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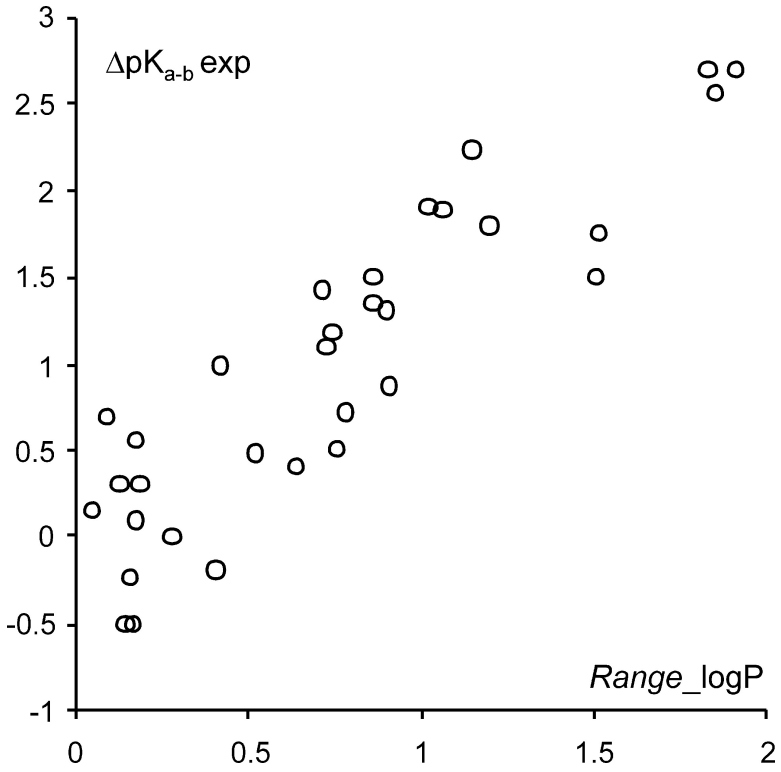

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Range and Sensitivity as Descriptors of Molecular Property Spaces in Dynamic QSAR Analyses

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In this paper, we report the first study aimed at correlating pharmacological properties with molecular parameters derived from the physicochemical property space of bioactive molecules. A dataset of 36 ligands of the α_{1a}-, α_{1b}-, and α_{1d}-adrenoceptors as published by Bremner et al. (*Bioorg. Med. Chem.* **2000**, *8*, 201−214) was used. One thousand conformers were generated for each ligand by Monte Carlo conformational analysis, and four 3D-dependent physicochemical properties were computed for each conformer of each ligand, namely virtual lipophilicity (log *P*), dipole moment, polar surface area (PSA), and solvent-accessible surface area (SAS). Thus, a space of four physicochemical properties was obtained for each ligand. These spaces were assessed by two descriptors, namely their range and their sensitivity (i.e., the variation amplitude of a given physicochemical property for a given variation in molecular geometric properties). Little or no correlation was found to exist between the physicochemical properties and their range or sensitivity, indicating that the latter descriptors do not encode the same molecular information as the former properties. As expected, neither the range nor the sensitivity of any of the four physicochemical properties correlated with receptor affinities. In contrast, range and sensitivity showed promising correlations with ΔpK_{a-b} (i.e., the α_{1a}/α_{1b} selectivity) for the complete dataset. The correlations were lower for ΔpK_{a-d} (i.e., the α_{1a}/α_{1d} selectivity), whereas there was no correlation at all with ΔpK_{b-d}. These results are consistent with the results of Bremner et al., which indicate that the α_{1a}-AR ligands bind in an extended geometry, whereas the α_{1b}-AR and α_{1d}-AR ligands assume more folded conformations. Since the property space descriptors presented here take structural variability into account, their correlation with ΔpK_{a-b} and ΔpK_{a-d} indicates that these selectivities are indeed driven by differences in conformational behavior and hence in property spaces.

