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A COMPUTATIONAL STUDY OF THE STERIC STRAIN OF –N=O GROUPS IN SATURATED NITROSAMINES

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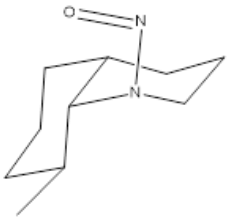
One of the most intensely studied features in the chemistry of nitrosamines is the restricted rotation around the N-N bond and, consequently, the estimation of the energy strain (E_{str}) determined by the NO group. This is rationalized in terms of the interaction between the electron lone-pairs of the amine nitrogen and the π electrons of the –N=O group (nN-πNO* conjugation). Combining the results of DFT calculations on 43 nitrosamines (11 acyclic, 20 mono- and bicyclic and 12 tricyclic) with a multiple linear regression analysis, the paper affords a number of additive increments, which, by appropriate summation, are able to predict with a good accuracy the total energy of the nitroso compound (E) and the energy strain (E_{str}) values of the –N=O group for any acyclic or cyclic saturated nitrosamine.



INTRODUCTION

Owing to the various reaction capabilities of their functional group, nitrosamines became valued intermediates in syntheses of numerous organic compounds, and their chemical, biochemical, photochemical and physical properties are subject of continuously increasing research efforts. One of the most intensely studied features is the restricted rotation about the N—N bond in nitrosamines, rationalized by the interaction between the electron lone-pairs of the amine nitrogen and the electrons of the –N=O group (n_N-π_{NO*} conjugation), which confer a partial double-bond character to these N—N bonds, and a preference for a planar geometry (or very nearly so) to the amine nitrogens.[1,2] Thus, the amine nitrogen possesses chemically distinct alkyl substituents in *syn* and *anti* positions with respect to the in-plane nitroso oxygen. The energy barriers to the restricted N—N rotation have been determined for a considerable number of nitrosamines[3-9] and values ranging from 51 kJ/mol[8,9] up to 100 kJ/mol[8,9] were reported. It has been noted that nitrosamines with the bulkiest alkyl substituents at the amine nitrogen atom show the lowest energy rotational barriers (within 56–84 kJ/mol),[2,8,9] whereas those bearing small substituents, typically exhibit of the highest rotational barriers (95–100 kJ/mol)[2,6,7,9]. The explanation of this effect resides in the modification of the ground state energy due to the substituents. Although the general trend in nitrosamine N—N rotational barriers as a function of substituent size are known, thus far it is not yet obvious, how large alkyl substituents at the amine N atom will affect the height of nitrosamine rotational barriers.[7] In cycloaliphatic nitrosamines with sterically hindered –N=O groups, to relieve steric strain, the cyclic frameworks often assume configurations that cannot appear in the parent secondary amines.[10-14] Thus,

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** Francisc Potmischil was for 40 years professor of Organic Chemistry at the Faculty of Chemistry, University of Bucarest. All this time and after his retirement he was continuously preoccupied by all the aspects of the research in the field of organic chemistry, synthesis, NMR spectroscopy and chemical reactivity. His main contributions were in the field of octahydroacridine compounds. Professor Potmischil passed away in 2021 letting in a final but unpublished form of this paper.

base-catalyzed equilibration of sterically hindered nitrosamines, followed by *N*-denitrosation, can become a valuable synthesis route leading to otherwise inaccessible or hardly accessible stereoisomers of saturated azaheterocycles. Obviously, the stronger the hindrance of the –N=O group, the easier and faster will the nitrosamine undergo this reaction. Possession of a means to estimate and express the degree of steric strain of the –N=O groups could be very helpful in the understanding and prediction of certain physico-chemical behaviour of, *e.g.*, the height of the N—N rotational barriers, or which of the nitrosamines may be expected to undergo a base-catalyzed isomerization and which may not. Furthermore, we suspect that the power of the carcinogenic action of nitrosamines[15,16] could also be connected and correlated with the degree of steric strain of the –N=O group.

METHODS

Due to the increasing interest in the application of rigorous quantum chemistry methods to large systems including biopolymers, drug-protein systems, and to the estimation of the inter- and intramolecular energies, several methods and software were developed to allow for obtaining reliable results at a convenient computational cost. They are based either on performing an energy decomposition analysis[17,18] or on decomposing the whole system in smaller molecular fragments for which rigorous calculations are possible.[19,20]

We present here a three-step computational procedure, allowing to assess the relative values of the steric strain-energies (E_{str}) of the –N=O groups in saturated nitrosamines:

- The DFT calculation of the total energies of the amines and the correspondent nitrosamines.
- Starting with these values, the estimation of the steric strained induced energies of the nitroso group E_{str}-NO.
- A multiple linear regression analysis in respect with characteristic features of the different molecular positions susceptible to exert a sizeable influence upon the magnitude of the steric strain-energy of the –N=O group.

