast to what was done for determining the SE structures of the amino acids.[6−8]

An example of the successful application of the mixed estimation method is *cis,trans*-1,4-difluorobutadiene, where the GS rotational constants for each of the singly substituted deuterium isotopologues plus the 1,4-d_2 species and for each of the $^{13}C_1$ isotopologues were insufficient for a complete structure.[14] A satisfactory SE structure was reported recently for this 10-atom, 17-parameter problem based on the mixed estimation method.[15] It led us to attempt an extension of the method to the more challenging examples of the equatorial conformers of 4-*N*-methylpiperidone (MPIP) (19 atoms) and tropinone (23 atoms). Schematic structures are shown in Figure 1. These molecules are of considerable interest because they contain the motif of many pharmacologically active species with neurostimulant activity. Ground state rotational constants were recently reported for all the heavy atom isotopologues and

the parents for both substances from microwave investiga-tions.[16,17] Observing GS rotational constants for deuterium isotopologues of these molecules would have required unimaginably difficult synthetic work. Thus, additional information, in particular about the CH bond lengths and bond angles, would come from QC calculations at a medium level of theory.

The microwave papers reported provisional substitution (r_s) and effective (r_0) structures for the heavy atom backbones of MPIP and tropinone.[16,17]

2. COMPUTATIONAL DETAILS

For large systems, lower-level electronic structure methods have to be used, for instance, second-order Møller−Plesset perturbation theory (MP2)[18] or Kohn−Sham density func-tional theory (DFT),[19] in particular, with Becke's three-parameter hybrid exchange functional[20] and the Lee−Yang−Parr correlation functional,[21] together denoted as B3LYP.

During the structure optimizations with the MP2 method performed in this work, the cc-pVTZ basis set was employed, as implemented in Gaussian 03 (G03).[22] B3LYP computations were also performed with the split-valence 6-311+G(3df,2pd) basis set, because it is known[23,24] to give relatively accurate results with the B3LYP DFT technique. Furthermore, as this basis is rather small compared to the aug-cc-pVTZ or VQZ basis sets, it enables the computation of equilibrium structures of large molecules.

Quadratic and cubic force constants were computed at the B3LYP/cc-pVTZ level of theory with G03 (E.01) for both species. The B3LYP method was preferred to the MP2 method because it is more affordable from the point of view of computer time and memory. These force constants and the optimized molecular structures were used in program VIBROT to compute vibration−rotation interaction constants, the so-called α-constants.[25] These constants, which depend on the cubic force field, permit the derivation of the equilibrium rotational constants from the ground state ones. For an asymmetric top

$$B_e^g = B_0^g + \frac{1}{2}\sum_{i=1}^{3N-6} \alpha_i^g$$

(1)

B

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where $g = a, b, c$ and N is the number of atoms. Table 1 contains the observed GS rotational constants[16,17] and the equilibrium rotational constants found with the $(1/2)\alpha$ sums.

The program used to determine the molecular parameters by linearized least squares is a modified version of the program described in appendix Va of ref 26. Briefly, the derivatives of the inertial moments with respect to the molecular structural parameters are calculated analytically. In the modified version,

it is possible to introduce predicate observations or to use the method of iteratively reweighted least squares.

3. DETERMINATION OF THE PREDICATES

In this context "predicate" values are understood to be the bond parameters predicted from theory.[9-11] For the mixed estimation method, the predicate bond parameters must be estimated carefully and accompanied by reasonable uncertainties.

It is difficult to obtain accurate equilibrium values of the CH bond length either by gas-phase electron diffraction or by rotational spectroscopy. On the contrary, it is now easy using quantum chemical computations. Already at the inexpensive level of theory, the MP2/6-31G** model furnishes accurate values,[27] and at the MP2/cc-pVTZ level, the computed values are very close to the equilibrium values.[15]

The situation is less favorable for the C–C bond. However, a study of 28 CC bond lengths from the short C≡C triple bonds to the long C–C single bonds shows that the MP2/cc-pVTZ level of theory reproduces the equilibrium CC bond lengths with a mean offset of −0.005 Å.[28] However, this offset is not constant. If the comparison is limited to C–C single bonds, although the basis set convergence is not achieved at this level, there is a partial compensation of errors, and the MP2/cc-pVTZ result is close to the equilibrium value (see Table 2). This agreement exists for a variety of bond types ranging from sp^3-sp^3 to sp^3-sp except for pyrrole, furan, and cyclopropane. It is possible to explain this outlying behavior because the CC bond is not a single bond in these molecules. The exceptions are π-electron systems. This property is confirmed by the large value of the bond ellipticity ε, which is also given in Table 2. The bond ellipticity provides a measure of the extent to which the charge is preferentially accumulated at a given angle in a plane perpendicular to the bond path and, for this reason, is a measure of the π-character of the bond.[29] It can be calculated with the atoms-in-molecules (AIM) theory with its implementation in G03 by Cioslowski et al.[30] It appears that when the bond ellipticity is small, the MP2/cc-pVTZ level of theory predicts well the length of the C–C bond and is more accurate than the B3LYP/6-311+G(3df,2pd) method. The results of the DFT method are also given in Table 2 with the computed value being too large.