1. Introduction

The growing computational power available to researchers is proving an invaluable tool to investigate the dynamic behavior of molecular systems,[1] showing that a molecule cannot be considered as a static object but as an animated subject whose conformational changes may significantly affect the profile of any of its computable property.[2,3]

Conformational hypersurfaces are a well-known metaphor to express the conformational behavior of flexible molecules, while the ensemble of all conformers of a given compound is often taken as defining a conformational space.[4,5] In a similar manner, many molecular properties can be shown to vary with the 3D-geometry of the molecule. Some of these properties will show very limited variation with changes in 3D-geometry (e.g. molecular volume), whereas others can vary quite broadly as conformation fluctuates. Interestingly, many physicochemical properties that express *recognition forces* and are thus of great pharmacological and biological relevance are strongly dependent on 3D-geometry. Such properties and recognition forces include the dipole moment (which encodes the distribution of electrostatic forces), virtual log *P* (i.e., the computed lipophilicity of a single conformer, which encodes hydrophobicity, H-bonding capacity, and polarizability), and the polar surface area (PSA, which encodes polarity and H-bonding capacity).[6]

For each of the above properties, a conformer-specific value can be computed for each 3D-geometry in the conformational space (i.e., for each possible and realistic conformer), thus defining a range of allowed values for each computable property. This range represents the corresponding property space, itself interdependent with other molecular properties and constrained by the environment.

Until now, the concept of property space has been understood in an essentially different manner, being applied to a large series of compounds, with a single value being used to characterize each considered property of each compound. Applications of this approach include the evaluation of chemical libraries obtained by combinatorial chemistry or the estimation of the optimal value a given molecular property should exhibit for biological relevance (e.g., indices of drug-likeness).[7−12] In contrast to the above, the concept of property space is just beginning to be used to gain a comprehensive understanding of the dynamic behavior of a single compound. In this dynamic vision, a molecular property can be described either (a) by an average value or (b) by descriptors defining its property space.

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The average value of a property, and especially a weighted average, contains more information than a conformer-specific value (even if of the lowest energy conformer or of the hypothetical bioactive conformer). However, this average value does not yield information on the property space itself. To this end, one should use descriptors specifying the property range and distribution in relation to conformational changes and other property profiles.

A property space can be defined using two classes of descriptors. The first class includes descriptors quantifying the variability (spread) of values, e.g., statistical functions such as variance, standard deviation, range, and average difference. The range is probably the most intuitive descriptor in this context. The second class of descriptors relates the dynamic behavior of a given property with other geometric or physicochemical properties. Such correlations can reveal if and how two molecular properties change in a coherent manner.

In the present study, attention is focused on the meaning and applications of relationships between physicochemical properties on one hand and geometric descriptors on the other hand. These relationships describe the ability of a physicochemical property to fluctuate when the 3D-geometry fluctuates. These relationships also lead us to the concept of *molecular sensitivity*, since there will be *sensitive* molecules, whose property values are markedly influenced by small geometric changes, and *insensitive* molecules, whose properties change little even during major geometric fluctuations. It is our postulate that molecular sensitivity can affect biological properties, as the latter are dynamic properties in themselves, whose emergence will depend on the ability of a molecule to fit into and interact with an active site.

The objective of this study is to verify whether range and sensitivity can be successfully used as descriptors of the space of relevant physicochemical properties and correlated with bioactivity. To this end, we have chosen a heterogeneous set of ligands of α_1-adrenoceptors (α_1-ARs) characterized by their large differences in binding affinities and receptor subtype selectivities. [13] Such compounds are also of interest for other reasons, namely their major role in the treatment of lower urinary tract symptoms,[14] the many data accumulated on their pharmacological profile,[15] and a number of published QSAR and molecular modeling studies (pharmacophore mapping) offering predictions of ligand affinity and selectivity.[13,16−21] Furthermore, several studies have reported that α_1-AR affinities can be successfully correlated with electronic and hydrophobic descriptors. Thus, the α_1-AR affinities of a homogeneous set of 32 arylpiperazine derivatives was shown to correlate with the π (lipophilic) and F (electronic) values of their substituents in the aryl moiety, underlining the key role of hydrophobic interactions and $\pi-\pi$ stacking in complex stabilization.[22] Another study has correlated the selectivity of α_1-AR ligands using quantum chemical indices and shape parameters, suggesting a crucial role for electrostatic interactions and shape fitting in selective binding.[23]