The studied compounds are displayed in Figs. 1–3. The amines are labelled by their corresponding number in the figures, and the nitrosamines labelled with the same number as their parent amines, followed by the letter "**n**".

Throughout this paper, by convention, in the decahydroquinolines series, the nitrosamine conformers with the –N=O oxygen atom oriented "*syn*" with respect to the C-8a carbon are named and noted as *syn*-conformers ("*s*-conformers"), whereas those with the –N=O oxygen atom oriented in the opposite direction (towards C-2) are named and noted as *anti*-conformers ("*a*-conformers"). For further details regarding position numbering and nomenclature of decahydroquinolines, see Refs.[10-12] In the tetradecahydroacridine series, the nitrosamine conformers with the –N=O oxygen atom oriented "*syn*" with respect to the C-4a carbon are named and noted as *syn*-conformers ("*s*-conformers"), whereas those with the –N=O oxygen atom oriented in the opposite direction (towards C-10a) are named and noted as *anti*-conformers ("*a*-conformers"). For further details regarding position numbering and nomenclature of tetradecahydroacridines, see Refs.[13,14]

RESULTS

DFT Calculation of the total energy. The potential energy surfaces (PES) in respect with the dihedral angle (τ) defining the position of the nitroso group were calculated in acetonitrile (ACN) using the Gaussian program [21] and considering the B3LYP functional [22,23] and 6-31G basis set. The solvent was introduced in the frame of the PCM model. The conformations corresponding to the minimum point energy (for τ values around 0 and 180 deg) were fully optimized and their energy further considered.

Estimation of the steric strained induced energies of the nitroso group. This step is based on two assumptions. Firstly, we consider that the energy modification brought about by the nitroso group E(NO) can be obtained by the difference between the DFT-calculated energies of the nitroso compound and that of the parent amine (1).

$$E(NO) \approx E_{nitrosoamine} - E_{parent\ amine} \qquad (1)$$

We may not expect to get the most precise calculation results straightforward from relation (1), since relation (1) obviously is not properly balanced (e. g., amongst others, it does not account for the provenance of the N-H hydrogen in the amine, after the rupture of the N-N bond in the nitroso derivative). However, we may reasonably assume that the rupture of the N-N bond in N-nitroso-dimethylamine implies the same or nearly

the same mechanism. Containing the smallest *N*-alkyl substituent at the amine nitrogen, N-nitroso-dimethylamine possess undoubtedly the less strained **–N=O** group of all saturated nitrosamines, and therefore we use it, by convention, as a zero-point reference in a relative scale of the strain energies (2).

$$E_{str}(NO)_{nitrosamine} = E(NO)_{nitrosamine} - E(NO)_{N\text{-nitroso-dimethylamine}} \quad (2)$$

The results obtained for the amines **1-11** and nitrosamines **1n-11n** are presented in Table 1, and those for the amines **12-35B** and the nitrosamines **12n-35Bn**, are listed in Table 2.