The situation for the C–N single bond is quite similar to that of the C–C single bond (see Table 3). Thus, the MP2/cc-pVTZ value for the C–N bond length is almost identical to the equilibrium value, except for aziridine and diazirine. Here again, it is possible to explain this outlying behavior because the C–N bond is not a "true" single bond in these two molecules. This conclusion is confirmed by the large value of the bond ellipticity ε, which is also given in Table 3. Here again, when the bond ellipticity is small, the MP2/cc-pVTZ level of theory predicts well the length of the C–N bond and is more accurate than the B3LYP/6-311+G(3df,2pd) method, for which results are also given in Table 3. The bond ellipticity ε was calculated for the C–C and C–N bonds in N-4-methylpiperidone and in tropinone (see Table 4). For both molecules, it is quite small, indicating that the MP2/cc-pVTZ level of theory is likely to give an accurate estimate for these bond lengths.

From a study of 47 accurate equilibrium CO bond lengths, a linear relationship was found between the best equilibrium bond length and its B3LYP/6-311+G(3df,2pd) estimate, permitting predictions of the CO bond length with an accuracy of about 0.002 Å:[31]

Table 1. Rotational Constants of N-Methylpiperidone and Tropinone (MHz)

		ground state	equilibrium	e − c[a]
MPIP[b]				
normal	A	4321.52	4349.931	−0.002
	B	1504.15	1520.555	−0.006
	C	1208.03	1222.431	−0.003
^{18}O	A	4311.73	4338.907	0.000
	B	1444.08	1459.858	0.003
	C	1169.70	1183.705	−0.002
^{15}N	A	4319.01	4347.092	0.006
	B	1495.62	1511.857	−0.002
	C	1202.74	1217.024	−0.002
1-^{13}C	A	4268.28	4296.292	0.007
	B	1501.90	1518.281	0.002
	C	1202.60	1216.917	−0.007
2-^{13}C	A	4258.43	4286.173	0.006
	B	1501.19	1517.468	−0.002
	C	1201.87	1216.138	−0.002
3-^{13}C	A	4321.48	4349.775	−0.010
	B	1494.16	1510.394	0.007
	C	1201.62	1215.869	0.008
7-^{13}C	A	4320.68	4348.912	−0.006
	B	1470.89	1486.898	0.002
	C	1186.55	1200.661	0.004
Tropinone[c]				
normal	A	2391.394	2425.806	−0.130
	B	1162.846	1177.474	−0.004
	C	1116.810	1128.236	−0.008
^{18}O	A	2391.430	2425.853	0.164
	B	1122.471	1136.653	0.048
	C	1079.556	1090.740	0.026
^{15}N	A	2384.880	2419.086	0.167
	B	1157.678	1172.141	0.022
	C	1113.538	1124.846	0.013
1-^{13}C	A	2369.910	2403.669	−0.033
	B	1160.065	1174.581	0.022
	C	1110.825	1122.164	−0.024
2-^{13}C	A	2390.390	2424.643	−0.418
	B	1155.387	1169.875	−0.041
	C	1110.145	1121.473	−0.014
6-^{13}C	A	2376.770	2410.803	−0.042
	B	1161.988	1176.575	−0.002
	C	1112.809	1124.177	0.002
7-^{13}C	A	2362.010	2395.890	0.067
	B	1156.508	1171.101	−0.037
	C	1114.168	1125.622	0.004
14-^{13}C	A	2385.960	2420.887	−0.146
	B	1143.491	1157.796	−0.005
	C	1100.116	1111.194	−0.002

[a]Equilibrium (e) − calculated (c) residuals of the fit. [b]Reference 16. [c]Reference 17.

C

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Table 2. C–C Bond Lengths (Å) Computed with the Use of MP2 and B3LYP Methods and VTZ and 611+G Basis Sets

		r_e	MP2/VTZ	e − c[a]	B3LYP/611+G[b]	e − c[a]	ε[c]	ref
c-C$_4$H$_5$N		1.422	1.416	0.006	1.421	0.001	0.194	e
H$_2$C=CHCN		1.433	1.429	0.004	1.426	0.007	0.058	f
c-C$_4$H$_4$O		1.434	1.426	0.008	1.432	0.002	0.161	g
CHF=CH—CH=CHF	C$_2$–C$_3$	1.449	1.448	0.001	1.447	0.002	0.099	h
CH$_3$C≡CH		1.458	1.458	0.000	1.455	0.003	0.000	i
CH$_3$CN		1.459	1.458	0.001	1.455	0.004	0.000	j
c-C$_2$H$_4$O		1.462	1.462	0.000	1.463	−0.001	0.281	g
CH$_3$CH$_2$CN	CH$_2$–CN	1.464	1.461	0.003	1.460	0.004	0.013	k
C$_2$H$_2$(CO)$_2$O		1.485	1.485	0.000	1.487	−0.002	0.109	l
CH$_3$CH=CH$_2$		1.496	1.495	0.000	1.497	−0.001	0.032	m
CH$_3$CHO		1.499	1.499	0.000	1.501	−0.002	0.057	n
HCOCH$_2$OH		1.502	1.502	0.000	1.504	−0.002	0.100	o
c-C$_3$H$_6$		1.502	1.498	0.004	1.504	−0.002	0.544	p
c-C$_3$H$_4$		1.505	1.507	−0.002	1.506	−0.001	0.750	q
(CH$_3$)$_2$C=O		1.508	1.509	−0.001	1.514	−0.006	0.053	r
CH$_3$CH$_2$OH		1.509	1.510	−0.001	1.515	−0.006	0.039	o
CHO—CHO		1.515	1.514	0.000	1.525	−0.010	0.085	s
CH$_3$CH$_3$		1.522	1.523	−0.001	1.527	−0.005	0.000	t
HCOCOOH		1.526	1.524	0.002	1.534	−0.008	0.100	u
CH$_3$CH$_2$CN	Me-CH$_2$	1.528	1.529	−0.001	1.535	−0.008	0.012	k
c-C$_3$H$_5$NO	C$_2$–C$_3$	1.540	1.541	−0.001	1.545	−0.005	0.061	v
c-C$_3$H$_5$NO	C$_3$–C$_4$	1.549	1.547	0.002	1.553	−0.004	0.009	v
MAD[d]				0.001		0.004		