2. The Concept of Molecular Sensitivity

As described in the Introduction, the dynamic nature of a molecular property can be seen as its ability to span a possible range, simultaneously influencing the behavior of related properties. This implies that a property can be fully understood only by monitoring its variations as a function of variations in other properties. From a mathematical point of view, such an analysis may be carried out by considering the regression coefficients obtained by correlating pairs of properties. A good coefficient would suggest that the two properties change coherently, while a poor coefficient would reveal a lack of interdependence. However, using regression coefficients as independent variables may lead to mathematical dead-ends. We thus looked for a descriptor of property space that would be both informative and simple to use. The descriptor we propose and evaluate here is the *sensitivity*, namely the amplitude of variation of a given physicochemical property for a given variation in molecular geometry.

If we consider a physicochemical property X for which conformer-specific values can be computed (e.g., dipole moment, polar surface area, virtual log P), its pairwise sensitivity value ($\text{PairwiseSensitivity}_{X,G_{ij}}$) for two given conformers (i, j) and a given geometric descriptor G (e.g., an intramolecular distance, a torsion angle) can be defined as the ratio between the absolute value of the difference of X and the corresponding absolute value of the difference in G (eq 1):

$$\text{PairwiseSensitivity}_{X,G_{ij}} = \frac{|X_i - X_j|}{|G_i - G_j|} \qquad (1)$$

The *global sensitivity* ($\text{Sensitivity}_{X,G}$, eq 2) will be the average of the pairwise sensitivities computed for all possible pairs of N conformers (i.e., for $N(N-1)$ pairs):

$$\text{Sensitivity}_{X,G} = \frac{\sum \text{PairwiseSensitivity}_{X,G_{ij}}}{N(N-1)} \qquad (2)$$

For any given physicochemical property of a molecule, one can calculate several sensitivity values according to the geometric descriptors being used. For each compound, such an analysis can reveal the geometrical descriptors that play a key role in determining the dynamic profile of a given physicochemical property. But when investigating a set of heterogeneous compounds, it becomes impossible to take specific geometric descriptors into account. A geometric descriptor applicable to all molecules must therefore be selected. In the present study, we used the RMSD value (root-mean-square deviation) of atomic coordinates, a well-known and universally applicable parameter that aptly describes geometric differences between pairs of conformers as a function of their atomic positions. Equation 2 thus becomes

$$\text{Sensitivity}_{X_{ij}} = \frac{X_i - X_j}{\text{RMSD}_{ij}} \qquad (3)$$

where RMSD_{ij} is the root-mean-square deviation of atomic coordinates for the conformers i and j. Equation 3 allows one to define a single sensitivity value for a given physicochemical property X, and the global sensitivity for X can be computed by averaging molecular sensitivity values for all possible pairs of conformers.

Table 1. Biological Data for the Compounds under Consideration, Namely Affinities for α_{1A}-, α_{1b}-, and α_{1d}-Adrenoceptors (expressed as pK_{1A}, pK_{1b}, and pK_{1d}, Respectively) and Selectivities (expressed as ΔpK_{a-b}, ΔpK_{a-d}, and ΔpK_{b-d})