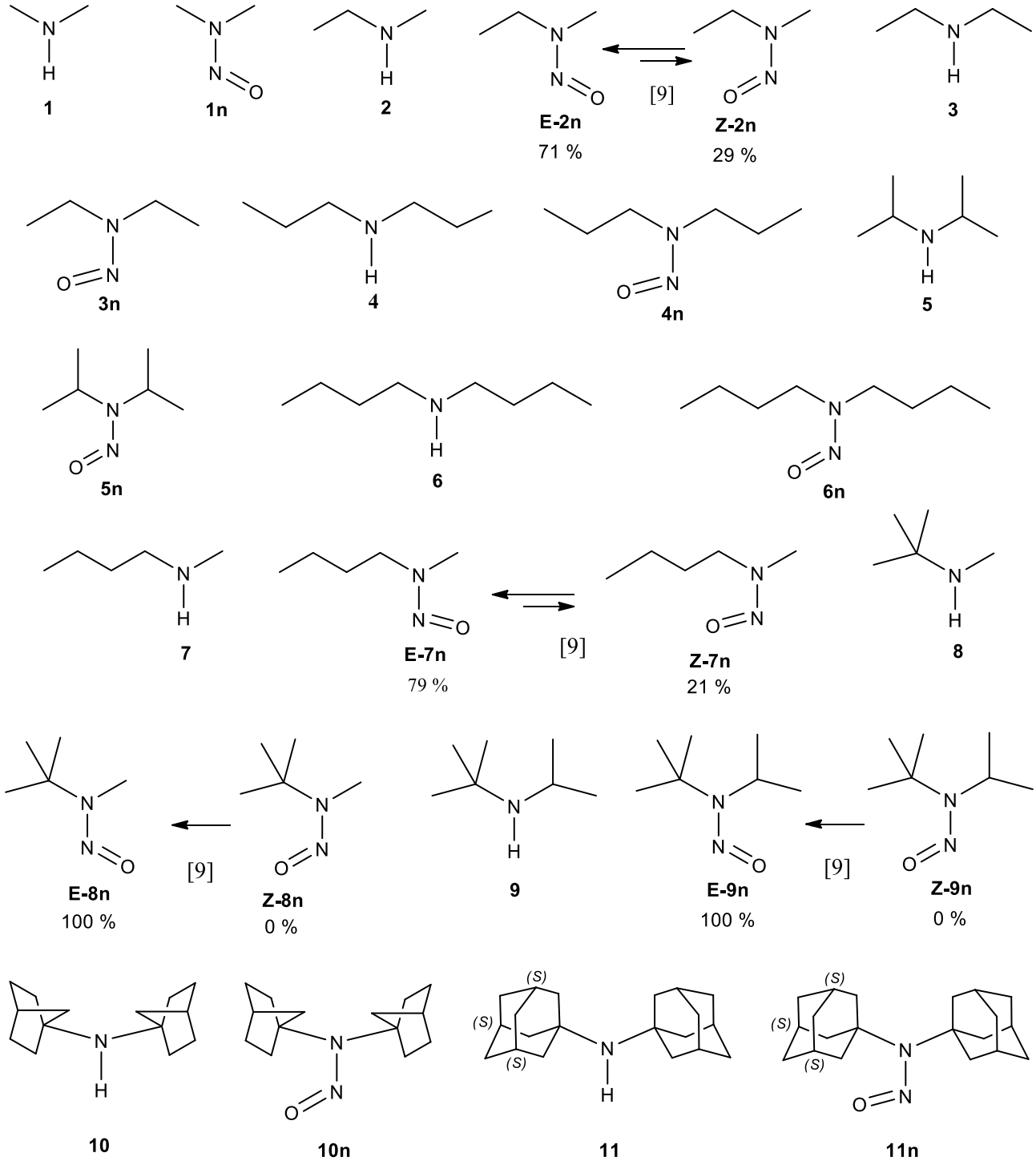

Fig. 1 – Selected nitrosamines and their parent amines, with the amino nitrogen atom member of an acyclic chain.