[a]e − c is equilibrium − calculated. [b]6-311+G(3df,2pd). [c]Bond ellipticity computed at the B3LYP/6-311+G(3df,2pd) level. [d]Median of absolute deviations. [e]J. Demaison, unpublished results. [f]Askeland, E.; Møllendal, H.; Uggerud, E.; Guillemin, J. C.; Aviles Moreno, J.-R.; Demaison, J.; Huet, T. R. *J. Phys. Chem. A* **2006**, *110*, 12572−12584. [g]Demaison, J.; Császár, A. G.; Margulès, L.; Rudolph, H. D. *J. Phys. Chem. A* **2011**, *115*, 14078− 14091. [h]Demaison, J. ; Craig, N. C. *J. Phys. Chem. A* **2011**, *115*, 8049−8054. [i]Schulz, B.; Botschwina, P. *Mol. Phys.* **1996**, *89*, 1553−1565. [j]Puzzarini, C.; Cazzoli, G. *J. Mol. Spectrosc.* **2006**, *240*, 260−264. [k]Demaison, J.; Margulès, L.; Mäder, H.; Sheng, M.; Rudolph, H. D. *J. Mol. Spectrosc.* **2008**, *252*, 169−175. [l]Vogt, N.; Demaison, J.; Rudolph, H. D. *Struct. Chem.* **2011**, *22*, 337−343. [m]Demaison, J.; Rudolph, H. D. *J. Mol. Spectrosc.* **2008**, *248*, 66− 76. [n]Demaison, J.; Császár, A. G. *J. Mol. Struct.* **2012**, in press. [o]Demaison, J.; Herman, M.; Liévin, J. *Int. Rev. Phys. Chem.* **2007**, *26*, 391−420. [p]Gauss, J.; Cremer, D.; Stanton, J. F. *J. Phys. Chem. A* **2000**, *104*, 1319−1324. [q]Margulès, L.; Demaison, J.; Boggs, J. E. *Struct. Chem.* **2000**, *11*, 145− 154. [r]Lovas, F. J.; Groner, P. *J. Mol. Spectrosc.* **2006**, *236*, 173−177. [s]Larsen, R. W.; Pawlowski, F.; Hegelund, F.; Jørgensen, P.; Gauss, J.; Nelander, B. *Phys. Chem. Chem. Phys.***2003**, *5*, 5031−5037. [t]Puzzarini, C.; Taylor, P. R. *J. Chem. Phys.* **2005**, *122*, 054315. [u]Bakri, B.; Demaison, J.; Margulès, L.; Møllendal, H. *J. Mol. Spectrosc.* **2001**, *208*, 92−100. [v]Demyk, K.; Petitprez, D.; Demaison, J.; Møllendal, H.; Wlodarczak, G. *Phys. Chem. Chem. Phys.* **2003**, *5*, 5038−5043.

Table 3. C–N Bond Lengths (Å)

		MP2/VTZ		B3LYP/611+G[b]			
	r_e	calc	e − c[a]	calc	e − c[a]	ε[c]	ref
HCC–NC	1.314	1.314	0.000	1.305	0.009	0.000	e
H$_2$N–CN	1.348	1.351	−0.003	1.340	0.009	0.098	f
HC(O)NH$_2$	1.355	1.358	−0.003	1.357	−0.002	0.147	f
CH$_3$CONH$_2$	1.362	1.367	−0.005	1.365	−0.003	0.145	f
c-C$_4$H$_5$N	1.369	1.368	0.001	1.368	0.001	0.211	g
C$_3$H$_5$NO	1.370	1.374	−0.003	1.371	−0.001	0.176	h
OC((NH$_2$)$_2$	1.382	1.386	−0.004	1.382	−0.001	0.164	f
H$_2$C=CHNH$_2$	1.395	1.393	0.001	1.388	0.007	0.085	i
CH$_3$NC	1.422	1.420	0.002	1.419	0.003	0.000	j
CH$_3$NH$_2$	1.461	1.463	−0.002	1.463	−0.003	0.035	f
c-H$_2$CN$_2$	1.476	1.482	−0.007	1.477	−0.002	0.642	k
c-C$_2$H$_4$NH	1.470	1.481	−0.011	1.469	0.001	0.499	g
MAD[d]			0.003		0.002		