no.	compd	pK_{1a}	pK_{1b}	pK_{1d}	ΔpK_{a-b}	ΔpK_{a-d}	ΔpK_{b-d}
1	prazosin	9.70	9.60	9.49	0.10	0.20	0.11
2	cyclazosin	7.92	9.89	8.49	−1.97	−0.57	1.39
3	abanoquil	10.40	10.10	10.40	0.30	0.00	−0.30
4	REC-15/2615	8.72	9.52	8.59	−0.80	0.14	0.94
5	alfuzosin	8.00	8.00	8.50	0.00	−0.50	−0.50
6	doxazosin	8.50	9.00	8.40	−0.50	0.10	0.60
7	terazosin	8.20	8.70	8.60	−0.50	−0.40	0.10
8	bunazosin	9.30	9.00	9.00	0.30	0.30	0.00
9	niguldipine	9.82	7.26	7.00	2.56	2.82	0.26
10	SNAP-5089	9.64	7.89	7.18	1.75	2.46	0.71
11	SNAP-5399	9.19	6.49	6.40	2.70	2.79	0.09
12	SNAP-5150	8.72	6.48	6.40	2.24	2.32	0.08
13	WB-4101	9.80	8.60	9.60	1.19	0.19	−1.00
14	phentolamine	8.80	8.10	8.10	0.69	0.69	0.00
15	5-Me-uropidil	9.20	7.40	8.00	1.80	1.20	−0.60
16	KMD-3213	10.40	7.70	8.70	2.70	1.70	−1.00
17	AH-11110A	5.60	7.12	5.56	−1.52	0.04	1.56
18	BMY-7378	6.60	6.20	8.20	0.40	−1.60	−2.00
19	SKF-104856	7.36	7.20	8.28	0.16	−0.93	−1.08
20	discretamine	6.21	6.44	7.60	−0.23	−1.39	−1.16
21	corynanthine	6.85	6.29	6.60	0.56	0.25	−0.31
22	benzoxathian	9.70	8.40	9.40	1.30	0.30	−1.00
23	spiperone	8.10	9.30	7.89	−1.20	0.22	1.41
24	(+)-YM-617	8.37	7.02	7.66	1.35	0.71	−0.64
25	SNAP-8719	6.53	6.72	8.80	−0.19	−2.26	−2.08
26	indoramin	8.40	7.40	6.80	1.00	1.60	0.60
27	RS-17053	9.22	7.80	7.80	1.43	1.43	0.00
28	A-131701	9.66	8.16	9.01	1.50	0.64	−0.86
29	NAN-190	8.70	7.82	9.10	0.88	−0.40	−1.27
30	WAY-100635	7.24	6.73	7.20	0.51	0.04	−0.47
31	RS-100,975	9.00	7.10	7.00	1.90	2.00	0.10
32	REC-15/2739	9.00	7.49	8.60	1.51	0.40	−1.11
33	SNAP-1069	7.80	6.70	6.10	1.10	1.69	0.60
34	SL-89.0591	8.60	7.89	8.60	0.72	0.00	−0.72
35	JHT-601	9.40	8.92	8.92	0.48	0.48	0.00
36	GG-818	9.70	7.80	7.60	1.90	2.10	0.19

Of the three equations above, eq 3 is the only one used in this study, i.e., a sensitivity based on the RMSD descriptor.

3. Results

3.1. Correlations between Physicochemical Properties and between Property Space Descriptors. Table 1 reports the biological data of the compounds under consideration, namely their affinities for the α_{1a}-, α_{1b}-, and α_{1d}-adrenoceptors (expressed as pK_{1a}, pK_{1b}, and pK_{1d}, respectively), and selectivity ratios (expressed as ΔpK_{a-b}, ΔpK_{a-d}, and ΔpK_{b-d}). Tables S1 and S2 (see Supporting Information) report the property averages and the descriptors of property space (range and sensitivity) of the four monitored properties (virtual log *P*, dipole moment, PSA and SAS). Table S1 also includes molecular flexibility indices, namely RMSD averages and the number of conformational clusters produced during the conformational analyses.

The first step in correlating descriptors was a search for significant correlations (a) between average physicochemical properties in Table S1, (b) between descriptors of property space in Table S2 (as reported in Table 2A), and (c) between average physicochemical properties and property space descriptors (Table 2B). The first two types of correlations can reveal whether the properties monitored are independent or may contain comparable information. The correlations of the third type are useful to decide whether the property space descriptors are innovative or are closely related to known descriptors.