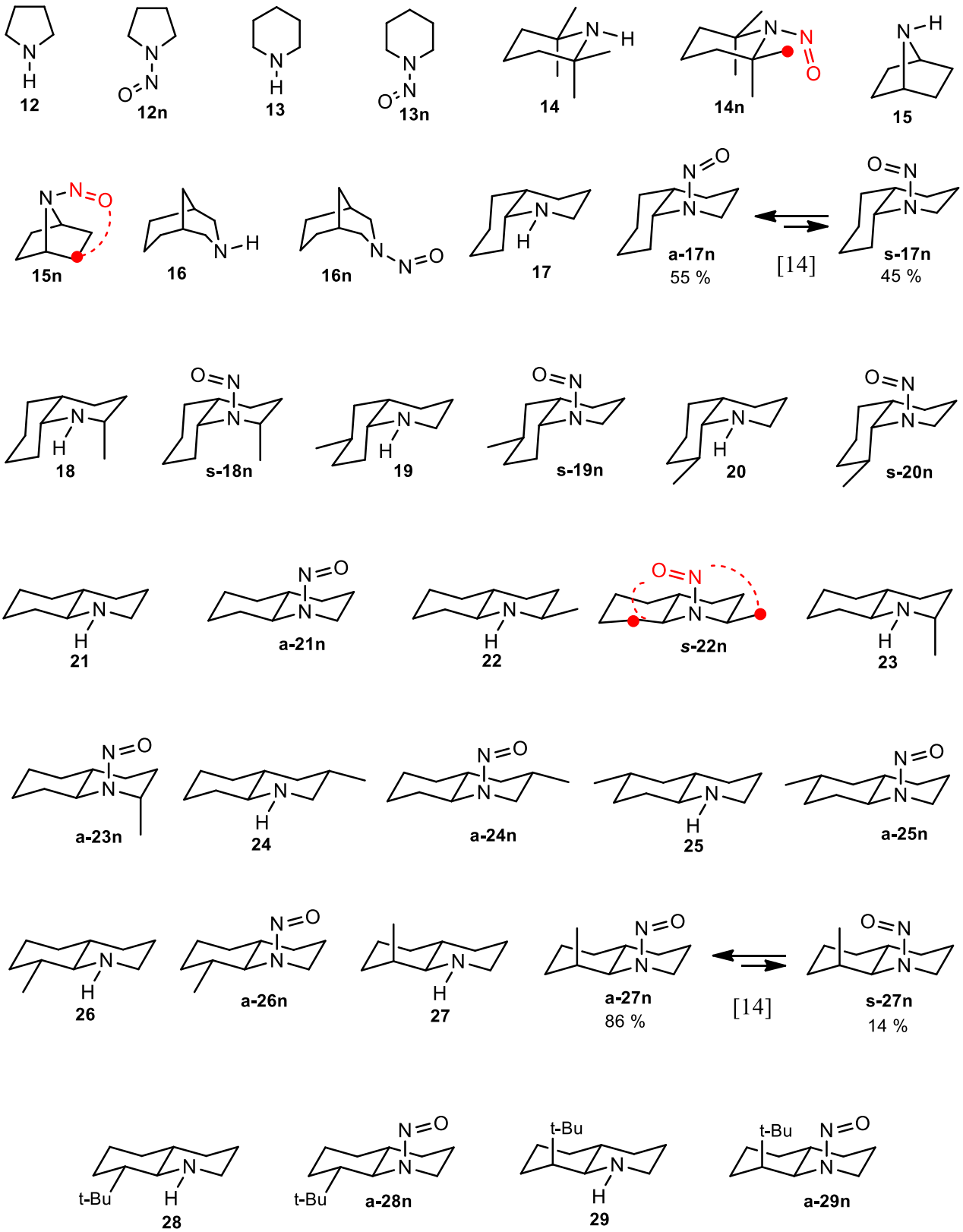

Fig. 2 – Selected nitrosamines and their parent amines, with the amino nitrogen atom member of a mono- or bicyclic ring system.