[a]e − c is equilibrium − calculated. [b]6-311+G(3df,2pd). [c]Bond ellipticity computed at the B3LYP/6-311+G(3df,2pd) level. [d]Median of absolute deviations. [e]Botschwina, P.; Horn, M.; Seeger, S.; Flügge, J. *Chem. Phys. Lett.* **1992**, *195*, 427−434. [f]Demaison, J.; Császár, A. G.; Kleiner, I.; Møllendal, H. *J. Phys. Chem. A* **2007**, *111*, 2574−2586. [g]J. Demaison, unpublished results. [h]Demyk, K.; Petitprez, D.; Demaison, J.; Møllendal, H.; Wlodarczak, G. *Phys. Chem. Chem. Phys.* **2003**, *5*, 5038−5043. [i]Askeland, E.; Møllendal, H.; Uggerud, E.; Guillemin, J. C.; Aviles Moreno, J.-R.; Demaison, J.; Huet, T. R. *J. Phys. Chem. A* **2006**, *110*, 12572−12584. [j]Margulès, L.; Demaison, J.; Rudolph, H. D. *J. Mol. Struct.* **2001**, *599*, 23−30. [k]Puzzarini, C.; Gambi, A.; Cazzoli, G. *J. Mol. Struct.* **2004**, *695*, 203−210.

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Table 4. Bond Ellipticities ε and Bond Critical Point Densities ρ_b (au) for *N*-Methylpiperidone and Tropinone (Calculated at the B3LYP/6-311+G(3df,2pd) Level

	ε	ρ_b
N-Methylpiperidone		
$r(C_1-C_2)$	0.038	0.243
$r(C_2-C_3)$	0.050	0.259
$r(C_3-C_4)$	0.050	0.259
$r(C_4-C_5)$	0.038	0.243
$r(C_1-N)$	0.061	0.274
$r(C_5-N)$	0.061	0.274
$r(N-C7)$	0.052	0.273
$r(C_3{=}O)$	0.082	0.427
Tropinone		
$r(C_1-C_2)$	0.055	0.255
$r(C_2-C_3)$	0.055	0.255
$r(C_3-C_4)$	0.036	0.244
$r(C_4-N)$	0.052	0.267
$r(C_1-C_6)$	0.036	0.244
$r(N-C_6)$	0.052	0.267
$r(C_6-C_7)$	0.013	0.236
$r(C_4-C_8)$	0.013	0.236
$r(C_7-C_8)$	0.015	0.233
$r(C_2{=}O)$	0.080	0.427

$$r_e(CO) = 0.9780(29)\{r_e^{BO}[\text{B3LYP/6-311+G(3df,2pd)}]\}$$
$$+ \; 0.0283(37) \tag{2}$$

with a correlation coefficient of $\rho = 0.9996$. It has also to be noted that, contrary to the MP2/cc-pVTZ value, the B3LYP/6-311+G(3df,2pd) value is close to the equilibrium value, with the computed value being slightly smaller.

Likewise, an analysis of 35 bond angles shows that the MP2/cc-pVTZ level of theory is able to predict bond angles with an accuracy of about $0.3-0.4°$.[32] The situation is worse for torsional angles because the force constant corresponding to a torsional angle is generally smaller than the force constant corresponding to a bond angle deformation. In other words, much less energy is needed to change a torsional angle by a certain amount than to change a bond angle by the same amount. In conclusion, it is much more difficult to compute accurate torsional angles. This problem is particularly apparent when low-torsional vibrations are present. In such a case, different levels of theory give significantly different results. Considering torsional frequencies is an indirect way to estimate the accuracy of the computed torsional angles. This difficulty is particularly relevant for tropinone, for which the minimum of the potential hypersurface is very flat.

4. SEMIEXPERIMENTAL STRUCTURES

To check the compatibility of the data, the mixed estimation method is applied in three steps. In the first step, the bond lengths and bond angles to all the hydrogen atoms are held fixed at their predicate values, while the parameters for the heavy atoms are fitted to the equilibrium rotational constants. This is still an ordinary least-squares fit. In the second step, a structure is fitted to both the equilibrium rotational constants and the predicate values for the hydrogen atoms with their estimated uncertainties. In this step, the values of the internal coordinates of the heavy atoms are also fitted; however, their predicate values are not used. This is a (limited) mixed estimation. In the third step, the predicate values for the internal coordinates of the heavy atoms as well as for the internal coordinates for the hydrogen atoms are floated in a fit that includes the equilibrium rotational constants. This third mixed estimation step has two advantages: (i) if there are no significant differences or sudden deviations between the results of the three steps, we may infer that all the data are compatible and that there is no outlier; (ii) it significantly improves the conditioning of the system of normal equations[9] which is particularly welcome in the case of a structure determination.

4.1. *N*-4-Methylpiperidone. *N*-4-Methylpiperidone has a plane of symmetry, and its structure is completely defined by 28 parameters. Atoms on two sides of the plane of symmetry are linked by symmetry. Atoms on the plane of symmetry were fixed on this plane. For use in defining some internal angle coordinates, dummy atoms were placed halfway between C_1 and C_5 and halfway between C_2 and C_4 on the plane of symmetry. With these definitions, as given in Table S1 in the Supporting Information, 17 predicate parameters were defined for unique hydrogen atoms either on the plane of symmetry or on one side of this plane. Six coordinates are for unique CH bond lengths, three are for bond angles and a torsion angle for the CH_3 group, and the remaining eight coordinates relate angles for the C_5H_{11}, C_5H_{12}, C_4H_{13}, and C_4H_{14} bonds to dummy atoms. These definitions for the predicates are in Table S1 in the Supporting Information. For the predicates for the heavy atoms, the two dummy atoms were included to give seven "bond" lengths. The four adjustable bond angles were related to the dummy atoms, as seen in Table S1 in the Supporting Information.