The average property values (Table S1) do not show significant correlations, with r^2 values ranging from 0.01 to 0.37 for the pair SAS−PSA (data not shown). Table 2A, which presents the correlations among property space descriptors, can be divided into three meaningful quadrants: sensitivity−sensitivity (upper left), range−range (lower right), and range−sensitivity (lower left). The correlations among property ranges (lower right quadrant) reveal the highest r^2 values. Specifically, the dipole moment does not yield any significant correlation, while log *P* descriptors are related to PSA descriptors in agreement with the fact that log *P* and PSA both encode polarity and H-bonding capacity.

The lower left quadrant shows the relations among sensitivity values and property ranges. It is interesting to note that the range and sensitivity of a given physicochemical property (bold diagonal values) are not correlated. In other words, these two parameters describe different features of a property space. The correlations among sensitivity values in the upper left quadrant confirm a noteworthy correlation between descriptors of the log *P* and PSA spaces. It suggests that parameters of different property spaces cannot be used in the same relationships, while range and sensitivity of a single property space can be simultaneously used in a two-variable correlation as they encode unrelated information.

Table 2B reports correlations between average physicochemical properties and property space descriptors. None of the sensitivity values is related to a property average, whereas the property ranges show some modest correlations ($r^2 < 0.5$), for example between average log *P* and range_logP. This lack of meaningful correlations implies that sensitivity and range contain information not encoded in the physicochemical properties themselves, suggesting that they might contain information on the dynamic behavior of these physicochemical properties.

3.2. Correlations between Affinities and Property Spaces. A search for correlations between affinity data (pK_i) and descriptors of property spaces (range and sensitivity) failed to uncover any significant correlation (all *r* value < 0.5). This result is expected and understandable, since affinity depends on the ligand's ability to assume well-defined property values, a type of information not encoded in range and sensitivity.

3.3. Correlations between Selectivities and Property Spaces. Table 3 shows that significant correlations (expressed as *r* values) exist between some receptor selectivities and some property space descriptors. Indeed, ΔpK_{a-b} and ΔpK_{a-d} yield significant correlations ($r > 0.7$) with log *P*, PSA, and SAS ranges, whereas ΔpK_{b-d} yields no correlation whatsoever ($r < 0.1$).

A clear trend is also apparent among the physicochemical properties, since the lipophilicity range yields the best correlations for both ΔpK_{a-b} and ΔpK_{a-d}, while the dipole space yields the lowest. In other words, the capacity of the property spaces to correlate with ΔpK_{a-b} and ΔpK_{a-d} shows the following ranking: virtual log *P* > SAS > PSA > dipole moment. The correlations

Table 2. Search for Correlations (r^2 Values) between Decriptors

A. Between Descriptors of Property Space

descriptors of property space		sensitivity				range		
		log *P*	dipole moment	PSA	SAS	log *P*	dipole moment	PSA
sensitivity	dipole moment	0.05						
	PSA	0.36	0.02					
	SAS	0.01	0.01	0.05				
range	log *P*	**0.16**	0.06	0.07	0.17			
	dipole moment	0.08	**0.08**	0.11	0.12	0.36		
	PSA	0.13	0.12	**0.19**	0.05	0.66	0.36	
	SAS	0.06	0.10	0.11	**0.13**	0.57	0.21	0.63

B. Between Average Physicochemical Properties and Property Space Descriptors

descriptors of property space		average values of physicochemical properties			
		log *P*	dipole moment	PSA	SAS
sensitivity	log *P*	0.01	0.11	0.02	0.01
	dipole moment	0.01	0.02	0.02	0.01
	PSA	0.01	0.12	0.02	0.16
	SAS	0.01	0.02	0.03	0.02
range	log *P*	0.49	0.28	0.13	0.07
	dipole moment	0.27	0.04	0.17	0.12
	PSA	0.46	0.17	0.10	0.22
	SAS	0.47	0.26	0.12	0.09

Table 3. Correlations (expressed as *r* values) between α1-Adrenoceptor Selectivities (Δp*K*s) and Property Space Descriptors

property	descriptor	ΔpK_{a-b}	ΔpK_{a-d}	ΔpK_{b-d}
log *P*	range	0.81	0.68	0.00
	sensitivity	0.42	0.29	0.02
dipole moment	range	0.52	0.54	0.01
	sensitivity	0.13	0.04	0.01
PSA	range	0.66	0.67	0.01
	sensitivity	0.12	0.15	0.01
SAS	range	0.71	0.66	0.00
	sensitivity	0.21	0.09	0.00

obtained with the range and sensitivity show the same rank order, with ranges giving better regression coefficients.