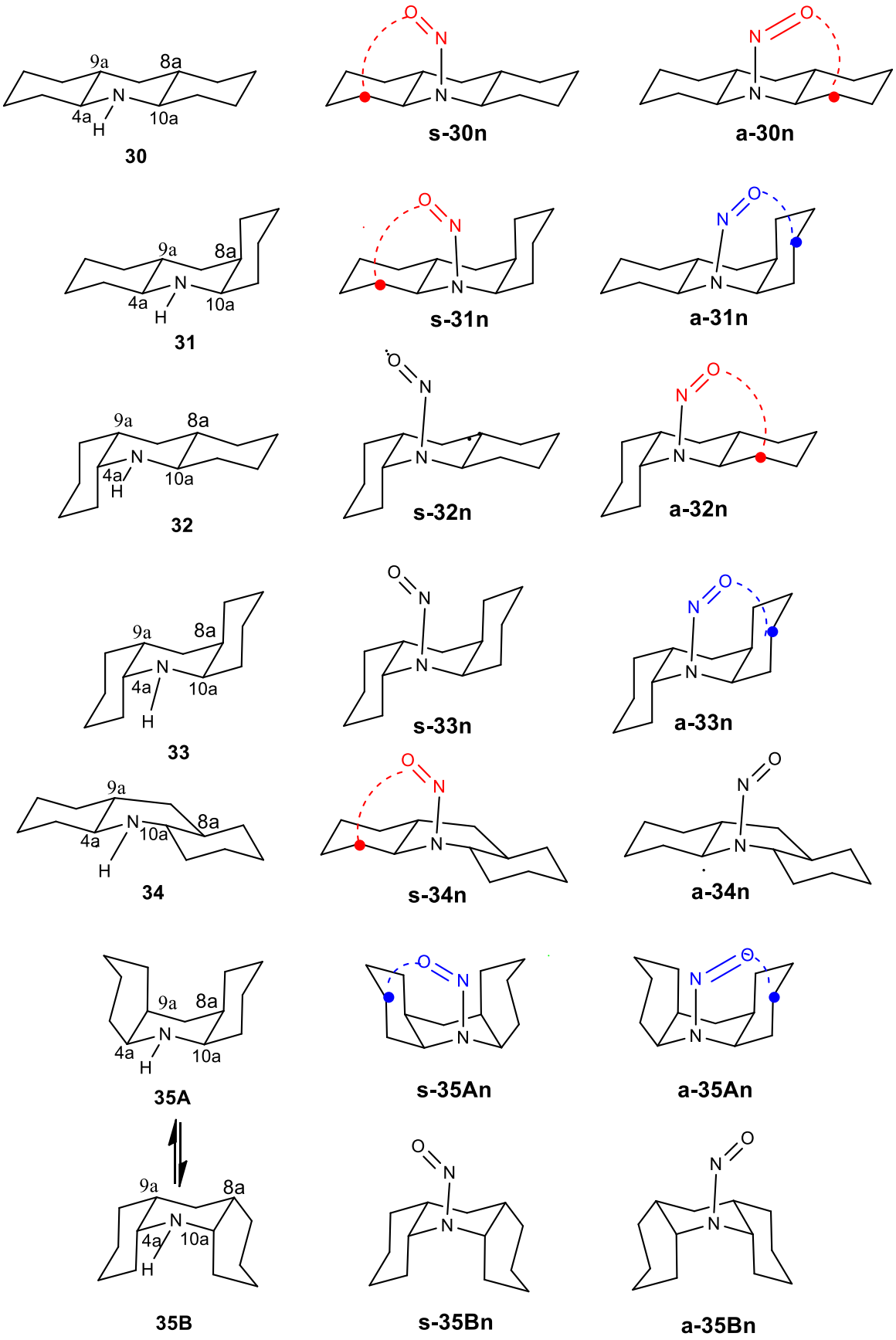

Fig. 3 – Selected nitrosamines and their parent amines, with the amino nitrogen atom member of a tricyclic ring system.

Table 1

Energies (Kcal/mol) of selected acyclic saturated secondary amines (1-11), their nitrosamines (1n-11n), the corresponding N=O groups and the NO steric strain energies.

R,R'NH		R,R'N-NO			
Comp.	E (R,R'NH)	Comp.	E (R,R'N-NO)	E (NO)[a]	E_{str}(NO)[b]
1	**-84788.6778**	**1n**	-165907.9694	-81119.29	0
2	-109458.01735	**E-2n**	-190573.3550	-81115.34	+3.95
		Z-2n	-190573.0252	-81115.01	+4.28
3	-134123.495	**3n**	-215237.064	-81113.56	+5.73
4	-183450.855	**4n**	-264564.465	-81113.61	+5.68
5	-183449.638	**5n**	-264565.912	-81116.27	+3.02
6	-232778.047	**6n**	-313891.755	-81113.71	+5.58
7	-158785.66752	**E-7n**	-239898.6700	-81113.00	+6.29
		Z-7n	-239899.6924	-81114.02	+5.27
8	-158787.34598	**E-8n**	-239900.8689	-81113.52	+5.77
		Z-8n	-239891.3394	-81103.99	+15.3
9	-208116.12252	**E-9n**	-289227.2803	-81111.15	+8.14
10	-377709.1515	**10n**	-458817.1654	-81108.01	+11.28
11	-524200.9621	**11n**	-605302.9618	-81101.99	+17.30

[a] E(NO) ≈ E(R,R'N-NO) – E (R,R'NH)
[b] E_{str}(NO) ≈ E(R,R'N-NO) – E(Me_2N-NO)

Table 2

Energies (Kcal/mol) of selected mono-, bi-, and tricyclic saturated secondary amines (**12**-**35**), their nitrosamines (**12n**-**35n**), the corresponding N=O groups and the NO steric strain energies

Comp	E(R,R'NH)	Comp.	E(R,R'N-NO)	E(NO)[a]	E_{str}(NO)[b]
12	-133362.8050	**12n**	-214479.8090	-81117.0	+2.29
13	-158030.6046	**13n**	-239145.1570	-81114.5	+4.74
14	-256686.5045	**14n**	-337794.2900	-81107.7	+11.51
15	-181927.1859	**15n**	-263035.8830	-81108.6	+10.6
16	-231260.7769	**16n**	-312376.9330	-81116.1	+3.14
17	-255928.6956	***s*-17n**	-337043.9570	-81115.2	+4.03
		***a*-17n**	-337043.9930	-81115.2	+4.00
18	-280591.3063	***s*-18n**	-361707.1560	-81115.8	+3.44
19	-280593.3913	***s*-19n**	-361708.5480	-81115.1	+4.13
20	-280592.7366	***s*-20n**	-361708.0180	-81115.2	+4.01
21	-255932.1951	***a*-21n**	-337044.9330	-81112.7	+6.55
22	-280598.4039	***s*-22n**	-361705.2020	-81106.7	+12.49
23	-280595.9745	***a*-23n**	-361709.0500	-81113.0	+6.22
24	-280596.8377	***a*-24n**	-361706.4560	-81109.6	+9.67
25	-280596.7330	***a*-25n**	-361709.5500	-81112.8	+6.48
26	-280595.6966	***a*-26n**	-361707.7950	-81112.0	+7.20
27	-280594.0339	***s*-27n**	-361700.0300	-81105.9	+13.30
		***a*-27n**	-361705.5770	-81111.5	+7.75
28	-354579.4144	***a*-28n**	-435689.1840	-81109.7	+9.52
29	-354574.2162	***a*-29n**	-435683.0150	-81108.7	+10.49
30	-353833.7314	***s*-30n**	-434937.1120	-81103.5	+15.83
		***a*-30n**	-434938.7490	-81105.0	+14.27
31	-353831.4284	***s*-31n**	-434935.6380	-81104.2	+15.08
		***a*-31n**	-434936.1200	-81105.1	+13.79
32	-353830.3079	***s*-32n**	-434943.3570	-81113.0	+6.24
		***a*-32n**	-434937.3500	-81107.0	+12.25
33	-353827.7130	***s*-33n**	-434940.9550	-81113.2	+6.04
		***a*-33n**	-434943.0600	-81113.5	+5.77
34	-353826.8115	***s*-34n**	-434934.5550	-81107.7	+11.55
		***a*-34n**	-434940.9030	-81114.0	+5.20
35A	-353825.8053	***s*-35An**	-434937.8080	-81112.0	+7.29
35B	-353825.2100	***s*-35Bn**	-434941.3130	-81116.1	+3.19