The structure was first optimized at two different levels of theory, MP2/cc-pVTZ and B3LYP/6-311+G(3df,2pd), to determine the predicate values. As anticipated from the discussion in section 3, the C—N bond lengths are almost identical for the two methods and the B3LYP C—C bond lengths are significantly longer than the MP2 ones. There are also significant differences for some dihedral angles, in particular those involving the bond C_3—O. This outcome may be explained by a low-frequency skeletal frequency calculated at 78 cm^{-1} (B3LYP/cc-pVTZ level) involving this bond. Except for the predicate value of the C=O bond, which was calculated with eq 1, the MP2/cc-pVTZ values were used as predicates.

Semiexperimental equilibrium rotational constants are available for the parent species as well as for all monosubstituted heavy-atom species. In principle, these constants allow us to determine the structure of the heavy-atom skeleton. It is tempting to use Kraitchman's equations for the substitution method.[33] However, all *c*-coordinates are small, with the largest one being $|c(O)| = 0.38$ Å. Therefore, the derived structure will be extremely inaccurate,[34] all the more so because the derived equilibrium rotational constants are not accurate. In a first fit, we have fixed the bond lengths and bond angles to all hydrogen atoms to the MP2/cc-pVTZ structure. The results are given in the fourth column of Table 5. The derived structure is in good agreement with the MP2/cc-pVTZ structure, except for the dihedral angle $\tau(C_1C_2C_3O)$ where the difference is as large as $3°$, which is in accord with the estimate of the accuracy of the MP2/cc-pVTZ dihedral angles (see section 3). In this case, the fitted value might be more accurate.

In a second fit, all the parameters were free, with the internal coordinates of the hydrogen atoms being used as predicate observations; the uncertainties used for the weighting were 0.02 MHz for the rotational constants, 0.002 Å for the C—H bond

Table 5. Structure of *N*-Methylpiperidone Computed with the Use of MP2 and B3LYP Methods and VTZ and 611+G Basis Sets[a,b]

predicate[d]	MP2/cc-pVTZ	B3LYP/6-311+G[c]	least-squares fit		
			0	17	28
$r(C_7-N)$	1.453	1.454	1.4521(4)	1.4521(7)	1.4525(22)
$r(N-C_1)$	1.455	1.458	1.4553(3)	1.4556(6)	1.4562(15)
$r(C_1-C_2)$	1.527	1.533	1.5255(5)	1.5270(10)	1.5268(26)
$r(C_2-C_3)$	1.509	1.515	1.5083(3)	1.5097(5)	1.5102(14)
$r(C_3=O)^e$	1.218	1.209	1.2126(4)	1.2113(8)	1.2108(20)
$r(C_1-H_{18})$	1.090	1.090		1.0904(9)	1.0905(33)
$r(C_1-H_{19})$	1.104	1.105		1.1046(9)	1.1033(32)
$r(C_2-H_{16})$	1.088	1.089		1.0883(9)	1.0884(33)
$r(C_2-H_{17})$	1.092	1.094		1.0925(9)	1.0910(32)
$r(C_7-H_8)$	1.088	1.090		1.0887(9)	1.0884(33)
$r(C_7-H_{10})$	1.101	1.103		1.1009(9)	1.1007(33)
$\angle(NC_7H_{10})$	112.33	112.87		112.29(13)	112.41(48)
$\angle(NC_7H_8)$	109.63	109.78		109.62(13)	109.60(48)
$\angle(C_1NC_7)$	110.11	111.87	110.29(2)	110.32(4)	110.31(12)
$\angle(C_1C_2C_3)$	109.99	111.69	110.63(2)	110.57(4)	110.54(10)
$\angle(NC_1C_2)$	110.63	111.26	110.82(2)	110.78(4)	110.69(11)
$\angle(OC_3C_2)$	123.10	122.79	122.81(2)	122.91(4)	122.96(9)
$\angle(C_1NC_5)$	109.83	111.24	110.01(4)	110.03(7)	109.93(18)
$\angle(C_2C_3C_4)$	113.78	114.43	114.36(4)	114.37(4)	114.07(18)
$\angle(NC_1H_{18})$	108.52	108.61		108.71(13)	108.72(47)
$\angle(C_2C_1H_{18})$	109.92	109.6		109.88(14)	109.77(48)
$\angle(NC_1H_{19})$	110.91	111.14		111.01(15)	111.09(55)
$\angle(C_2C_1H_{19})$	109.44	109.27		109.15(22)	109.34(81)
$\angle(H_{18}C_1H_{19})$	107.36	106.86		107.25(20)	107.16(72)
$\angle(C_1C_2H_{17})$	108.33	108.64		108.33(9)	108.33(35)
$\angle(C_3C_2H_{17})$	108.36	107.42		107.41(14)	107.60(46)
$\angle(C_1C_2H_{16})$	111.65	111.5		111.65(13)	111.68(50)
$\angle(C_3C_2H_{16})$	109.14	109.08		109.62(13)	109.60(46)
$\angle(H_{16}C_2H_{17})$	109.31	108.37		109.15(17)	108.99(61)
$\tau(H_8NC_7H_{10})$	−120.54	−120.64		−120.5(2)	−119.79(75)
$\tau(C_1NC_7H_{10})$	−119.37	−117.21	−119.148(18)	−119.11(4)	−119.18(11)
$\tau(OC_3C_2C_1)$	128.81	135.30	131.771(57)	132.03(11)	131.90(23)
$\tau(C_7NC_1C_2)$	175.17	172.82	174.943(26)	174.84(5)	174.72(19)
$\tau(NC_1C_2C_3)$	55.51	52.18	54.235(22)	54.45(7)	54.67(18)
$\tau(C_7NC_1H_{18})$	54.50	52.10		54.01(16)	54.06(56)
$\tau(C_3C_2C_1H_{18})$	175.33	172.31		174.58(17)	174.69(54)
$\tau(C_7NC_1H_{19})$	−63.19	−65.18		−63.73(21)	−63.61(78)
$\tau(C_3C_2C_1H_{19})$	−66.99	−70.9		−68.17(14)	−68.02(50)
$\tau(NC_1C_2H_{17})$	−62.76	−66.13		−63.00(14)	−62.99(49)
$\tau(OC_3C_2H_{17})$	−112.95	−105.67		−109.96(17)	−109.99(46)
$\tau(NC_1C_2H_{16})$	176.83	174.51		176.79(13)	176.97(53)
$\tau(OC_3C_2H_{16})$	5.99	11.593		8.51(20)	8.39(59)