Interestingly, all significant correlation coefficients are positive, implying that α_1-ARs selectivities are mainly proportional with variations in physicochemical properties, as expressed mainly by range.

The above observations may imply that the ability to selectively interact with the α_{1a}-AR is encoded in property space descriptors and especially in the lipophilicity space, whereas selective interaction with the α_{1b}-AR is only partially encoded in property space descriptors and α_{1d}-AR selectivity not at all.

To expand and clarify this interpretation, we take an axis symbolizing ligand selectivity and divide it into two regions (Figure 1), namely strong selectivity (with $|\Delta pK| > 1$) and modest selectivity (with $0 < |\Delta pK| < 1$). Both strongly and modestly selective α_{1a}-AR ligands correlate with their property space descriptors (mainly the range), whereas only modestly selective α_{1b}-AR ligands do so, and no α_{1d}-AR selective ligand does. In other words, Table 3 suggests that property space descriptors are not able to predict a strong selectivity for the α_{1b}-AR, nor any α_{1d}-AR selectivity. The question is left unanswered whether this lack of correlation for the α_{1b}-AR and α_{1d}-AR lies in the physicochemical properties or in the descriptors of property space. Future investigations using a broader set of 3D-dependent properties could solve this problem.

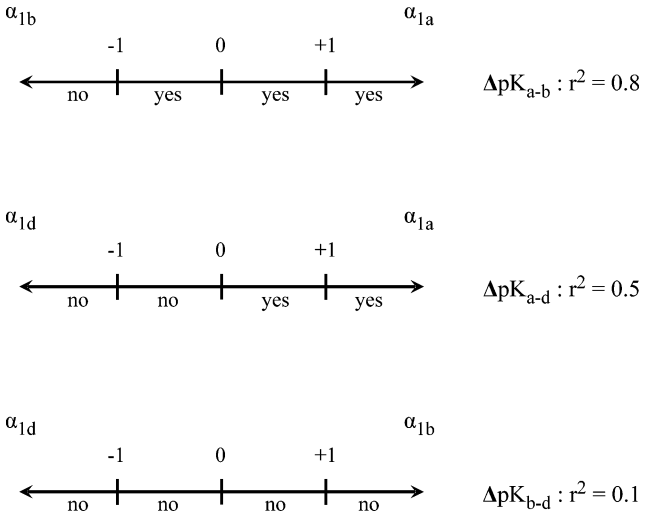

Figure 1. The three selectivity ratios considered (ΔpK_{a-b}, ΔpK_{a-d}, and ΔpK_{b-d}) and their domain af predictability. The figure shows three axes symbolizing ligand selectivities, divided into strong selectivity ($|\Delta pK| > 1$) and modest selectivity ($0 < |\Delta pK| < 1$). Both strongly and modestly selective α_{1a}-AR ligands correlate with their property space descriptors, whereas only modestly selective α_{1b}-AR ligands do so, and α_{1d}-AR selective ligands do not.

To verify the above hypothesis, we recalculated regressions coefficients between ΔpK_{a-b} selectivity and property space parameters, removing the strongly selective α_{1b}-AR ligands (compounds **2**, **4**, **17**, and **23**). This indeed produced a slight increase (about 0.05−0.10) in all correlation coefficients between property spaces and ΔpK_{a-b}. The best correlation, namely between range_logP and ΔpK_{a-b}, is shown in eq 5 and Figure 2:

$$\Delta pK_{a-b} = 1.49(\pm 0.12)\{\text{range\_logP}\} - 0.12(\pm 0.13) \quad (5)$$

$$n = 32;\ r^2 = 0.79;\ q^2 = 0.78;\ s = 0.41$$

Clearly, this equation cannot take into account α_{1b}-selective ligands (i.e. with $\Delta pK_{a-b} < 0$). Indeed, a