[a] E (NO) ≈ E (R,R'N-NO) – E (R,R'NH)
[b] E_{str}(NO) ≈ E (R,R'N-NO) – E (Me_2N-NO)

Calculations of increments corresponding to different structural fragments of the molecule susceptible to lead to the steric strain energy of the nitroso group. The values of the steric strain-energies previously obtained, were used in a multiple linear regression analysis together with appropriate structural features of the nitrosamine molecules, susceptible to exert a sizeable influence upon the magnitude of the steric strain-energy of the N=O group. At the beginning we subjected to linear regression analysis all the compounds listed in Tables 1 and 2, and found that, although the results can be quite satisfactory, the procedure is somewhat inconvenient because it requires a relatively large number of independent variables (e.g., in our experiments with a bulk of 34–39 various nitrosamines, 14–16 independent variables were required to obtain an analysis with a high correlation coefficient). We supposed that more precise results could be achieved, using even lesser independent variables, if the regression is performed either with only acyclic or with only cyclic nitrosamines. This fact determined us to elaborate two different settings of increments, one specific for acyclic nitrosamines (Table 3), and the other one specific for nitrosamines with the amino nitrogen member of a mono- or polycyclic ring system (Table 4).

Table 3

Regression analysis of empiric additive parameters of the total energy (E) and of the steric strain-energy (E_{str}) of the –N=O groups in saturated acyclic nitrosamines (kcal/mol)

Total energy (E)				Steric strain-energy (E_{str})			
No. of observations: 15 No. of independent variables: 10 Multiple correlation coefficient: r = 0.98544 Standard deviation in predictions: σ = ± 1.55 Degrees of freedom: df = 4 Constant term: Ct = -81127.77 ± 2.71				No. of observations: 15 No. of independent variables: 10 Multiple correlation coefficient: r = 0.98534 Standard deviation in predictions: σ = ± 1.6 Degrees of freedom: df = 4 Constant term: Ct = -8.52 ± 2.71			
Variables and coefficients[a]:				Variables and coefficients[a]:			
Symbols & no. of occurrences		Values	Student *t* ratio	Symbols & no. of occurrences		Values	Student *t* ratio
anti-αp	(4)[b]	10.21 ± 2.38	4.29	anti-αp	(4)[b]	10.25 ± 2.39	4.29
anti-αs	(5)	8.01 ± 2.33	3.43	anti-αs	(5)	8.04 ± 2.33	3.45
syn-αs	(5)	-2.55 ± 1.19	2.14	syn-αs	(5)	-2.55 ± 1.19	2.14
syn-αt	(2)	-6.50 ± 1.57	4.14	syn-αt	(2)	-6.53 ± 1.58	4.13
anti-αq	(4)	0.68 ± 1.57	0.43	anti-αq	(4)	0.72 ± 1.58	0.45
βp	(24)	4.50 ± 0.55	8.18	βp	(24)	4.50 ± 0.55	8.18
βs	(18)	3.18 ± 0.48	6.62	βs	(18)	3.18 ± 0.48	6.62
γp	(2)	1.17 ± 1.07	1.09	γp	(2)	1.17 ± 1.07	1.09
γt	(6)	1.01 ± 0.36	2.80	γt	(6)	1.00 ± 0.36	2.78
δp	(4)	1.82 ± 0.98	1.85	δp	(4)	1.83 ± 0.98	1.86