[a]Equivalent atoms: $C_1 = C_5$; $C_2 = C_4$; $H_8 = H_9$; $H_{13} = H_{16}$; $H_{14} = H_{17}$; $H_{12} = H_{18}$; $H_{11} = H_{19}$. [b]Distances in angstroms and angles in degrees. [c]6-311+G(3df,2pd). [d]Number of predicate values used in the fit; see text. [e]The predicate value calculated from eq 1 is 1.211 Å.

lengths, 0.3° for the bond angles, and 0.5° for the torsional angles. The uncertainty used for the equilibrium rotational constants is much smaller than their expected error, but the dominant part of this error is systematic and affects the results only slightly.[35] The main effect is that the predicate values are downweighted. The results of the fit are in good agreement with the preceding fit, and inspection of the residuals does not indicate any anomaly; in particular, the analysis of the residuals confirms that the chosen weights have the correct order of magnitude.[10]

Finally, in a third fit, the internal coordinates of the heavy atoms were added as predicate observations with an uncertainty of 0.003 Å for the bond lengths. The corresponding Cartesian coordinates are given in Table S2 of the Supporting Information. This final fit is in good agreement with the previous ones and with the MP2/cc-pVTZ values. In Table S2, the B3LYP/6-311+G(3df,2pd) parameters are also given for the sake of comparison. There is a general satisfactory agreement with the exception of the two torsional angles $\tau(O_{15}C_3C_2H_{16})$ and $\tau(O_{15}C_3C_2H_{17})$, for which neither the MP2/cc-pVTZ predictions nor the B3LYP/6-311+G(3df,2pd) ones seem to be reliable. This discrepancy is also true, but to a lesser degree, for the torsional angle $\tau(O_{15}C_3C_2C_1)$. Taking into account the fact that the B3LYP/6-311+G(3df,2pd) method tends to slightly overestimate single bond lengths by about 0.0024 Å,[23] there is a satisfactory agreement for the bond

lengths. In conclusion, it appears that the new SE equilibrium structure of MPIP is accurate to a few thousandths of an angstrom for the bond lengths, a few tenths of a degree for the bond angles, and as large as a few degrees for the less well determined torsional angles, in particular those involving the atoms O_{15}, C_3, and C_2.

4.2. Tropinone. Tropinone also has a plane of symmetry, and its structure is completely defined by 34 parameters. Definitions of predicate internal coordinates for use in the fitting were analogous to those used for *N*-methylpiperidone. The definitions of the internal coordinates are in Table S3 in the Supporting Information.

The structure was first optimized at two different levels of theory, MP2 and B3LYP. With the B3LYP method, three different basis sets were used: cc-pVTZ, cc-pVQZ, and 6-311+G(3df,2pd). These three basis sets give almost identical results. With the MP2 method, two basis sets were used: cc-pVTZ and 6-311+G(3df,2pd). They also give almost identical results. Comparing the MP2 and B3LYP results, the following points have to be noted. First, the C−N bond lengths are almost identical for the two methods, which is an indication that they might be close to the equilibrium value. The B3LYP C−C bond lengths are significantly longer than the MP2 ones. The difference was expected, and the MP2 values are likely to be closer to the equilibrium values. Finally, there are large differences for some dihedral angles, in particular those involving the $O_{21}C_2C_1$ atoms. This discrepancy was also expected because these atoms, together with the neighboring hydrogen atoms, participate in a low-frequency skeletal vibration, 73 cm^{-1}, at the B3LYP/cc-pVTZ level.