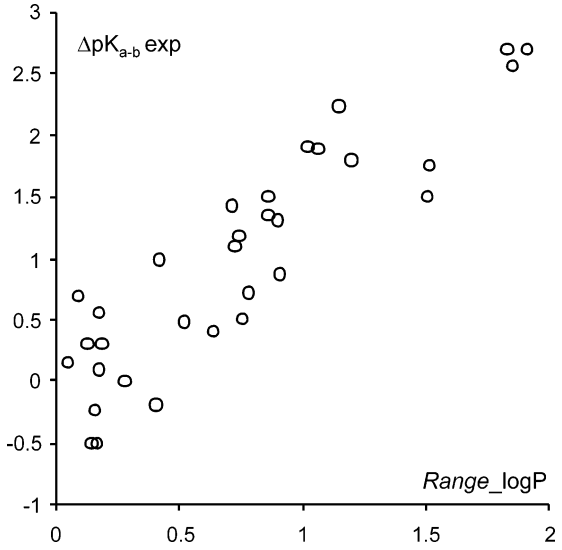

Figure 2. Best one-variable correlation between ΔpK_{a-b} and range_logP (eq 5).

hypothetical molecule with an impossibly low range_logP of 0 would be predicted to have a ΔpK_{a-b} equal to −0.12. Nevertheless, the goodness of fit of this equation is remarkable considering the heterogeneous nature of the ligands and its high q^2 value (i.e., good predictive power) obtained with a single independent variable.

In a similar manner, we recalculated regressions coefficients between ΔpK_{a-d} selectivity and property space parameters, removing all α_{1d}-AR selective ligands (compounds **2**, **5**, **7**, **18**−**20**, **25**, and **29**). Remarkably, the α_{1a}-selective ligands taken alone gave better correlations between property spaces and ΔpK_{a-d} than the full set, even if the new relationships remain of modest significance (data not shown).

Given the absence of correlation between the sensitivity and range descriptors (Table 2A), we also examined whether a two-variable equation would improve on eq 5. As shown by eq 6, the inclusion of two independent variables in the same equations improves their predictive capacity:

$$\Delta pK_{a-b} = 1.61(\pm 0.13)\{\text{range\_logP}\} + 0.34(\pm 0.04)\{\text{sensitivity\_logP}\} - 0.76(\pm 0.19) \quad (6)$$

$$n = 32;\ r^2 = 0.84;\ q^2 = 0.83;\ s = 0.38$$

Compared to eq 5, eq 6 shows a slight statistical improvement. Also, it has a better predictability for α_{1b}-selective ligands, since a hypothetical molecule with very low range_logP and sensitivity_logP values would be predicted to have a ΔpK_{a-b} equal to −0.76. This seems to confirm that the property space parameters considered here are devoid of interest for highly selective α_{1b}-ligands (i.e., ligands with $\Delta pK_{a-b} < -1$). Combining the range and sensitivity of PSA (or of SAS) also yielded improved correlations compared to range alone (Table 3), but these remained below the significance of eqs 5 and 6. Interestingly, the independent variables have positive coefficients in all these equations. This it taken to mean that the ΔpK_{a-b} selectivity is proportional to property space parameters. In contrast, the intercept value is always negative, allowing it to take α_{1b}-selective ligands into account.

4. Discussion

The first question to be addressed is why property space descriptors correlate well with only ΔpK_{a-b}, while their correlation with ΔpK_{a-d} is modest and that with ΔpK_{b-d} nil. When examining the pharmacophoric elements of the α_{1a}-, α_{1b}-, and α_{1d}-AR ligands as computed by Bremner et al.,[13] one sees that they are similar, namely, (1) a positively charged group, (2) an aromatic moiety, and (3) a H-bonding group. The major difference between the three models is the relative 3D-position of the pharmacophoric elements. In particular, the model of the α_{1a}-AR ligands reveals an extended geometry, whereas the α_{1b}-AR and α_{1d}-AR ligands assume more folded conformations. In other words, an α_1-adrenoceptor ligand unable to easily adopt an extended geometry will interact preferentially with the α_{1b}- and/or α_{1d}-subtype, whereas an α_1-AR ligand unable to easily adopt a folded geometry will interact preferentially with the α_{1a}-AR.