[a] "*anti*-αp" applies when a primary carbon atom is present in an *alpha* position relative to the amino N atom, and oriented *anti* relative to the nitroso oxygen atom (*e.g.*, as in **1n**, **Z-2n, Z-7n, Z-8n**); "*anti*-αs" applies for a secondary carbon atom present in an *alpha* position relative to the amino N atom and oriented *anti* relative to the nitroso oxygen atom (*e.g.*, as in **E-2n**, **3n**, 4**n, 6n, E-7n**); "*syn*-αs" is for a secondary carbon atom present in an *alpha* position to the amino N atom and oriented *syn* relative to the oxygen atom (*e.g.*, as in **Z-2n**, **3n**, 4**n, 6n, Z-7n**); "*syn*-αt" is for a tertiary carbon atom in an *alpha* position to the amino N atom and oriented *syn* relative to the oxygen atom (*e.g.*, as in **5n**, **E-9n**); "*anti*-αq" is for a quaternary carbon atom in an *alpha* position to the amino N atom and oriented *anti* relative to the oxygen atom (*e.g.*, as in **E-8n**, **E-9n**, **10n**, **11n**); "βp" is for a primary carbon atom present in a *beta* position to the amino N atom (*e.g.*, as in: **E-2n**, **Z-2n**, **3n**, **5n**, **E-8n**, **Z-8n**,**E-9n, Z-9n**); "βs" is for a secondary carbon atom present in a *beta* position relative to the amino N atom (*e.g.*, as in **4n**, **6n**, **E-7n**, **Z-7n**, **10n, 11n**); "γp",is for a primary carbon atom present in a *gamma* position relative to the amino N atom (*e.g.*, as in 4**n**); "γt is for a tertiary carbon atom present in a *gamma* position relative to the amino N atom (*e.g.*, as in **11n**); "δp" is for a primary carbon atom present in a *delta* position relative to the amino N atom (as, *e.g.*, in **6n**, **E**-7**n, Z-7n**).

[b] The figures in parentheses show the number of occurrences of the parameter.

Table 4

Regression analysis of empiric additive parameters of the total energy (E_{tot}) and the steric strain-energy (E_{str}) of the –N=O groups in saturated cyclic nitrosamines (kcal/mol)

Total energy (E_{tot})				Steric strain-energy (E_{str})			
No. of observations: 32 No. of independent variables: 13 Multiple correlation coefficient: r = 0.9741 Standard deviation of the fit: σ = ± 1.18 Degrees of freedom: df = 18 Constant term: Ct = -81140.55 ± 7.63 Variables and coefficients[a]:				No. of observations: 32 No. of independent variables: 13 Multiple correlation coefficient: r = 0.9767 Standard deviation of the fit: σ = ± 1.12 Degrees of freedom: df = 18 Constant term: Ct = -21.33 ± 7.25 Variables and coefficients[a]:			
Symbols & no. of occurrences		Values	Student *t* ratio	Symbols & no. of occurrences		Values	Student *t* ratio
Sr	(21) [b]	-3.39 ± 0.61	5.55	Sr	(21) [b]	-3.40 ± 0.58	5.86
αs	(18)	6.89 ± 1.83	3.71	αs	(18)	6.91 ± 1.74	3.97
βp	(7)	4.88 ± 1.14	4.28	βp	(7)	4.90 ± 1.08	4.53
βs	(57)	6.74 ± 2.02	3.33	βs	(57)	6.76 ± 1.92	3.52
βt	(48)	8.04 ± 1.99	4.04	βt	(48)	8.06 ± 1.89	4.26
γs	(109)	-1.77 ± 0.68	2.60	γs	(109)	-1.77 ± 0.64	2.76
cis	(5)	5.28 ± 1.72	3.07	cis	(5)	5.24 ± 1.64	3.19
trs	(10)	8.77 ± 1.70	5.16	trs	(10)	8.74 ± 1.62	5.39
C,C	(4)	6.25 ± 3.37	1.85	C,C	(4)	6.19 ± 3.20	1.93
T,T	(4)	10.25 ± 3.21	3.19	T,T	(4)	10.26 ± 3.04	3.37
C,T	(4)	10.97 ± 3.24	3.38	C,T	(4)	11.08 ± 3.08	3.59
gNO	(8)	4.99 ± 0.85	5.87	gNO	(8)	4.87 ± 0.81	6.01
1,3-di	(5)	2.23 ± 0.84	2.65	1,3-di	(5)	2.12 ± 0.80	2.65

[a] "Sr", *i.e.* "strained ring", applies when the amino N atom of the nitrosamine is member of a strained ring, *e.g.*, as in **12n**, **14n**, **15n**, **16n**, **s-22n**, **s-31n**, **a-31n**, **a-33n**, **s-35n**; the variables "αs", "βp", "βs", "βt", "γs", have the same significance as described for their analogues in Table 3; "*cis"* applies when in a bicyclic nitrosamine with fused rings, the rings are fused by a *cis* junction, *e.g.*, as in **a-17n**, ***s*-17n – *s*-20n** (Fig. 2); "*trs"* applies when in a bicyclic nitrosamine with fused rings, the rings are fused by a *trans*-junction, *e.*g., as in ***a*-21n** – ***a*-29n**, ***s*-22n** (see Fig. 2); "C,C" applies when in a tricyclic nitrosamine the rings are fused by two *cis*-junctions, e.g., as in ***s*-33n**, ***a*-33n**, ***s*-35Bn**, ***s*-35An** (Fig. 3); "C,T" applies when in a tricyclic nitrosamine the rings are fused by one *cis*- and one *trans*-junction, *e.g.*, as in ***s*-31n**, ***a*-31n**, ***s*-32n**, ***a*-32n** (Fig.3); "gNO" applies when the –N=O group is involved in a *gauche*-type steric interaction with a carbon of the nitrosamine framework, e.g., see the red-marked molecular fragments in the formulas of **14n**, **15n**, ***s*-22n** (in Fig. 2) and of ***s*-30n, *a*-30n**, ***s*-31n**, ***a*-32n** and ***s*-34n** (in Fig. 3); "1,3-di" applies when the –N=O group undergoes a 1,3-diaxial-type steric interaction with a carbon of the nitrosamine framework, *e.g.*, as in the blue marked molecular fragments in the formulas ***a*-31n**, ***a*-33n**, in ***a*-35An** (Fig. 3).