The structure of tropinone was determined in a way similar to that used for MPIP. In a first fit, we have fixed the bond lengths and bond angles for all the hydrogen atoms to the MP2/cc-pVTZ structure. The results are given in the fourth column of Table 6. The derived structure is not precise because the system of normal equations is not well conditioned, with the condition number being as large as 2432. However, the 14 heavy-atom parameters are in good agreement with the MP2/cc-pVTZ structure, except for the torsional angle $\tau(OC_2C_1C_6)$ where the difference is as large as 7°, which is in accord with the estimate of the accuracy of the MP2/cc-pVTZ dihedral angles (see section 3). In this case, the fitted value might be more accurate. The second step of fitting with only the predicate values for CH bonds floated is not reported because it does not bring any new information.

In the final fit, all the parameters were free, and the internal coordinates of all atoms were used as predicate observations. The uncertainties used for the weighting were first 0.10 MHz for the A rotational constants, 0.06 MHz for the B and C rotational constants, 0.002 Å for the C−H bond lengths, 0.003 Å for the other bond lengths, 0.3° for the bond angles, and 0.5° for the torsional angles. The analysis of the residuals led us to increase the uncertainty of the A rotational constant of the $^{13}C_6$ isotopologue, from 0.10 to 0.30 MHz, as well as the uncertainty of the predicate angle $\angle(C_2m_{13}m_{46})$, from 0.3° to 2.0°, with m_{13} being the middle of the distance C_1C_3 and m_{46} being the middle of the distance C_4C_6. The final fit is given in the last column of Table 6. The corresponding Cartesian coordinates are given in Table S4 of the Supporting Information. All the parameters are well determined, with the exception of the bond length of the bridge, $r(C_7-C_8) = 1.554(7)$ Å. This semi-experimental value is slightly larger than both ab initio values, which are 1.546 Å at the MP2/cc-pVTZ level and 1.551 Å at

the B3LYP/6-311+G(3df,2pd) level. A plausible explanation is a slight incompatibility between the SE rotational constants and the predicate values. Indeed, Kraitchman's equations[33] give $r(C_7-C_8) = 1.562(3)$ Å. Compared to the ab initio results, this value is definitely too large. As the b Cartesian coordinate used to calculate this bond length is not small, 0.78 Å, the questionable result indicates that the semiexperimental rotational constants are not accurate. It has to be noted that the B3LYP structure used to compute the force field is not accurate, and this deficiency probably undermines the quality of the force field.

Table 6. Structure of Tropinone Computed with the Use of MP2 and B3LYP Methods and VTZ and 611+G Basis Sets[a,b]

predicate[d]	MP2/ cc-pVTZ	B3LYP/6-311+G[c]	least-squares fit 0	least-squares fit 34
$r(C_2{=}O)$[e]	1.2188	1.209	1.207(10)	1.2110(15)
$r(N_5-C_6)$	1.470	1.473	1.467(6)	1.4712(20)
$r(N_5-C_{14})$	1.459	1.458	1.456(6)	1.4595(21)
$r(C_1-C_2)$	1.511	1.521	1.515(6)	1.5140(19)
$r(C_1-C_6)$	1.530	1.536	1.529(10)	1.5300(20)
$r(C_6-C_7)$	1.547	1.556	1.556(12)	1.5454(22)
$r(C_7-C_8)$	1.546	1.551	1.533(10)	1.5561(74)
$r(C_1-H_{22})$	1.0889	1.090		1.0889(16)
$r(C_1-H_{23})$	1.0920	1.094		1.0919(16)
$r(C_6-H_{13})$	1.0897	1.089		1.0897(16)
$r(C_7-H_{11})$	1.0892	1.089		1.0891(16)
$r(C_7-H_{12})$	1.0884	1.089		1.0882(16)
$r(C_{14}-H_{15})$	1.0887	1.090		1.0886(16)
$r(C_{14}-H_{17})$	1.0978	1.100		1.0977(16)
$\angle(C_1C_2C_3)$	114.49	115.93	115.5(9)	114.73(17)
$\angle(C_1C_2O)$	122.73	122.03	122.3(4)	122.61(8)
$\angle(C_2C_1C_6)$	109.47	112.12	110.6(3)	110.99(15)
$\angle(C_1C_6N)$	107.68	107.68	108.4(7)	107.65(14)
$\angle(C_4NC_6)$	101.66	101.98	102.4(6)	101.79(16)
$\angle(C_4NC_{14})$	111.36	113.77	112.1(4)	111.44(11)
$\angle(C_1C_6C_7)$	110.61	111.51	110.1(7)	110.51(19)
$\angle(C_6C_7C_8)$	103.69	103.73	104.0(2)	103.61(18)
$\angle(C_2C_1H_{22})$	108.73	108.48		108.85(26)
$\angle(C_2C_1H_{23})$	108.60	107.10		108.58(30)
$\angle(C_1C_6H_{13})$	110.04	109.58		109.98(26)
$\angle(NC_{14}H_{17})$	114.00	114.49		114.50(25)
$\angle(NC_{14}H_{15})$	109.08	109.26		109.07(24)
$\angle(C_6C_7H_{11})$	111.42	111.84		111.40(37)
$\angle(C_6C_7H_{12})$	110.93	170.70		110.93(37)
$\tau(OC_2C_1C_6)$	−133.53	−147.91	−140.7(17)	−138.29(34)
$\tau(C_2C_1C_6N)$	−60.08	−54.65	−57.2(1.3)	−57.97(20)
$\tau(C_3C_4NC_{14})$	165.67	160.74	164.8(5)	165.37(19)
$\tau(C_2C_1C_6C_7)$	55.04	60.62	57.1(11)	57.22(27)
$\tau(OC_2C_1H_{22})$	−10.79	−23.28		−10.96(40)
$\tau(OC_2C_1H_{23})$	108.17	92.93		108.02(48)
$\tau(C_2C_1C_6H_{13})$	−179.54	−174.26		−177.50(31)
$\tau(C_6NC_{14}H_{17})$	−56.35	−58.11		−56.48(11)
$\tau(C_6NC_{14}H_{15})$	64.72	63.09		64.52(42)
$\tau(NC_6C_7H_{11})$	147.32	147.81		147.15(33)
$\tau(NC_6C_7H_{12})$	−93.04	−92.97		−93.15(34)