The results of the present study are compatible with this mechanism of selectivity. Since the property space descriptors take structural variability into account, their correlation with ΔpK_{a-b} (and to a lesser but real extent with ΔpK_{a-d}) indicates that these selectivities are indeed driven by differences in conformational behavior and hence in property spaces. Similarly, the lack of correlation with ΔpK_{b-d} indicates that this selectivity does not depend on conformational behavior but on other pharmacophoric differences. Why α_{1a}/α_{1d} selectivity (i.e., ΔpK_{a-d}) should correlate less well with property space than α_{1a}/α_{1b} selectivity is difficult to explain. Presumably, the computed properties (log *P*, dipole moment, PSA, and SAS) do not encode fully those recognition forces involved in binding to the α_1-ARs.

The good correlations between property space descriptors and ΔpK_{a-b} may also mean that the α_{1a}-AR can accept both folded and extended conformers and hence shows a good adaptability, while the α_{1b}-AR and α_{1d}-AR subtypes accept only folded geometries. The greater flexibility of α_{1a}-AR may suggest a general explanation for our results. Indeed, one can imagine that a flexible ligand cannot interact with a rigid target because loss of entropy is not made up by interaction energy. In contrast, a flexible target can allow multiple binding so that the ligand can preserve its flexibility during the interaction without a dramatic decrease of entropy. Moreover, a rigid ligand can interact with both flexible and constrained targets because the interaction energy can compensate a limited loss in entropy.

From a methodological viewpoint, our results suggest that range and sensitivity are useful descriptors of property spaces and can parametrize the capacity of a given molecule to span broad conformational and property spaces. In other words, range and sensitivity appear as promising descriptors of the dynamic behavior of a molecule. Their application to other dynamic QSARs (in particular ADME behavior) is under investigation.

Computational Methods

Setup of the Ligand Database. The dataset of 36 α_1-AR ligands was taken from Bremner et al.[13] The compounds were set in their protonated form as recognized by the α_1-ARs. The molecules were built using the ChemNote module in the Quanta/CHARMM package (MSI). After a preliminary energy minimization to discard high-energy intramolecular interac-

tions, the overall geometry and the atomic charges were optimized using MOPAC6.0 (keywords: "AM1", "PRECISE", "GEO-OK").

Conformational Analysis. The conformational behavior of the compounds was investigated by a Monte Carlo procedure that generated 1000 conformers by randomly rotating the rotors. All geometries so obtained were stored and optimized to avoid high-energy rotamers. The 1000 conformers were clustered according to similarity to discard redundant ones; in this analysis two geometries were considered as nonredundant if they differed by more than 60° in at least one torsion angle. For each compound, cluster analysis yielded a number of clusters proportional to the compound's flexibility, ranging from five clusters (compound **19**) to 34 (compound **3**). Only the lowest energy geometry was retained in each cluster.

Molecular Properties. The molecular properties considered in this study were virtual log *P*, dipole moment, polar surface area (PSA), and solvent accessible surface (SAS). The virtual log *P* was calculated by the molecular lipophilicity potential (MLP) approach.[24] The SAS values were calculated by taking a solvent of radius equal to 1.4 Å. The PSA values were calculated by subtracting the contribution of carbon atoms and nonpolar hydrogen atoms from the SAS.[25] All these properties were calculated for each conformer of all compounds using the VEGA package.[26] The property space of each monitored property was expressed by range and sensitivity calculated according eq 3.

Supporting Information Available: Table S1 reports description and average property values of the investigated ligands. The four properties monitored during conformation analyses are virtual log *P*, dipole moment, polar surface area (PSA), and solvent-accessible surface area (SAS). Table S1 also includes molecular flexibility indices, namely, RMSD averages, and the number of conformational clusters produced during the conformational analyses. Table S2 shows the property space parameters for investigated ligands, namely the range and sensitivity of the four properties monitored during conformation analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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