[b] The figures in parentheses show the number of occurrences of the parameter.

The independent variables for acyclic nitrosamines. The molecular models of the fifteen acyclic nitrosamines listed in Table 1 were examined to identify the structural features susceptible to exert a sizeable influence upon the magnitude of the steric strain-energy of a molecule. It resulted a list of 14 parameters, noted with following symbols: "*anti*-αp", "*syn*-αp", "*anti*-αs", "*syn*-αs", "*anti*-αt", "*syn*-αt", "*anti*-αq", "*syn*-αq", "βp", "βs", "γp", "γs", "γt" and "δp" (for the significance of these symbols, see the footnotes to Tables 3 and 4), and which should had become the independent variables in the intended multiple linear regression analysis. However, in the course of the regression operation, four parameters ("*syn*-αp", "*anti*-αt ", "*syn*-αq" and "γs") were ruled out (equalized to zero) by the software we used (the LINEST function in Microsoft Office Excel, 2007), and a new linear regression analysis was performed with the remained 10 independent variables. The values of these independent variables are given in the left-handed half of Table 3, along with the appropriate statistical summary. A separate regression analysis has been performed with the 15 values of the steric strain-energies and the same 10 independent variables as in the previous case. The results are given in the right-handed half of Table 3.

As can be seen, there is an excellent match between the coefficients of the 10 independent variables of the total energy and those of the 10 independent variables of the steric strain energy, which show practically identical values. So, the entire difference between the magnitude of the total energy and that of the steric strain-energy of a –N=O group is simply reflected by the difference between the values of the constant terms.

The 10 independent variables and the constant terms given in Table 3 allow to approach any kind of acyclic saturated nitrosamine. The values of energies computed by summation of the appropriate increments are very close to the values obtained by the DFT-calculations (which we named the "first computation procedure"). The correlation coefficients for the values calculated by the additive increments versus the DFT-calculated values are r=0.9854 for the total energy, and r=0.9853 for the steric strain-energy, in the whole series of the 15 nitrosamines listed in Table 1.

The independent variables for cyclic nitrosamines. The molecular models of all the 32 cyclic nitrosamines were examined for structural features able to become independent variables in the multiple linear regression analysis. From the obtained data, we succeeded to compile a set of 13 parameters which, used in the multiple linear regression analysis, provided a quite satisfactory high correlation coefficient. Eight of them (noted with the symbols "Sr", "*cis*", "*trs*", "C,C", "T,T", "C,T", "gNO", and "1,3-di") are concerned with the cyclic moiety of the nitrosamine molecules, whereas the other five ("αs", "βp", "βs", "βt" , and "γs") are connected with the acyclic moiety, too. For the significance of the used symbols, see the footnotes to Table 4. A multiple linear regression analysis was performed considering the energies of the -N=O groups and the 13 independent variables. The values of the coefficients for the independent variables are given in the left-handed half of Table 4, along with the appropriate statistical summary. A second regression analysis has been performed considering the 32 NO steric strain-energies and the same 13 independent variables as in the previous case. The obtained results are given in the right-handed half of Table 4, along with the appropriate statistical summary. The 13 independent variables and the constant terms given in Table 4 allow to approach any kind of cyclic saturated nitrosamine. The values of energies computed by summation of the appropriate increments are very close to the values obtained by the DFT-calculations. The correlation coefficients for the values calculated by the additive increments versus the DFT-calculated values are r = 0.9741 for the total energy, and r = 0.9767 for the steric strain-energy, in the whole series of the 32 nitrosamines listed in Table 2.

CONCLUSIONS

The additive increments resulted from the multiple linear regression analyses can approach any aliphatic or cycloaliphatic nitrosamine, require no DFT calculations, and afford results of the same accuracy as DFT calculations can do (correlation coefficients of r = 0.9741 – 0.9853).

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