[a]Equivalent atoms: $C_1 = C_3$; $C_4 = C_6$; $C_7 = C_8$; $H_9 = H_{12}$; $H_{10} = H_{11}$; $H_{13} = H_{18}$; $H_{15} = H_{16}$; $H_{19} = H_{23}$; $H_{20} = H_{22}$. [b]Distances in angstroms and angles in degrees. [c]6-311+G(3df,2pd). [d]Number of predicate values used in the fit; see text. [e]The predicate value calculated from eq 1 is 1.2108 Å.

With the exception of the C_7-C_8 bond length and the $\tau(OC_2C_1C_6)$ torsional angle, comparison with the ab initio structures indicates an overall good agreement for the structure of tropinone. The fitted torsional angle is likely to be more accurate than the ab initio values. On the other hand, the MP2/cc-pVTZ value, 1.546 Å, is probably the most accurate value for the $r(C_7-C_8)$ bond length. In conclusion, as for MPIP, it appears that the new SE equilibrium structure of tropinone is accurate to a few thousandths of an angstrom for the bond lengths and a few tenths of a degree for the bond angles, apart from the $r(C_7-C_8)$ bond length and the $\tau(OC_2C_1C_6)$ torsional angle.

5. DISCUSSION

The C=O bond lengths in both MPIP and tropinone are close to the value found for acetone, 1.211(2) Å.[36] Likewise, the $\angle(OCC)$ bond angle is similar for the three molecules: 123.0° in MPIP, 122.6° in tropinone, and 121.8° in acetone. The C–C bonds lengths are similar to the value found for ethane, 1.522 Å,[37] or larger in the case of the two-carbon bridge in tropinone, where $r(C_7-C_8)$ is as large as 1.556(7) Å. These large values can be rationalized using the AIM theory.[29] The bond length is mainly determined by the amount of electron density shared between the two bonded atoms, which is given by the bond critical point density, ρ_b. These values (Table 4) have to be compared with the value found for the C–C bond in ethane, which is the prototype of a single bond, $\rho_b = 0.242$. The ethane value is much larger than the value found for the C_7-C_8 bond in tropinone, $\rho_b = 0.233$. The distance between the methyl carbon and nitrogen is 1.453(2) Å for MPIP and 1.460(2) Å for tropinone. These values are comparable to the value found for methylamine, 1.461 Å.[38] In Table 7, the angles between the

Table 7. Angles (degrees) between the Heavy Atoms for N-Methylpiperidone, Tropinone, and Piperidine

angle	piperidine		r_e	
	MP2/VTZ[a]	ED[b]	MPIP	tropinone
C(=O)CC	110.16	109.3(17)	110.5(1)	111.0(2)
CC(=O)C	110.43	112.8(15)	114.1(2)	114.7(2)
CCN	109.19	110.5(17)	110.7(1)	107.7(2)
CNC	110.94	109.8(21)	109.9(2)	101.8(2)
CNX[c]	109.40		110.3(1)	111.4(1)
CCCN	57.97	56.9(4)	54.7(2)	58.0(2)
CCNC	63.68	63.6(12)	63.4(2)	75.7(2)
CC(=O)CC	53.78	51.9(18)	47.6(3)	39.4(3)
CCNX[c]	175.54		174.7(2)	165.4(2)

[a]MP2/cc-pVTZ value. [b]Electron diffraction value.[39] [c]X = H for piperidine and X = C(H_3) for MPIP and tropinone.

heavy atoms of MPIP and tropinone are compared to the angles of piperidine, c-$C_5H_{10}NH$, as found with the MP2/cc-pVTZ model and with electron diffraction.[39] The bond angle $\angle(CNC)$ is 109.9(2)° in MPIP, close to the value found in piperidine, 110.9° (MP2/cc-pVTZ value), but much larger than the value found in tropinone, 101.8(2)°. The $\angle(NCC)$ angle of the six-membered ring is 110.7(1)° in MPIP, again close to the value found in piperidine, 109.2°, but once more larger than the value found in tropinone, 107.7(2)°. The dihedral angles of MPIP and piperidine are close but significantly different from those of piperidine.

6. CONCLUSION

This study shows it is possible to determine an accurate equilibrium structure for molecules as large as MPIP (19 atoms) and tropinone (23 atoms) by using the method of mixed estimation, where the semiexperimental equilibrium moments of inertia are fitted together with carefully chosen auxiliary information (predicate values) coming from midlevel ab initio calculations. This method is general and could by applied to still larger molecules. In contrast, using the r_s method of Kraitchman's equations for equilibrium rotational constants of the heavy atoms alone fails to give reliable structural information for the heavy atom framework.

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Notes

The authors declare no competing financial interest.

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